QuapoS 4

Quality Standard
for the Oncology Pharmacy Service
with Commentary

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as the result of the Conference for Standardisation in Oncology
Pharmacy, September 2008 in Luxembourg and the continuing
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'Moving Forward: The United Way'

In Europe and especially in the Union of 27 national countries we share a social health care that stands as a model to the world including the United States of America. This system however is under constant threat because of the increasing demands by our ageing society and the economical burden to the same society.

It seems rather defiant to dream of even better services and quality of life for the millions of cancer patients that we treat each year when Mr. Barroso speaks of a reality of 27 different nations that disagree on though decisions and is lukewarm to consider a European Cancer Plan.

But there is hope, in part by the interest of the European Commission, the straightforward policies of the previous commissioner Mrs. A. Vassiliou, the understanding from the European Ministers towards the cancer problem and last but not least the initiatives of MAC, the members of the European Parliament, leading the fight against cancer.

It would be unacceptable if the stakeholders of our health care would stay out of this fight. The most effective call to action is undoubtedly the union of ECCO 15 - 34 ESMO in Berlin next September. They are the symbol of our knowledge that collaboration of all expertise and shared care leading to an European Academy of Cancer Sciences will be a major step forward to increase the survival and quality of life of the European cancer patient.

We can testify, as secretary of Europa Uomo, that the patient support organisations understood the call and believe in the message by collaborating in the Patient Advisory Board of ECCO.

It is even clearer that the European Society of Oncology Pharmacists (ESOP) started their own crusade in 1996 with their Quapos, standards of care, culminating in this volume. It is an impressive showcase of bringing expertise together ranging from their obligatory expertise on all aspects of medical drugs and treatment to supporting patients with advice on their last will as well as research and development. Their message is loud and clear. We cannot afford to build more and more hospitals where our cancer expertise will be diluted and the need for transmural care, in- and outside the cancer hospital and services, can be given by the great majority of health care workers as doctors, pharmacists, nurses, technicians and social workers just to name a few. They also serve as a needed link to translational health care from bench and industry to the bedside. A process that we see as too expensive in financial resources and too slow for the urgent need of innovative treatment and orphan drugs. A shared risk of all involved stakeholders including the governments of our 27 European states could be a major start.

Last but not least we can only win if we value and respect the specific expertise of all partners. This is why we would like to change the word multidisciplinary, meaning all doctors, changed to multiprofessional, meaning all professions serving the patients.

We congratulate all members of ESOP, representing 33 countries in Europe, and especially their president, Klaus Meier, for their dedication and success.

Antwerp, July 20, 2009

Prof. Dr. Louis Denis

Secretary Europa Uomo
Chair PAC committee ECCO

Preface to the 4th Edition of the Quality Standard for Oncology Pharmacy Services (QuapoS 4) 2008

The patient is the focus of our attention. This is a view with which everyone will surely agree, although at times some may be tempted to add "ultimately". Ultimately it is not enough to recognise the importance of the principle; we also require the capacity – technical and economic – to implement it.

The European Union again has identified new members who are keen to join, as are their peoples. Since 2000 ESOP (the European Society of Oncology Pharmacy) has been experiencing growing affinity with many experts involved in oncology pharmacy, calling on all of them to participate actively in the unification process.

Such was the spirit at the First Conference on QuapoS in September 2001 in Luxemburg. Standardisation, as we realised early on, is both an enormous challenge and an opportunity for oncology pharmacy. This spirit is alive and the participants of the workshops in 2004 and 2008 have continued in their mutual exchange. The fruits of this spirit lie not only in harmonisation and the benchmarking that results, but also in the freedom we have to develop in accordance with our local conditions – usually dependent on our social framework – and to identify and record differences.

For as we know, standards are not just about the identical things we have in common, but also about things that will remain different in future. Nothing is more depressing than attending courses or congresses that describe situations elsewhere that seem seductively desirable, but that cannot be implemented under conditions back home, in either the near or distant future. Sticking to the devil we know is often the regrettable consequence.

QuapoS, developed by German hospital and public oncology pharmacists who were members of the DGOP (German Association for Oncology Pharmacy), should be seen as a symbol of progress.

- *The first quality standard was published in 1997 and concentrated primarily on pharmacy services in the narrower sense, i.e. conditions to comply with in the production of cytotoxic substances.*

- *In 2000 the second edition reaffirmed and extended existing guidelines. It also incorporated services provided by oncology pharmacists as partners within an interdisciplinary team treating the patient. Furthermore, DGOP began certifying oncology pharmacy departments in pharmacies on the basis of QuapoS.*
- *In the third edition, the field of pharmaceutical care was comprehensively examined. A holistic view of the patient and the orientation of pharmaceutical services towards the patient have now been reflected in the quality standard.*
- *Now in the fourth edition we have incorporated the results of the Luxembourg Conference for Standardisation in Oncology Pharmacy working groups from 2001 to 2008. In addition patient demands have been given more consideration.*

Let me emphasise once more that the aim of QuapoS is not to apply German findings to the rest of the world. Rather we are attempting to approach any interested parties in their home country and in their own language, and to facilitate their entrance into the European debate. We are fully aware that the English language will be the bridge linking us in our common scientific purpose. I wish to express my gratitude to the delegates, members and friends who have made this possible.

Klaus Meier
President ESOP

Many Thanks to those who made this publication as well as the publication of the standard in 21 languages possible:

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1. Staff

1.1. Staff handling Cytostatics

Persons handling cytostatics who are working within the immediate sphere of influence of the pharmacy comprise:

Pharmaceutical staff:

- **Pharmacists (m/f) and persons in training for the pharmaceutical profession**
- **Pharmaceutical-technical assistants (m/f) and persons in training for the pharmaceutical-technical occupation**
- **Pharmacy assistants (m/f)**
- **Pharmaceutical engineers (m/f)**

Non-pharmaceutical staff such as

- **Pharmaceutical trading clerks (m/f)**
- **Skilled pharmacy workers (m/f)**
- **Unskilled pharmacy workers (m/f)**
- **Storage employees (m/f)**
- **Cleaning and maintenance employees (m/f)**
- **Transport employees (m/f)**

Hannelore Kreckel, Gießen

Before assuming any relevant task and at least once a year all persons must be instructed in handling cytostatics (see chapter 1.3: Risk assessment, operating procedures and instructions).

Pharmaceutical staff

see chapter 1.2: Persons involved in preparation

Non-pharmaceutical staff

Non-pharmaceutical staff may be assigned only to tasks supporting preparation. This includes keeping the store stocked with excipients and active ingredients, documentation, preparations for delivery including sealing of the cytostatics solutions ready for use and jobs in disposal.

The modes of documentation, labelling and delivery must be intelligible and familiar to the staff. The modalities of disposal of individual materials must be defined comprehensibly and communicated to the staff involved.

Procedures for handling of sterile single-use products and calculation of the stock of of all materials and products used, both for any particular procedure and for the department's storage, must be communicated. The prescribed storage conditions must be known, kept and verified regularly.

For persons with training not specific to pharmaceutics (such as storage staff), recognition of cytostatics-containing medical products may be facilitated by placing images of the relevant products where they are easily seen, and by marking storage spaces for cytostatics products as such.

Transport staff

The transport staff may accept for delivery only containers which are duly approved for delivery, properly packaged and labelled for delivery to the appropriate departments. They are responsible for correct and in-time delivery of the ready-to-administer cytostatics solutions.

Cleaning and maintenance staff

The cleaning and maintenance staff are responsible for cleaning and maintenance of the floor, the walls and the surfaces of the furnishings. The cleaning and maintenance staff must be instructed with regard to the special requirements of a clean-room and the special risks and dangers of a preparation area for ready-to-administer cytostatics solutions.

Compliance with the cleaning and disinfection plan is to be documented.

1.2 Staff involved in Preparation

Only pharmaceutical staff may be assigned to the preparation of ready-to-administer cytostatics solutions. These employees must be sufficiently educated and trained and instructed with regard to aseptic procedures and handling of hazardous substances before assuming work.

Quality standards should be discussed with all employees to stimulate and promote understanding and sensitivity for the various problems of an oncology pharmacy service.

Hannelore Kreckel, Gießen

Persons working in preparation have access to the preparation area, and so have persons performing cleaning and maintenance work.

There are job profiles for all groups of people working in the cytostatics area.

Pharmaceutical staff

Preparation of ready-to-administer cytostatics solutions may be entrusted to pharmaceutical staff only. The ready-to-administer cytostatics solutions prepared are approved for delivery by a pharmacist.

The staff assigned to the preparation of cytostatics must be proficient both in handling hazardous substances and in the procedures of aseptic preparation of pharmaceutical products. The staff must be instructed, trained and thoroughly familiarized with the work and is obliged to regularly participate in further education or training (1).

Instruction of staff for the preparation of cytostatics requires planning in terms of time and contents to make sure that on the one hand the person to be instructed is not overcharged while at the same time he/she gets the chance to

acquire the skills for preparation as well as the theoretical knowledge necessary for understanding.

It is recommended to organize a program where the necessary steps are subdivided into units, opening the possibility for the person to be instructed to logically and systematically study the complex field of work in the preparation of cytostatics. To this end, a competent contact person must be provided (see 1.6: Education, Training and Skill Enhancement of Employees).

Theoretical knowledge may be acquired by instruction talks, auto-didactically or during training seminars. The basics should be defined, verified and delimited from advanced knowledge.

Correct aseptic working techniques must be demonstrated regularly (1,2).

Non-pharmaceutical staff

see chapter 1.1 Persons handling cytostatics

Both the preparation and the supporting staff are to align their activities during preparation with the production processes. Unnecessary movements within the manufacturing area affect the air flow and therefore must be avoided.

Activities producing particles are to be restricted to the absolutely indispensable amount.

All activities negatively affecting concentration of the staff are to be stopped during the preparation process. In a survey among Australian colleagues, essential affecting factors named were isolation, physical detraction by temperature, noise and room size and an ergonomic workplace at the cytostatics safety hood (3). A convenient, ergonomic workplace contributes to concentration as much as observance of breaks, since work at the cytostatics safety hood may be very isolating and restrictive. The ISOPP standards suggest having a break every two hours (2). In order to avoid any feelings of uncertainty, the staff must be able to understand why and how the working environment and technique are monitored. Safe and prudential actions forms the best basis for good work.

The quality of work in a centralised cytostatics preparation department is essentially determined by the staff constituting the department. Motivated staff are the essential guarantee for the department's success.

Having motivated staff is a great advantage which, however, cannot be obtained without effort. It is a promising approach to provide the individual employees with copious information, to comment this information and to ensure its dissemination. Employees must be given sufficient time to comprehend and digest the information. All the staff in the specific problem zone of a cytostatics department should have the feeling of their questions and fears being taken serious, so that their need for information and safety can be taken into account.

This includes informing staff about how the department is integrated into the overall structure of the pharmacy on the one hand and into the overall structure of patient treatment and care on the other hand. Only thus it is possible to understand, to comprehend and to solve the problems and needs of the department to be supplied. In order to create the necessary conditions, it is recommended to offer employees a chance to learn about everyday life on station for several days during introduction, and to constantly maintain personal contact with the supervised units during work.

Dealing with problems and suggestions submitted to the department implies that clearly defined competences must have been established and the employees precisely know their individual authority so that they can fulfil their tasks independently.

(1) PIC/s Guide to Good Practices for the Preparation of Medicinal Products in health Care establishments, April 2008

(2) ISOPP Standards of Practice. J Oncol Pharm Practice 2007 : 12, 1 – 81

1.3. Hazard Evaluation, Working Rules and Instruction

Before starting work in cytostatics preparation, a documented hazard evaluation must be performed (Workplace Health and Safety Act, Ordinance on Hazardous Substances). The employees must be given instructions based on the results. In addition to the persons responsible for carrying out the preparation, all staff handling and using cytostatics must be trained as defined in the hazardous substances regulations (§3 Ordinance on Hazardous Substances). This also includes the cleaning and maintenance staff and the employees working in the transport service.

Appropriate instructions must be provided for each of the different occupational groups.

Depending on the particular requirements this will include (among others) the following points:

- **effects of drugs**
- **proper handling of cytostatics**
- **hazards and protective measures**
- **aseptic working procedures**
- **disposal of contaminated materials and equipment as well as of cytostatic residues**
- **occupational preventive medicine**
- **action in the case of accidents.**

According to §20 II Ordinance on Hazardous Substances, the instruction session must be repeated annually; the accident prevention rules published by the accident insurance providers specify instruction twice a year.

Written working rules must be prepared for each particular workplace (§20 I Ordinance on Hazardous Substances).

Cytostatics are classified according to their properties and included in the pharmacy's list of hazardous substances (§16 IIIa Ordinance on Hazardous Substances). This list must be extended whenever significant changes occur, and it must be checked at least once a year. In case of changes, a new hazard evaluation must be performed.

Accidents must be documented in an accident protocol; in case of personal injury, RVO (Rechtsverordnung, executive decree) §1552 ff. mandates that the accident be either recorded in the first aid log book (minor injuries, inability to work for a period of less than three days) or notified to the statutory insurance provider.

Susanne Rüggeberg, Lehrte

Hazard Evaluation

According to the provisions of the Workplace Health and Safety Act (Arbeitsschutzgesetz, ArbSchG) §5 I and the amendment of the Ordinance on Hazardous Substance (Gefahrstoffverordnung, GefStoffV) of January 1st, 2005, the employer must perform a hazard evaluation during which the dangers associated with the work are ascertained and appropriate protective measures are defined. The employer may delegate these tasks to persons who are capable, qualified and reliable as defined by the law. This delegation has to be set down in writing in a «Duty Delegation Document». Safety experts or company physicians should be available in an advisory capacity.

The recommended procedure for hazard evaluation comprises the following steps:

• *Definition* of the work areas to be evaluated, e. g. cytostatics preparation laboratory, reception of goods, store, transport, laboratory, etc.

• *Ascertainment* of hazards and burdens, e. g. classification of the hazardous substances into the hazardous substances list (see above) using the material safety data sheets provided by the manufacturers, but also mechanical dangers arising from equipment and physical and mental stress factors such as fatigue, stress, monotony, noise, light, etc.

• *Evaluation* of these hazards and burdens in the form of hazard evaluation form sheet as published by the Deutscher Apotheker Verlag, Stuttgart. The protective aim is almost always specified in laws or regulations [Ordinance on Hazardous Substances, TRHS (technical rules for hazardous substances) 201, TRHS 440, TRHS 525, TRHS 905, AOLG (working group of the highest regional health authorities), brochure M620 of the BWG (professional association for the health service and social services), BuBaV (procedure recognised by the professional association) (LASI (committee of the Laender for industrial safety and safety technology)), ApBetrO (Ordinance on the Operation of Pharmacies), etc.)]

• *Decision* on the measures required. If possible, dangers should be countered at their place of origin. Here technical protective measures have precedence over organisational and these in turn over staff-related measures.

• *Control of the efficacy* of the measures. Whenever measures have been taken, their efficacy is to be evaluated. The protective measures are re-evaluated to determine whether they are effective or may even produce new hazards.

• *Documentation*: The hazard evaluation must be documented in writing and signed by the staff working in the area.

For pharmacies in particular, a workbook «GP 5,5 – Basics of prevention, detection and evaluation of hazards – Pharmacies –» may be ordered from the BGW which lists all the legal requirements and comprises the working tables required for hazard evaluation.

According to §19 Ordinance on Hazardous Substances, the competent authorities may demand documents:

• Result of hazard evaluation including documentation

• Operating instructions (see below) and the information upon which the evaluation is based

Hazardous Substances List

Hazardous substances in the sense of Ordinance on Hazardous Substances (*Gefahrstoffverordnung*, GefStoffV) are hazardous substances and preparations in accordance with §3a Chemicals Act (*Chemikaliengesetz*, ChemG). This defines hazardous substances as «substances or preparations which (...) 12. are carcinogenic, 13. endanger reproduction, 14. are mutagenic». Carcinogenic substances are defined in greater detail in Appendix 1 No. 1.4.2.1. of the Ordinance on Hazardous Substances. This states for Category 2 that substances should be regarded as carcinogenic for humans if sufficient evidence exists to support the assumption that exposure of a human to the substance may cause cancer. This assumption is generally based upon appropriate long-term animal studies and/or other relevant information.

Since neither the Chemicals Act in §3a nor the Ordinance on Hazardous Substances make an exception for medicines in dealing with hazardous substances (§2 III Ordinance on Hazardous Substances), it may be concluded that the regulations also apply to the preparation of cytostatics.

Accident prevention decree VBG 113 («Handling carcinogenic hazardous substances») expressly also names carcinogenic drugs as hazardous substances in §1 III. Among the special groups of substances, Technical Rules for Hazardous Substances (TRHS) 905 lists carcinogenic drugs since these are based on a genotoxic therapeutic mechanism of action.

The cytostatics directive published in September 1998 by the AOLG stipulates that the employer must include all cytostatics with CMR properties (carcinogenic, mutagenic or reproduction-toxic drugs) in a hazardous substances list and classify them appropriately (§16 IIIa Ordinance on Hazardous Substances).

Since introduction of the concept of «protection classes», CMR drugs have been classified as class 4 drugs. Here the duration of exposition must be limited, and the danger area must be marked with hazard signs.

Assistance for classification is provided in TRHS 440 «Ascertainment and evaluation of dangers caused by hazardous substances at the workplace». The information must then be recorded in writing or stored on data carriers. The list must contain at least the following information (15):

1. Name of the hazardous substance
2. EU number
3. Classification of the hazardous substance with R and S phrases
4. Range of quantities of the hazardous substance in the establishment with location
5. Comments

For every hazardous substance available in the pharmacy a safety data sheet must be printed. According to M620, a computer system which is readily accessible for all the staff will be sufficient.

As an alternative, the hazardous substances list may be integrated into the working rules provided that the the above information is included (§6 VIII TRHS 440).

Classification of the cytostatics in the hazardous substances list must be known to all employees handling these directly or indirectly. This requirement derives from the fact that although drugs with dangerous properties according to §2 Chemicals Act are excluded from the Ordinance on Hazardous Substances requirements for labelling user packaging, they are still subject to the handling regulations of §19 Chemicals Act and §§5 and 6 Ordinance on Hazardous Substances.

The AOLG cytostatics directive states that dealing with carcinogenic substances, but also with cytostatics, which are or may be carcinogenic, must be notified to the responsible authorities and the responsible accident insurance provider (§37 Ordinance on Hazardous Substances, §7 UVV VBG 113 (accident insurance provider decree)). Information as to which authorities are responsible is available from local government offices, the relevant department of the administrative

district (*Landkreis*) or municipal authorities of towns with their own administration (*kreisfreie Staedte*), in particular from the industrial inspectorates.

This notification, which must list the names and quantities held of all hazardous substances, must take place no later than 14 days before the first preparation of cytostatics. It must be renewed every 5 years. If further hazardous substances are handled, these must be notified without delay. Notification can be carried out using the BGW form "Notification of carcinogenic hazardous substances" (ZH 1/82).

Operating procedures

The Ordinance on Hazardous Substances and the UVV VBG 113 demand written operating procedures in every area where hazardous substances are handled.

According to § 20 Ordinance on Hazardous Substances the operating procedures must comprise:

- description of the workplace / activity
- name of hazardous substance
- labelling of the hazardous substance at the workplace
- hazards for persons and environment
- protective measures and rules of behaviour
- action in case of danger
- first aid emergency telephone number / poisons centre telephone number
- organisational rules at the workplace
- restrictions
- proper disposal
- date of posting, signature of the employee.

Sample working rules are to be found in the BGW brochure M620 dated April 2008.

The general remarks in the AOLG directive clearly indicate that the employer shall be responsible for adapting the organisation and implementation of the cytostatics preparation to the latest safety standards (see for example §§16 II, 19 IV, 26 I, 36 II and III Ordinance on Hazardous Substances, §§8 IV, 10 III, 13 I VBG 113, TRHS 525).

Instruction

All persons directly or indirectly handling cytostatics must be instructed. This includes not only pharmaceutical staff entrusted with the preparation of the cytostatics (see Chapter 1.2. Persons Involved in Preparation) but also non-pharmaceutical staff such as pharmacy assistants, pharmacy sales staff and skilled workers employed in the pharmacy who can perform auxiliary work in preparation and in maintaining stocks (see Chapter 1.1. Persons Handling Cytostatics). The instruction process must also include the cleaning and maintenance staff responsible for cleaning the rooms of the cytostatics department as well as the employees of the transport and delivery service. These employees must in any case be informed orally about the special hazards and told what action to take in the event of an incident.

Oncological practices and wards usually have a high need for consulting with regard to the legal basis for handling CMR drugs. Here support by the oncology pharmacist is desirable, even though responsibility will remain with the employer.

The Ordinance on Hazardous Substances demands that before starting work, employees handling hazardous substances must be instructed on the basis of the working rules about existing hazards and protective measures. This instruction takes place orally and in a way appropriate to the particular workplace and is given by the safety officer or the respective supervisor. The instruction must be documented in writing and the following information recorded:

- date
- performed by

- topics instructed, e.g.:
- effects of drugs
- proper handling of cytostatics: acceptance of goods (see Chapter 3.1), store keeping, making ready (see Chapter 3.6), transport (see Chapter 3.7)
- hazards and protective measures
- aseptic procedures (see Chapter 3.4)
- disposal of contaminated materials and equipment and of cytostatics residues (see Chapter 4.1)
- occupational preventive medicine (see Chapter 1.5)
- action in the case of incidents or accidents, not only in theory but also practical exercises of possible exposure to hazardous substances (see Chapter 3.6.2)
- proper use of the personal protective equipment (see Chapter 3.5)
- novel methods or substances
- basis: statutory requirements and working rules
- department, name, date of birth, job title and signature of the person receiving instruction.

BGW brochure M 620 «Safe handling of cytostatics» and TRHS 525 require instruction to take place annually; UVV VBG 113 and the AOLG cytostatics directive require that the employee be instructed twice a year, additional instruction sessions are necessary whenever new staff is hired, when procedures are changed or new hazardous substances are in use.

In addition, work techniques and the proper use of the protective equipment during the work process must be inspected at regular intervals by the supervisor in this area.

Protection of Working Mothers and Working Young Persons

According to §4 I of the MuSchG (*Mutterschutzgesetz*, law on protection of working mothers), pregnant women and nursing mothers must not be employed

for work in which they are exposed to the damaging effects of substances hazardous to health. In the MuSchRiV (*Mutterschutzrichtlinienverordnung*, guideline directive on protection of expectant and nursing mothers) issued pursuant to §4 IV MuSchG and in the Ordinance on Hazardous Substances there is no unrestricted prohibition of employment of expectant mothers in dealing with carcinogenic, embryotoxic or mutagenic hazardous substances. As long as the pregnant woman is not exposed to these hazardous substances while handling them in the prescribed way, she may continue to be employed (§5 I MuSchRiV, §15b VII Ordinance on Hazardous Substances). Similar wording is used in § 6 III UVV VBG 113.

In addition, according to §1 MuSchArbPlVO (*Mutterschutzarbeitsplatzverordnung*, directive on workplaces for working mothers) a hazard re-evaluation must take place immediately upon notification of an existing pregnancy or intended period of nursing. In order to exclude all recognisable risks the following measures must be taken in the order given:

1. Working conditions must be modified to exclude any danger. If this is not possible,

2. the employee must be transferred to a different workplace. If this is either impossible or unreasonable,

3. the employee must be exempt from work.

The result of the hazard evaluation and the protective measures must be notified not only to the person affected but also to all female employees (at least those performing similar work) and to the workers' council if applicable. Furthermore, the trade control must be informed about the pregnancy and the result of the hazard evaluation, e.g. with the sample in the appendix.

Since an incident during the preparation of cytostatics can never be completely ruled out, a rule must be established in accordance with the MuSchG prohibiting the handling of substances dangerous to health (in this case cytostatics) by expectant and nursing mothers.

The cytostatics directive of the Free State of Thuringia recommends in addition that the preparation of cytostatics be performed only by persons who have already completed their family planning (14).

Pursuant to §22 I 5 in combination with §26, the JArbSchG (*Jugendarbeitsschutzgesetz*, law on protection of working young people) prohibits the employment of young persons with hazardous substances according to §15b IV Ordinance on Hazardous Substances. This does not apply to young persons over the age of 16 years insofar as this work is necessary for attainment of their educational objectives and their protection is guaranteed through supervision by someone with appropriate knowledge (§22 II JArbSchG). In a company employing a company physician or a workplace safety specialist, this person must ensure that the young persons are cared for in respect of occupational medicine and safety. In addition, the Ordinance on Hazardous Substances stipulates that young persons must undergo a medical examination 12 weeks before the start of their employment. Young persons may then only accept the offer of employment if the physician verifies that there are no health-related doubts against the employment.

Instructions can specify an employment prohibition for employees who must undergo immunosuppressive therapy (e.g. cortisone treatment) or are exposed to an additional risk of cancer as a result of other diseases and their associated therapeutic and diagnostic methods (e.g. X-ray examinations).

References:

1. Gesetz zum Schutz vor gefährlichen Stoffen (Chemikaliengesetz - ChemG) vom 27. September 1994, (BGBl. I, S. 2705)
2. Verordnung zum Schutz vor gefährlichen Stoffen (Gefahrstoffverordnung - GefStoffV), zuletzt geändert 2005
3. Technische Regeln für Gefahrstoffe TRGS 905 "Verzeichnis krebserzeugender, erbgutverändernder oder fortpflanzungsgefährdender Stoffe", BarbBl. 9/2005
4. Technische Regeln für Gefahrstoffe TRGS 440 "Ermitteln und Beurteilen der Gefährdungen durch Gefahrstoffe am Arbeitsplatz: Vorgehensweise", Ausgabe Oktober 1996
5. Technische Regeln für Gefahrstoffe TRGS 525 "Umgang mit Gefahrstoffen in Einrichtungen zur humanmedizinischen Versorgung", Bundesarbeitsblatt 5/1998
6. Gesetz zum Schutze der erwerbstätigen Mutter (MuSchG) vom 16.06.2002 (BGBl I, S. 2318)

7. Verordnung zur ergänzenden Umsetzung der EG-Mutterschutz-Richtlinie (Mutterschutzrichtlinienverordnung) vom 15. April 1997, (BGBl. I, S. 782)

8. Gesetz zum Schutze der arbeitenden Jugend (JArbSchG) vom 12. April 1976, zuletzt geändert am 21.12.2000

9. TRGS 400 "Gefährdungsbeurteilung für Tätigkeiten mit Gefahrstoffen", Januar 2008

10. TRGS 401 "Gefährdung durch Hautkontakt – Ermittlung, Beurteilung, Maßnahmen", BArbl. 5/2006

11. TRGS 402 "Ermitteln und Beurteilen der Gefährdungen bei Tätigkeiten mit Gefahrstoffen – Inhalative Exposition", Ausgabe Januar 2008

12. Merkblatt M 620 "Sichere Handhabung von Zytostatika", BGW, Stand April 2008

13. Gifte und gefährliche Stoffe, Textausgabe mit Erläuterungen von Dr. H. Gebler, 2002, Govi-Verlag

14. Herstellung applikationsfertiger Zytostatikalösungen in Apotheken (aus Bundesgesundheitsblatt Nr. 9/1998, S. 404), mit Erläuterungen veröffentlicht in der Dtsch. Apoth. Ztg., 138, S. 4176-4182 (1998)

15. Diedrich, R.: Zytostatika-Richtlinie der Länder, Erläuterungen und Kommentar. Dtsch. Apoth. Ztg., 138, S. 4122-4138 (1998)

16. Helmut Hörath: Gefahrstoffverzeichnis, 5.Aufl. 2003, Deutscher Apothekerverlag Stuttgart

1.4. Permanent Workplaces

The staff must be of sufficient size for the dimensions of the preparation work and well-trained.

Permanent workplaces should be avoided in the centralised cytostatics preparation area.

According to §36 VI of the Ordinance on Hazardous Substances, however, the number of potentially exposed persons is to be reduced to a minimum.

Susanne Rüggeberg, Lehrte

Essentially, only centralized preparation of cytostatics in a pharmacy or dispensary offers considerable benefits for workplace safety.

The relevant regulations define conflicting goals: On the one hand, permanent workplaces should be avoided in the centralised cytostatics preparation area, on the other hand the number of potentially exposed persons should be kept as small as possible (§36 VI of the Ordinance on Hazardous Substances).

Although the employer is obliged to implement state-of-the-art procedures for preventing release of cytostatics, a release cannot be excluded with 100% certainty (see chapter 1.5: Occupational preventive medicine). Therefore, internal rotation among the experienced preparation staff is indispensable also in order to minimize potential personal exposure.

The required specialized knowledge acquired by education and continuing training in combination with continued preparation practise (see 1.6: Education, Training and Skill Enhancement) is enough to limit the number of preparing employees in the pharmacy.

To guarantee proper supply of cytostatics formulations, a sufficient number of employees must be trained to cover inactive periods of the preparing employees due to further training, vacations, illness or other reasons.

It is important to establish regular rotation of the preparation staff during preparation, since concentrated work in special protective clothing causes a high degree of stress. The required rhythm of rotation should be agreed upon among the preparation staff. Schedules with daily or weekly rotation may be envisioned. Optimally, the employees currently not working in preparation should be deployed to documentation or patient counselling.

References:

1. M620, Zytostatika im Gesundheitsdienst, Merkblatt des Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege Hamburg (eds.), April 2008.

2. TRGS 525: Umgang mit Gefahrstoffen in Einrichtungen zur humanmedizinischen Versorgung, May 1998 – http://www.baua.de (Themen von A-Z/Gefahrstoffe/TRGS)

1.5. Occupational Preventive Medicine

Employees working in the area of cytostatics preparation are constantly handling CMR drugs. They must be offered regular occupational medical check-ups.

These check-ups should include:

1. **Initial examination before taking up employment.**
2. **Follow-up examinations during their employment at intervals of 12 to 24 months.**
3. **Examinations at the request of the employee if there is a suspicion of work-related impairment to health.**

Despite its limited meaningfulness, it is recommended that biomonitoring be included in the follow-up examinations as a means of performing spot checks on the effectiveness of the existing protective measures.

The employer must document the possible exposure to cytostatics and the preventive measures taken. This includes keeping records of the type and quantity of the cytostatics used and the frequency of the preparations carried out by each employee. Moreover, in the sense of occupational preventive medicine, the application of every technical and personal means of protection must be guaranteed by the implementation of standardised rules focussing on preparation, disposal, cleaning, accident and emergency management.

Prof. Robert Mader, Vienna

The basic issues of occupational preventive medicine for persons exposed to cytostatics derive from the characteristics of these CMR drugs; these substances are expected to remain at least in the next decade as one of the mainstays in

the therapy of malignant growths. Despite the impending introduction of new modes of action in haemato-oncology, the quantities of cytostatics used in hospitals will decline only slowly. From the viewpoint of occupational medicine, therefore, prevention is the central element. No matter what measures taken after a CMR drug has exerted an effect on a human being, there is no way to ensure that the effect of the damage has been neutralised completely. Especially the lack of reliable data on the chronic and subchronic toxicity of cytostatics underlines the necessity for always using the available personal protective equipment, for regular training of the exposed personnel, and for the installation and regular maintenance of technical equipment - as defined for example by the DIN 12980 standard for safety workbenches used in the preparation of cytostatics.

Risk evaluation of cytostatics

The danger presented by cytostatics is based on their genotoxic effect, which cannot be assigned a threshold value. This lack of a scientifically justified limit value derives from the stochastic dose-effect principle of CMR drugs: damage occurs randomly. Moreover, this damage is not an avoidable side-effect of these substances but is the intended therapeutic effect. Consequently, there exists a long tradition of epidemiological and toxicological studies which have attempted to quantify the risk to persons exposed in the course of their employment. After exposure by way of the skin, loss of appetite, nausea, vomiting, diarrhoea, coughing, shortness of breath, cardiac dysrhythmia and hair loss were observed as acute symptoms (Valanis et al, 1993). In addition to these symptoms, which are generally reversible, the literature contains a series of reports on the severe late sequelae of exposure. After many years of exposure to cytostatics, irreversible liver damage occurred in nurses and was classified as occupational (Sotaniemi et al., 1983). The question of an increased rate of spontaneous abortion in nurses was investigated several times and remains the subject of controversial discussion (first reported by Selevan et al., 1985). A further aspect subjected to investigation was menstrual dysfunction (Shortridge et al., 1995). Since in the extreme case this can lead to infertility, the hypothesis of an increased infertility rate as a further late sequela after exposure to cytostatics was investigated and - to a small extent - confirmed (Valanis et

al., 1997). For all the work cited there are also studies that failed to reproduce the results claimed. The resulting discussion about the effect of CMR drugs after chronic and subchronic exposure in low concentrations continues today. The questions thrown up cannot be clearly answered retrospectively because the working conditions and the associated exposure are often documented in a very fragmentary way. From today's point of view, new studies in this direction have become necessary because the situation has changed completely and the initial conditions in the past no longer apply to current safety standards. Nevertheless, there is no dispute about the extremely high potential danger presented by cytostatics.

Aim of the prevention

Because of the particularly toxic properties of cytostatics, several aspects are important for occupational preventive medicine:

- ascertaining risks that may lead to diseases in connection with possible loads at the workplace (precancerous stages, disturbances of the immune system, allergies, skin diseases, etc.);
- early detection of loads which in the case of CMR drugs are very probably associated with damage to health;
- early detection of work-related effects which may be triggered by cytostatics (allergies, skin diseases, genotoxic effects, etc.)

Load in this context means exposure of the employed person that can be proved by the analysis of cytostatics or their breakdown products in blood or urine (biological load monitoring). An additional aspect is the effect of the unwanted toxicity of cytostatics associated with their genotoxic effect. This is ascertained by biological effect monitoring - also known as cytogenetic effect monitoring. If occupational medical examination indicates a load or effect arising from cytostatics, biomonitoring is recommended in order to test selectively the effectiveness of the existing protective measures.

Who? When? For what?

Persons employed in the area of CMR drugs must be offered regular preventive occupational medical check-ups.

These check-ups should include:

1. Initial examination before taking up employment.
2. Follow-up examinations during their employment at intervals of 12 to 24 months.
3. Examinations at the request of the employee if there is a suspicion of work-related impairment to health.

It should be stated for the record at this point that these preventive check-ups are mandatory neither in Germany[1] nor in Austria[2]. However, there are recommendations by the Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (professional association for the health service and social services) and by the Bundesverband der Unfallkassen (federal association of accident insurance bodies) for that group of persons directly involved in the preparation and administration of cytostatics. This recommendation also includes cleaning and disposal personnel. In this connection it may be mentioned that persons exposed to radiation in the course of their employment are subject to much stricter regulations. These persons are continually monitored by means of dosimetry and must undergo an occupational medical examination at yearly intervals, whereby the employer is responsible for compliance with these requirements.

Nature of the occupational medical check-up

Particular attention should be paid to the following examinations:

- Anamnesis and employment anamnesis taking special account of previous exposure (initial examination); this should include recording the type of work with cytostatics, the quantity and nature of the substances and the protective measures taken.
- Physical status

1 Technische Regel für Gefahrenstoffe (technical rules for hazardous substances) 525 and Unfallsverhütungsvorschrift (accident prevention regulation) 100

2 Order of the Federal Chancellory of 13 February 1990 concerning protective measures for dealing with cytostatics

- Status of the skin and mucous membrane, since damage may occur as a result of direct contact with bleomycin, dactinomycin, dacarbazine, anthracyclines or vinca alkaloids; it is important to note recurrent or therapy resistant eczema, which can present a portal of entry for cytostatics.
- Recording of allergies such as can be triggered by bleomycin and cisplatin.
- Immune status.
- Recording of disturbances of the respiratory organs.
- Recording of disturbances of the liver and kidneys.
- Ascertainment of the lymph node status, e.g. swollen lymph nodes.

Clinical chemical investigations

- erythrocyte sedimentation rate
- complete blood count including reticulocytes
- liver function parameters (gamma-GT, SGOT, SGPT)
- creatinine

Circumstances that indirectly make working with cytostatics more difficult should also be taken into account. This includes, for example, allergies towards glove materials such as latex.

The above examinations are not intended to ascertain a specific load or effect, but serve for general orientation. Nonetheless, they are an essential part of the preventive process since problems at the workplace, whether in connection with the administration or preparation of cytostatics, are frequently associated with non-specific symptoms. Often these are manifested as impairment of the sense of taste, headache, nausea, accelerated hair loss and increased susceptibility to infection. If there is a definite suspicion of a load due to cytostatics, biomonitoring must be performed in order to determine the origin of the exposure. In this case the standardised rules for the individual work processes must be used since deviations from standard procedure are frequently the cause of toxic effects.

The employer must document the possible dangers to health as a result of handling cytostatics, and the preventive measures taken. In addition to reporting to the supervisory authorities, this also includes keeping records of the type and quantity of the cytostatics used and the frequency of their preparation, training courses held, and the implementation of the necessary protective measures.

Biomonitoring of load and effect

The technically easiest form of monitoring is environmental monitoring for the detection of contamination at the workplace by means of wipe tests. This type of investigation is very difficult to standardise and the results should therefore be interpreted as semiquantitative evidence. The sampling itself is simple to perform and the analysis can be carried out by a contract laboratory. The cytostatics cyclophosphamide, ifosfamide and 5-fluorouracil are currently available as parameters. These substances are very frequently part of the therapeutic protocol.

Investigations using this method for the above pilot substances have shown that the load in pharmacies where cytostatics are prepared is higher than on the wards where the therapy is administered (Connor et al., 1999). Moreover, contaminations were detected not only on cytostatics workbenches, but also on work surfaces, floors and personal protective equipment. Although these results indicate the problem, they contribute only indirectly to its solution. They can reveal the existence of a load but they do not enable its origin to be localised. Systematic investigations of the load have demonstrated the central role played by the combined effect of personal protective equipment and technical equipment in the hands of well-trained personnel, as reflected in the current state of the discussion. The danger presented by the decentralised preparation of cytostatics and the reduction of the load to quantities below the analytical detection threshold was demonstrated for methotrexate, even using high dose therapy as an example in the course of which dosages of 20 g were administered (Mader et al., 1996). This study documented the massive reduction in load for the pharmacist as a result of applying adequate protective measures. After the introduction of this safety standard everywhere, the situation had improved to such an extent that it was no longer possible to detect any load for the pharmacy personnel. In a long-term study in 21 hospitals with central

preparation it was found that accidental contamination during the preparation leads to measurable concentrations of anthracyclines in blood and is also associated with a reversible increase in the effect parameters (Pilger et al., 2000). This increase was characterised by a statistically significant increase in sister chromatid exchange (SCE), whereas it was possible to detect no more than a trend in the rate of micronuclei (MN). The major conclusion from this study, however, was that it was not possible to prove a systematic increase in load or effect over the representative period of two years. These results were confirmed in subsequent studies (Hessel et al., 2001), which is evidence for the generally high standard of safety within the German speaking region.

For the detection of exposure and genotoxic effect, biomonitoring today has available a set of instruments that is being continually extended. At the same time, however, this search for new methods is also an expression of the inadequacy of existing test systems (for a summary of the methods see Baker and Connor, 1996; Sessink und Bos, 1999). Even the expansion of this spectrum through the addition of molecular biological techniques such as the comet assay or through platinum compound induced DNA adducts can only describe the problem at a moment in time since many types of damage are reversible and can be detected for no more than a few weeks with the existing level of sensitivity. Occupational preventive medicine worthy of the name should therefore involve continuous measurement of individuals, as is performed using dosimetry for persons exposed to radiation in the course of their work. One approach to this would be the method of "personal air monitoring", in which the pharmacist performing preparations wears a small pump for collecting air with the same composition as the air breathed in (immission measurement). This technique involves sucking the ambient air continuously through a filter in order to separate the cytostatics it contains. Approaches of this kind are made more difficult by the fact that cytostatics not only spread through the air in the form of aerosols (as previously believed), but can also occur in the form of gaseous molecular dispersions (Kiffmeyer et al, 2002).

Conclusions

The selection of instruments currently available for occupational medical check-ups can be usefully complemented by the methods of biomonitoring.

The possibility of accidental contamination can never be completely excluded even if all the safety rules are observed. Long-term studies have confirmed the effectiveness and the high standard of the existing safety measures as an essential contribution to occupational preventive medicine.

References

Baker ES and Connor TH. Monitoring occupational exposure to cancer chemotherapy drugs. Am J Health-Sys Pharm 53: 2713-2723 (1996).

Connor TH, Anderson RW, Sessink PJM, et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. Am J Health-Sys Pharm 56: 1427-1432 (1999).

Hessel H, Radon K, Pethran A, et al. The genotoxic risk of hospital, pharmacy, and medical personnel occupationally exposed to cytostatic drugs - evaluation by the micronucleus assay. Mut Res 497: 101-109 (2001).

Kiffmeyer TK, Kube C, Opiolka S, et al. Vapour pressures, evaporation behaviour, and airborne concentrations of hazardous drugs: implications for occupational safety. Pharm J 268: 331-337 (2002).

Mader RM, Rizovski B, Steger GG, et al. Exposure of oncologic nurses to methotrexate in the treatment of osteosarcoma. Arch Environ Health 51: 310-314 (1996).

Pilger A, Koehler I, Stettner H et al.: Long-term monitroing of sister chromatid exchanges and micronucleus frequencies in pharmacy personnel exposed to cytostatic drugs. Int Arch Occup Environ Health 73: 442-448 (2000).

Selevan SG, Lindbohm ML, Hornug RW, et al. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. N Engl J Med 313: 1173-1178 (1985).

Sessink PJM and Bos RP. Drugs hazardous to health care workers. Drug Safety 4: 347-359 (1999).

Shortridge L, LeMasters G, Valanis B et al. Menstrual cycles in nurses handling antineoplastic drugs. Cancer Nurs 18: 439-444 (1995).

Valanis B, Vollmer W, und Glass A. Acute symptoms associated with antineoplastic drug handling among nurses. Cancer Nurs 16: 288-295 (1993).

Valanis B, Vollmer W, Labuhn K, et al. Occupational exposure to antineoplastic agents and self-reported infertility among nurses and pharmacists. JOEM 39: 574-580 (1997).

1.6. Education, Training and Further Training of Staff

Both theoretical knowledge and practical skills are imparted during the education, training and further training of the staff.

Theoretical knowledge:

- **legal principles and directives**
- **correct handling of hazardous substances**
- **dangers and protective measures**
- **accident prevention and action in the case of accident**
- **emergency management**
- **disposal of contaminated materials**
- **active substances and formulations**
- **stabilities, incompatibilities**
- **working in an aseptic work zone**
- **effects of drugs, pharmacology**
- **clinical pharmacy**
- **pathology**
- **departmental and procedural organisation**
- **quality assurance**
- **personal protective equipment.**

Practical training:

- **acceptance of goods**

- **aseptic procedures and inspecting these in connection with simulation of the working steps during the preparation of a formulation**
- **handling single-use articles**
- **simulation of and action in the case of accidents**
- **monitoring the rules**
- **dealing with the documentation system**
- **packaging, delivery, disposal**
- **handling the decontamination set.**

Ruth Hangen, Alheim

The aseptic preparation of ready-to-administer cytostatic solutions must be carried out exclusively by trained and instructed personnel (see 1.1. Persons Handling Cytostatics, 1.3. Hazard Evaluation, Working Rules and Instruction).

The guide to quality assurance - Aseptic preparation and inspection of ready-to-administer agents for parenteral use with toxic potential issued by the *Bundesapothekerkammer* (federal association of pharmacists) (*BAK-Leitlinie*) lists possible topics for training courses and instruction which are connected directly with the preparation (1).

The knowledge to be acquired in order to qualify for the Cytostatics Preparation certificate of the Thüringen *Landesapothekenkammer* (association of pharmacists of the *Bundesland*) (2) partly extends beyond the proposed content in the *BAK-Leitlinie.*

On the international level, the ISOPP (International Society of Oncology Pharmacy Practitioners) has produced standards which can be used as essential quality criteria for generating national standards (3).

The updated bulletin M 620 (now: *BGW Themen. Zytostatika im Gesundheitsdienst*) defines the aspects of preparation which are safety-related and considered as relevant by the professional society and hence must be communicated (4).

In addition to theoretical knowledge connected directly with the work performed, information should also be imparted about the pharmacology, effects, side-effects, interactions and aspects of the clinical pharmacy of the drugs used in order to enable the employees to understand what they are doing and to place it within the overall concept of the cytostatic treatment of patients.

References

1. *BAK Leitlinie zur Qualitätssicherung, Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential* of 28 November 2000 (is currently (beginning of 2003) being revised).

2. *Richtlinie des Thüringer Ministeriums für Soziales, Familie und Gesundheit* (guidelines of the Thüringen ministry for social services, family and health) of 9 April 2002, Measures for the protection of health during the preparation of ready-to-administer cytostatic solutions in pharmacies, *Thüringer Staatsanzeiger* No. 18 of 6 May 2002.

1.6.1. Training New Employees

Training new employees in the cytostatics preparation sector must be performed very carefully since the workplace involved is potentially very hazardous for person and product.

The content of the training and the time allocated to it must be properly planned (see above) and should take place according to a programme.

Ruth Hangen, Alheim

The specialised knowledge demanded by the AOLG (association of the highest regional health authorities) guidelines Preparation of ready-to-administer cytostatic solutions in pharmacies should be acquired in the course of training events and a safety training course (3). However, this can never be a substitute for systematic training.

The Th ringen guidelines on the preparation of cytostatic solutions (2) require that the personnel performing the preparation must possess the Cytostatics Preparation certificate. The award of this certificate requires proof of theoretical knowledge and practical skills. The theoretical knowledge is acquired at two training events, attendance of which is a requirement for participation in the practical part. The subsequent practical training comprises at least three days of working under the guidance of one of the pharmacists authorised by the association. The certificate finally awarded has restricted validity.

Special attention must be paid to the training of employees in the cytostatics preparation sector. The learning by doing method, which has been used all too often n the past, is not appropriate for a workplace with such potential hazards for person and product.

It is essential to plan the time and content of training in order not to ask too much of the persons being trained and also to give them the opportunity to

acquire in a logical context the necessary preparative skills and the theoretical knowledge needed for understanding.

Different aspects should be emphasised for the different professions. However, it is important to ensure that in an emergency all the pharmaceutical staff in a department must be able to perform every kind of preparation (substance, formulation).

The employee being trained must be allocated a competent contact partner - a sponsor - for all the questions that arise during the training period. The sponsor should be a member of the same profession as the new employee and must feel responsible for him/her during the training phase. In this way new employees have a means of discussing their anxieties, worries and problems outside any hierarchy and of asking their colleagues about their work.

It is advisable to prepare a programme for the training period.

This training programme should set out the content in modules, which are then imparted to the employee in stages. This makes it possible for familiarity with the complex work area of cytostatics preparation to be acquired in a logical and systematic way.

In addition to planning the content and the time allocated, the programme should also be methodical: how can the syllabus material be conveyed?

The following method can be used, for example, for imparting the necessary knowledge:

1. adequate preparation

2. demonstrate and explain, show and elucidate (what? how? why like this?)

3. imitate and have explained, correct

4. allow to work alone, correct results (methods of working)

A programme in which all the theoretical knowledge is taught first and practical skills afterwards may ask too much of the personnel. A more suitable approach would appear to be combining the theoretical and practical components into

logical units in order to associate practical experience with the corresponding theory and therefore improve recall considerably. As far as possible, individual modules should not follow too closely upon each other in order to enable the material learned to be consolidated and to allow time for analysis. Discussions during the course of individual modules represent one possibility for analysis.

All the measures performed must be documented and confirmed by the employee (1).

Knowledge and skills can be imparted using a diversity of methods:

Theoretical knowledge:

- during discussions with the sponsor or with colleagues
- by private study of suitable materials: scripts, computer programs[1]
- e-learning as a trend for the future
- by attending lectures/workshops/seminars/beginners' courses[2].

Knowledge of preparation in practice (including aseptic procedures):

- written standard operating procedures
- watching videos
- demonstrations by colleagues.

Practical skills:

The work described or demonstrated is performed using dummy material that should be as realistic as possible; the performance is evaluated (e.g.) using the above methods.

At the beginning of the practical phase it is necessary to decide on the minimum number of sample preparations to be performed of the individual formulations.

1. e.g. MARK: Management and awareness of the risk of cytotoxics, ISOPP
2. e.g. Crash-Kurs Zytostatica (cytostatics crash course), DGOP

The number of dummy preparations or the duration of training needed can vary from one person to the next, however, so that more training may prove to be necessary in the individual case.

Practical skills can be learned either in-house or also externally at courses or seminars, or in a pharmacy with an already established cytostatics preparation facility.

Possibilities for examining what has been learned:

Theoretical knowledge:

- multiple choice questions
- completion texts
- quiz
- computer program, e-learning program
- presentation of the material learned as part of the in-house training.

Practical skills:

- recording all preparation steps on video followed by evaluation and joint discussion; a checklist should be prepared beforehand for checking especially critical points, e.g. in connection with aseptic procedures (4, 5, 6, 7)
- observation of all preparation steps and their documentation by a different person using a checklist, followed by a discussion
- microbiological inspection of test solutions prepared and the working environment (e.g. work surface, gloves, containers, safety workbench)
- checking correct hand disinfection by means of fluorescent hand disinfecting agent
- checking for drip-free preparation by means of fluorescent solutions or solutions containing dye during the preparation.

Systematic training, examination of the skills learned and the final documentation facilitate the validation of the work process (see Chapter 3.4.1. Validation of Aseptic Procedures). The individual person cannot be validated, but simply the work process [in contrast to (8)]. Nonetheless, the qualification of the employees determines the quality of the work process, which in turn influences the scope of the validation procedures.

Examination of what has been learned should take place after completion of every individual training module and at the end of the entire training phase; it must be documented and confirmed by the employee.

The knowledge acquired for award of the Cytostatics Preparation certificate (2) of the Thüringen pharmacists association is basic training which, for example, can be completed before a cytostatics department is set up for the first time.

If employees of pharmacy with an established cytostatics preparation facility are trained externally, the particular in-house aspects must be imparted subsequently.

Retraining of employees, e.g. after rotation or a longer absence for other reasons, must also be properly planned in respect of time allocated and content. Practical exercises involving different formulations restore adequate confidence in the employees performing preparations. Innovations must be demonstrated. Revision and imparting new theoretical knowledge can take place during the annual instruction (see Chapter 1.3. Working Rules and Instruction) or by means of in-house or external training events.

References

1. *BAK Leitlinie zur Qualitätssicherung, Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential* (federal pharmacists association guide to quality assurance, aseptic preparation and inspection of ready-to-administer agents for parenteral use with toxic potential) of 28 November 2000 (currently (beginning of 2003) being revised).

2. *Richtlinie des Thüringer Ministeriums für Soziales, Familie und Gesundheit* (guidelines of the Thüringen ministry for social services, family and health) of 9 April 2002, Measures for the protection of health during the preparation of ready-to-administer cytostatic solutions in pharmacies, Thüringer Staatsanzeiger No. 18 of 6 May 2002.

3. Cytostatics Directive of the *AOLG*, „Production of ready-to-administer cytostatics solutions in pharmacies , *DAC 1999 / NRF 16. suppl. 199* or Federal Health Paper 9/1998 or Dtsch. Apoth. Ztg. 1998; 138: 4176-82

4. Krämer I. *Qualitätssicherung bei der Herstellung und Applikation von Zytostatikazubereitungen* (Quality assurance in the preparation and administration of cytostatic preparations). PZ Prisma 1998; 5: 35-41

5. Allwood M, Stanley A, Wright P (ed.). The Cytotoxics Handbook. 3rd ed. Radcliffe Medical Press, Oxford 1997

6. Harrison BR, Godefroid RJ, Kavanaugh EA. Quality-assurance testing of staff pharmacists handling cytotoxic agents. Am J Health-Syst Pharm 1996; 53: 402-7

7. Marshall JM, Adams JP, Janich JA. Practical, ongoing competency-assessment program for hospital pharmacists and technicians. Am J Health-Syst Pharm 1997; 54: 1412-7

8. Diederich R. *Selbstinspektion von zytostatikaherstellenden Apotheken. Fragebogen zur Zytostatikaherstellung.* (Self-inspection of pharmacies preparing cytostatics. Questionnaire on cytostatics preparation) PZ Prisma 2001; 8:197-210

1.6.2. Training and Further Training of Staff

Training and further training is intended to ensure that the knowledge possessed by the employees is kept constantly up to date with the latest scientific and technological developments.

In addition to the annual instruction required by the Gefahrstoffverordnung (hazardous substances regulations), persons engaged in preparation must be given sufficient opportunity to take part in both in-house and external training events.

Documentary proof of such participation must be provided.

Where offered, opportunities should also be grasped to take part in specialist further training in the field of oncology.

Ruth Hangen, Alheim

In times of rapid medical and scientific progress it is absolutely essential that employees engaged in the preparation of cytostatics take part in continual training and further training.

The hazardous substances regulations and TRGS 525 (9) require that instruction be given before starting work and subsequently at annual intervals (see Chapter 1.3. Risk Evaluation, Working Rules and Instruction). The content and scope of this instruction are oriented on the potential dangers associated with the substances used and with handling them. Practical exercises should also be carried out.

The BAK guidelines (1) specify that employees must receive training at regular intervals of no less than one year by means of internal training courses and external training if necessary.

Internal training can be organised as practice days or the presentation of innovations in the form of talks and demonstrations by the employees themselves.

In addition to the events already mentioned, external training also includes visiting other pharmacies in order to learn about their methods of working. Employees can also train themselves by means of studying the literature or using computer programs. Particular importance should be attached to practical work and the exchange of experience with colleagues; this is the only way that automatisms and blindness to the shortcomings of one's own company - which always creep in where routine work is performed - can be recognised and countered. Although this is relevant for pharmacists, it applies much more for pharmaceutical technicians who are generally the persons carrying out the preparations.

Training events focusing on innovations in cytostatics therapy are available at the national level, organised and/or supported by the pharmacists associations, professional bodies or by the pharmaceutical industry.

For pharmacists, the federal pharmacists association in collaboration with the pharmacists associations of all the Länder except Hamburg offers a certified training course in oncological pharmacy, which deals with the entire topic in depth (10, 11). The Hamburg pharmacists association offers further training as pharmacist for oncological pharmacy with similar content but which includes a far wider scope of practical exercises and lasts a minimum of 24 months; completion of this course entitles the participant to the corresponding additional title (12, 13). The DGOP (German association for oncological pharmacy) offers the Onkologischen Pharmazeuten DGOP with identical curriculum to the Hamburg pharmacists association for members of other sections of the association.

The title can also be used as an independent qualification.

The IFAHS is commissioned by the DGOP to offer a training course in cytostatics preparation (14). The possibility for pharmaceutical technicians also to acquire training points is currently under discussion and has already been implemented by the Th ringen pharmacists association. Events recognised as belonging to continual training are inspected and evaluated.

All training measures must be documented and the employees must confirm their participation (1).

There are currently no regulations as to how often training events on the topic of cytostatics should be attended. Defining this is made more difficult by the considerable differences in the quality of the individual events.

Opportunities offered for training and further training should be taken advantage of since this is the only way in which the qualification of the employees can be maintained at a consistently high standard. Moreover, the pharmacy regulations (15) require that cytostatic solutions be prepared in accordance with recognised pharmaceutical practice and the start of the art. This automatically generates a duty to undergo continual training and further training.

References

1. *BAK Leitlinie zur Qualitätssicherung, Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential* (federal pharmacists association guide to quality assurance; aseptic preparation and inspection of ready-to-administer agents for parenteral use with toxic potential) of 28 November 2000 (currently (beginning of 2003) being revised).

2. *Richtlinie des Thüringer Ministeriums für Soziales, Familie und Gesundheit* (guidelines of the Thüringen ministry for social services, family and health) of 9 April 2002, Measures for the protection of health during the preparation of ready-to-administer cytostatic solutions in pharmacies, Thüringer Staatsanzeiger No. 18 of 6 May 2002.

3. *Zytostatika- Richtlinie der AOLG, Herstellung applikationsfertiger Zytostatikalösungen in Apotheken*, (cytostatics directive of the *AOLG*), „Production of ready-to-administer cytostatics solutions in pharmacies, Federal Health Paper 9/1998, DAC 1999 / NRF 16. suppl. 1999 or Federal Health Paper 9/1998 or Dtsch. Apoth. Ztg. 1998;138: 4176-82

4. Krämer I. *Qualitätssicherung bei der Herstellung und Applikation von Zytostatikazubereitungen* (Quality assurance in the preparation and administration of cytostatic preparations). PZ Prisma 1998; 5: 35-41

5. Allwood M, Stanley A, Wright P (ed.). The Cytotoxics Handbook. 3rd ed.. Radcliffe Medical Press, Oxford 1997

6. Harrison BR, Godefroid RJ, Kavanaugh EA. Quality-assurance testing of staff pharmacists handling cytotoxic agents. Am J Health-Syst Pharm 1996; 53: 402-7

7. Marshall JM, Adams JP, Janich JA. Practical, ongoing competency-assessment program for hospital pharmacists and technicians. Am J Health-Syst Pharm 1997; 54: 1412-7

8. Diederich R. *Selbstinspektion von zytostatikaherstellenden Apotheken. Fragebogen zur Zytostatikaherstellung*. (Self-inspection of pharmacies preparing cytostatics. Questionnaire on cytostatics preparation) PZ Prisma 2001; 8:197-210

9. "Hazardous Substances Committee": New Technical Regulations for Hazardous Substances (*TRGS*). „Handling hazardous substances in facilities for human medical care", Dtsch. Apoth. Ztg. 1998;138: 2654-61

10. "Oncological Pharmacy Certificate", recommendations passed by the general meeting of the federal pharmacists association on 4 May 2000. www.abda.de

11. Staiger C. *Zertifizierte Fortbildung Onkologische Pharmazie*. (Certified training in oncological pharmacy). Pharm Ztg. 2000, 145: 3897-8

12. Further training directive of the Hamburg pharmacists association, 2nd amendment of 16 November 1999

13. IFAHS/ DGOP: *Inhaltskatalog Weiterbildung Onkologische Pharmazie* (oncological pharmacy further training content catalogue), c/o Conevent: Zum F rstenmoor 11, 21079 Hamburg. www.ifahs.org.

14. IFAHS: Pharmaceutical technician training, cytostatics preparation. www.ifahs.org.

15. Pharmacy regulations (*Apothekenbetriebsordnung-ApBetrO*) in the revision issued on 26 September 1995 (*BGBl*. I p. 1195), amended by s. 6 of the law dated 30 July 1996 (*BGBl*. I p. 1186).

Further Reading

Kratz HJ. "Successful integration of new employees". New Business Line: 50-Minuten-Script, 72., pub. Wirtschaftsverlag Ueberreuter Vienna 1997

American Society of Health-System Pharmacists. White paper on pharmacy technicians. Am J Health-Syst Pharm 1996; 53: 1991-4

American Society of Hospital Pharmacists. ASHP accreditation standard for pharmacy technician training programs. Am J Hosp Pharm 1993;50: 124-6

American Society of Hospital Pharmacists. ASHP technical assistance bulletin on outcome competencies and training guidelines for institutional pharmacy training programs. Am J Hosp Pharm 1982; 39: 317-20

American Society of Hospital Pharmacists. ASHP technical assistance bulletin on quality assurance for pharmacy-prepared sterile products. Am J Hosp Pharm 1993; 50: 2386-98

American Society of Hospital Pharmacists. ASHP technical assistance bulletin on the recruitment, selection and retention of pharmacy personnel. Am J Hosp Pharm 1994; 51: 1811-5

ASHP supplemental standard and learning objectives for residency training in oncology pharmacy practice. In: Practice Standards of ASHP 1994-95. Hick WE, ed. Bethesda, MD: American Society of Hospital Pharmacists; 1994.

Batty KT. Training, testing and continuous monitoring program for cytotoxic admixture dispensing. Aust J Hosp Pharm 1990: 274-9

Beaumont I, Nicolsson M. Cytotoxic reconstitution services: Development of service standards and an audit system. Hospital Pharmacist 1995; 2: 97-9

Krämer I, Maas B, Huber C. *Pharmazeutische Betreuung onkologischer Patienten – Therapiemonitoring in der zentralen Zytostatikazubereitung*. (Pharmaceutical care of oncology patienes - therapy monitoring in centralised cytostatics preparation), Krankenhauspharmazie 1997; 18: 56-63

Peters BG et al. Certification program in antineoplastic drug preparation for pharmacy technicians and pharmacists. Am J Hosp Pharm 1994; 51: 1902-6

Wachsmuth J. *Organisatorische Maßnahmen zur Qualitätssicherung im Zentralen Zytostatika-Service*. (Organisational measures for quality assurance in the centralised cytostatics service), PZ Prisma 1996; 3: 153-62

2. Central Cytostatics Department

The centralized preparation of CMR (carcinogenic, mutagenic and reprotoxic) drugs must take priority over distributed preparation. (TRGS 525, 5.3.1.(1))

2.1. Rooms and Equipment

Preparation takes place in a separate, clearly marked clean-room working area which is separated from the rest of the area by means of one or several locks. The general requirements for working areas must be complied with.

The area used must not be in spatial unity with the rest of the pharmacy.

The equipment of the department comprises, in addition to the technical equipment, the facilities and furniture relating to preparation, preparation and documentation.

The entire equipment of the preparation area must be documented in an installation layout plan and is to restricted to the necessary minimum.

Markus Dzierza, Brunswick

Working area

A cytostatics department ideally consists of the preparation area which must be separated from everything else, a make-ready area and, if required, a documentation area and a storage area, where the two latter may be combined if no other solution is spatially possible.

In addition to a preparation area, the Laender Cytostatics Directive (Guideline) specifies an area for keeping street-wear and working clothes, which should act as a lock. However, at least one further room is required, wherein the making-ready and documentation units can be lodged. If there is sufficient space, it is recommended to establish a making-ready area connected to the preparation area by means of a lock and a separate documentation area. This guarantees that persons working in the documentation area will never come into contact with CMR substances.

The working area should be used solely for the preparation of ready-to-administer cytostatics (EC GMP Directive). Exceptionally, the working area may be used for the preparation of other pharmaceutical products. Here it should be pointed out that other indications such as virustatics may have the same CMR properties as cytostatics. In some cases, this has been explicitly described in the technical information. In this case, organisational measures are required to ensure strict chronological separation of the individual preparation processes including making-ready activities and quality assurance.

In addition, working and storage areas are required to be of adequate dimensions (EC GMP Directive). Strict separation of making-ready processes from preparation and providing sufficiently large areas establishes conditions for avoiding errors. These measures serve to prevent the danger of contamination for different groups of persons (manufacturers, concentrators, transporters and clinical users) and to avoid cross-contamination, thereby protecting the product.

For the cytostatics preparation area exceptions from the spatial unity of the pharmacy rooms required by the Ordinance on the Operation of Pharmacies (Apothekenbetriebsordnung, ApBetrO) are permissible. However, the rooms must be on the same or on immediately adjacent premises.

Communication within the working area

Using an interphone, telephone or combined system, communication among the persons inside and outside the preparation area as well as with the medical staff in the practice or on the stations must be possible any time. The need for an interphone is emphasised by the requirement that during the preparation

process the doors to the preparation area must not be opened Directive; BuBaV (procedure recognised officially and by the professional association).

For safety reasons (e. g. workplace accident, interphone failure) there must always be intervisibility between all sections of the working area. Intervisibility may be implemented by installing wide window fronts or, more simply, window panes in the lock / room doors. Architectural measures such as separation of the changing room may be used to maintain the privacy of the staff, or the lock windows may be made of slightly frosted glass or another semi-opaque material.

Preparation area

According to the directive, the preparation area is a separate room which must be clearly marked by suitable warning and danger signs. The general requirements for working rooms, such as ventilation in accordance with the Workplace Ordinance (Arbeitsstaettenverodnung, ArbStättVO) must be complied with (see also chapter 2.2: Room ventilation equipment).

Access of daylight must be guaranteed (Occupational Health and Safety Act); however, existing windows must be blocked from opening or sealed, if they serve as escape routes. To be able to process extremely photosensitive substances, partial or complete dimming and thereby avoidance of direct sunlight should be possible. The doors to the preparation area must not be opened during the preparation process. Persons and material may enter the preparation area only via separate locks.

There are no legal regulations pertaining to the clean-room class, but a number of guidelines provide suggestions.

Ideally, a GMP-compliant area should be implemented.

For aseptic preparations, the EC Guide to Good Manufacturing Practice, Annex 1 stipulates that these are to be prepared under conditions of clean-room class A (corresponding, e. g., to a safety laminar flow hood = critical area) in an area of clean-room class B (= controlled area), unless the preparations are sterilized by filtration. No final decision has been made yet as to whether these conditions, which are applicable to large-scale commercial production,

do completely apply to aseptic preparation of administration-ready parenterals in pharmacies as well.

In some countries, national GMP guidelines for aseptic preparation of administration-ready parenterals in pharmacies are already in force, e. g. in the USA, in the Netherlands and in the United Kingdom, some of which interpret the risk definitions more liberally than the EC GMP guidelines do.

In the currently valid USP XXXI (chapter 797), valid since 06/2008, the following criteria are defined for aseptic preparations for parenteral use in ambulant medicine for a «low risk» preparation: preparation is performed in a class 100 laminar flow hood, which must be installed in a class 100,000 room for «low risk» preparations.

In the EU GMP guidelines, class 100 (USP) is assigned to classes A and B, class 10,000 (USP) to class C and class 100,000 (USP) to class D (table 1). Classes A and B (GMP) differ with regard to the maximally permissible number of viable micro-organisms (table 2). It will be noted that in USP XXXI the requirements for the clean-room classes for the preparation of aseptic preparations for parenteral use are defined more liberally: Installation of a suitable safety hood (class A) in a class D room is enough to fulfil the requirements for aseptic preparation. The crucial point is that the room used is of higher purity than the other rooms of the pharmacy are (see comment on cytostatics guidelines).

The BAK (Federal Association of Pharmacists) guidelines on aseptic preparation and control of ready-to-administer parenterals with toxic potential dated November 2008 likewise emulates USP XXXI by permitting installation of a safety hood in a class D room for preparation in a closed system. If preparation exceeds «low risk» conditions (e. g. when using previously opened packages or preparing in advance), clean-room class C is mandatory for the area surrounding the hood.

Even though at first glance USP requirements appear much more rigid, GMP requirements are actually more strict since the relation of 1 m^3 to 0.027 m^3 corresponds to approximately 37 : 1.

Thus, according to USP in a non-operational class B clean-room 3,700 particles are permissible.

GMP no. of particles / m³			**USP XXXI** no. of particles / cubic foot*		
class	› 0.5 µm	› 5 µm	class	› 0.5 µm	› 5 µm
			1	1	0
			10	10	0
A (LAF) not operational	3,500	0	100 (LAF)	100	0
- operational	3,500	0			
B (LAF) not operational	3,500	0	1,000	1,000	7
- operational	350,000	2,000			
C (LAF) not operational	350,000	2,000	10,000	10,000	70
- operational	3,500,000	20,000			
D (LAF) not operational	3,500,000	20,000	100,000	100,000	700
- operational	n.a.	n.a.			
*: 1 am. foot ~ 0.3 m; 1 cubic foot ~ 0.027 m³					

Table 1: Clean-room classes

Class	GMP	USP XXXIII
A	‹ 1	‹ 1
B	(5*)10	18
C	100	88
D	200 (500*)	n.a.

(*): EC GMP guidelines supplement 1 as of Sept. 1996

Table 2: Maximally allowable number of viable microorganisms per m³

The size of the room must be such as to guarantee unimpaired functioning of the safety hood. Thus, planning should be based upon appropriate ventilation technology calculations (see chapter 2.2: Ventilation equipment). Prior to commissioning and after any modifications to the room (such as alteration of the number or layout of the furniture) unambiguous proof of function must be provided. Modifications must be registered in the room or furniture layout plan.

There are the following minimum requirements to size and height of the room and free moving space (Guidelines, BuBaV, ArbStättVO):

- floor area size of room: at least 10 m²
- height of room: at least 2.50 m
- area of free movement at the workplace must not be less than 1.5 m² and no more narrow than 1 m at any point
- minimal distances: within 1.2 m and 0.3 m on the sides of the hood there must not be any furniture, devices or wall

Extensive information relating to minimal distances is given in British Standard BS 5726 Part 2, 1991.

Distance	
• before the hood (= disturbance-free zone):	1.0 m
• from lateral walls and pillars:	0.3 m
• from lateral working areas:	1.0 m
• from a lateral door:	1.0 m
• from a working area opposite:	1.5 m
• from a wall opposite:	2.0 m
• from a hood opposite:	3.0 m
• from a door opposite:	1.5 m
A disturbance-free zone of 1.0 m should also be observed on the sides of the hood.	

If the actual values fall short of those listed, in particular when due to lock of space two hoods are located adjacent to each other or to the wall, a KJ disk test should be performed to verify functioning of the safety hood. As there are currently several vendors on the market offering different hoods, the values may differ in detail, e. g. in the operating instructions. Nevertheless, the user should perform the KJ disk test on his own behalf, even if the competent authorities do not demand this, since this serves to exclude safety risks (NZW 2008 Hamburg).

Furniture should be arranged so that minimal distances to the hood are observed. Moving routes within the room should be defined so that no impairment of the protective function of the hood for people and products may result from the persons in the room moving about. The number of the persons present is thus to be limited to a minimum.

Regarding the structure of walls, ceiling and floor of the preparation area it is mandatory that they are easy to clean and to disinfect. In a GMP-compliant area, this excludes the use of tiles since due to the resulting inhomogeneous surfaces these do not permit simple cleaning (see chapter 3.3.1: Validation): For preparation areas established later, it is recommended to cover the walls with a an abrasion-proof cover of a latex paint according to DIN 53778 SG or SM, whose surface fulfils the requirements.

In addition to the safety hood, the furniture of the preparation area comprises the following:

- two-way interphone
- closed storage facilities for limited amounts of drugs, single-use articles and devices
- ergonomic, easy-to-clean seating furniture. It is recommended to take care that these, too, are easily disinfected and will not release any particles (e. g. upholstering, wide-pored plastic covering with foam plastic layer beneath)
- waste bins
- sufficiently large working and depositing area with bag sealer (plastic film welding machine). With regard to the sealers, sealing plates are recommended

to have the material at the same height as the sealer. The surfaces should not have any chinks; stainless steel is best-suited.

- facilities for immediate documentation of the preparation process.
- decontamination kit for cytostatics accidents (see chapter 4.2: Decontamination after accidental release)

An installation layout plan must be prepared and updated upon modification.

Lock

Following the Ordinance on Hazardous Substances, the directive require only establishment of an area for separate storage of street-wear and working clothes; the Explanation of Guideline 3.1 however details the function of this area: Ideally it should act as a lock. The requirement for a lock is also in accordance with the EC Guide to GMP, Annex 1.

Separate locks for persons and material before the preparation area are recommended. In the material lock, all materials entering the are can be disinfected (e. g. under a fume hood installed there) and kept ready for transfer to the preparation area. Visual contact with the preparation area should be possible through both locks. As the two locks are separate from each other, it is possible to use one lock only if required, without affecting the other one. This increase in safety has benefits e. g. in the case of an inadvertent release of cytostatics in the material lock; the uncontaminated staff lock may still be used.

In case of shortage of space, the lock may also be implemented as a combined material and staff lock before the preparation area.

Via window panes integrated into the doors, visual contact in both directions would be guaranteed. For the introduction of working materials, the window pane facing the preparation area would have to be opened using a slider mechanism. In the window pane area, for safety purposes there should be a sideboard which, however, presents the danger of unintended incidents, e. g. if materials to be introduced are still on the sideboard while a person is entering the preparation area.

If no sideboard is installed at all, there is the danger of materials falling to the floor while being passed through. Another possibility is to use dishes for introduction, thereby preventing shifting and dropping. However, the dishes should not be overloaded.

Contrary to earlier statements, washing basins and sinks should not be present in the controlled area (BAK guidelines, see above).

In the lock, prior to entering the preparation area preparation and protective clothing as well as shoes which are restricted to the area and preferably sterilizable / disinfectable are to be put on. The staff lock should be divided into a pure and an impure side. This should be done at least by a line on the floor (optical separation), but preferably by a «sit-over» (bench crossing the entire lock, which can be surmounted only by swinging over the legs while sitting). Care must be paid to deposing shoes into special shelves on the impure side and taking pure ones from storage shelves on the pure side.

During the preparation process, the lock to the preparation area must not be opened. Furthermore, it is mandatory that never both doors of the lock are opened at the same time. When using an electronic device dictating a pre-defined passage time, make sure that an emergency switch (panic button) allows

to leave the preparation area and thus the building in case of an emergency (e. g. fire), unless the windows are designed as emergency exits.

Make ready area

In the make ready area, the pharmaceutical products and materials required for preparation are duly stored and transferred to the preparation area through a lock.

Here solutions ready for dispensation are packaged into unbreakable, liquid-tight and sealable containers.

The containers should be labelled with an indicator for cytostatics, and if to be transported over public routes, with the address and telephone number of the pharmacy as well to allow for inquiries in case of danger. Furthermore, there should be a label reading «To be opened by instructed staff only» in order to

prevent, e. g., helpers in case of an accident from opening the transport packages and contaminating themselves or others.

Oral and visual contact with the preparation area must be guaranteed. The refrigerator for the storage of finished pharmaceutical products and partially emptied bottles is installed in the preparation area (if ventilation allows, such as individual aspiration or housing, it may also be installed in the clean-room).

Documentation area

The equipment of the documentation area comprises desk, phone, fax if required, interphone, computer, printer and shelf or drawer system to store literature and documents.

Documentation systems (cf. chapter 3.6.2: Documentation)

Computer-assisted preparation of administration-ready cytostatics is highly recommended, since comprehensive logging of the preparation process exceeding the documentation of individual formulations according to the ApBetrO is explicitly required (Guidelines 6.1, 6.2).

Currently, two differently functioning computer systems are being offered:
- mass-oriented computer-assisted working
- volume-oriented computer-assisted working

Authorized staff (see Chapter 1: Staff)

Access to the working area of central cytostatics preparation is permitted only for authorized staff whose number is to be limited to the necessary minimum. The following persons are to be considered authorized:

1. Pharmaceutical staff trained or in training to handle cytostatics (group 1: pharmacists (m/f), pharmaceutical-technical assistants (m/f), pharmacy interns, etc.)
2. Cleaning and maintenance staff (group 2)
3. Staff responsible for supply and transport (group 3)

Persons of groups 1 and 2 have access to the entire working area, whereas persons of group 3 may only enter the preparation area.

References:

I. Gesetzliche Regelungen und Verordnungen:

TRGS 525 Umgang mit Gefahrstoffen in Einrichtungen zur humanmedizinischen Versorgung. Bundesarbeitsblatt 5/1998. Dtsch Apoth Ztg 1998; 138: 2654-61

Richtlinie: Zytostatika Richtlinie der AOLG, Herstellung applikationsfertiger Zytostatikalösungen in Apotheken. Bundesgesundheitsblatt 9/1998. Dtsch Apoth Ztg 1998; 138: 4176-82

Erläuterungen der Richtlinie: Erläuterungen zur Zytostatika Richtlinie der AOLG, Herstellung applikationsfertiger Zytostatikalösungen in Apotheken. Bundesgesundheitsblatt 9/1998. Dtsch Apoth Ztg 1998; 138: 4176-82

Kommentar zur Zytostatika-Richtlinie: Diedrich R, Zytostatika-Richtlinie der Länder, Erläuterungen und Kommentar. Dtsch Apoth. Ztg. 1998; 138:61-8

Leitlinie der Bundesapothekerkammer und Kommentar zur Leitlinie Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential, Stand 25.11.2008

BuBaV: Behördlich und berufsgenossenschaftlich anerkanntes Verfahren: Anforderungen an den Betrieb von Sicherheitswerkbänken mit Luftrückführung für Arbeiten mit krebserzeugenden oder erbgutverändernden Zytostatika. Bundesarbeitsblatt 7-8/1998. Dtsch Apoth Ztg 1998; 138: 76-7

ArbStättVO: Arbeitsstätten Verordnung

Arbeitnehmer-Schutzgesetz

Gefahrstoffverordnung

ApBetrO: Apothekenbetriebsordnung

Thüringer Richtlinie: Richtlinie zur Durchsetzung der Maßnahmen zum Gesundheitsschutz beim beruflichen Umgang mit Zytostatika und deren Anwendung bei der Herstellung applikationsfertiger Zytostatikalösungen in Apotheken. ThürStAnz Nr 49/1996: 2202-5

British Standard BS 5726 Part 2, 1991

EG-GMP-Leitfaden Teil 1 [Anlage 2 zur Bekanntmachung des Bundesministeriums für Gesundheit zu § 2 Nr. 3 der Arzneimittel- und Wirkstoffherstellungsverordnung vom 27. Oktober 2006 (Banz. S. 6887)]

EG-GMP Leitfaden Annex 1: Herstellung steriler Arzneistoffe [Anlage zur Bekanntmachung des Bundesministeriums für Gesundheit zu § 2 Nr. 3 der Arzneimittel- und Wirkstoffherstellungsverordnung vom 12. März 2008 (BAnz. S.1217)]

United States Pharmacopeia and National Formulary, USP 31 / NF 26 Chapter ‹797› Pharmaceutical Compounding – Sterile Preparations, Rockville, USA 2008

Pharmaceutical Inspection Co-operation scheme (PIC/S): PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments. PE 010-3, October 2008. http://www.picscheme.org/publications.php?p=guides

Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege, Zytostatika im Gesundheitsdienst, 04/2008 http://www.bgw-online.de/internet/generator/Inhalt/OnlineInhalt/Medientypen/bgw_20themen/M620__Zytostatika__im__Gesundheitsdienst.html (Dezember 2008)

II. Literatur zum Thema:

Braun R (ed). Standardzulassungen für Fertigarzneimittel. Stuttgart: Dt Apoth Verlag 1997, 12. Erg. – Lfg., Kommentar: B 27-36

Krämer I. GMP in der aseptischen Herstellung applikationsfertiger Parenteralia in der Apotheke. Ein Vorschlag für eine spezifische, nationale Richtlinie. Krankenhauspharmazie 1999; 20: 129-37

Ohem N. GMP in der Krankenhausapotheke. Bericht vom 4. Symposium „Sterilherstellung in der Krankenhausapotheke“, Heidelberg, 12. November 1998. Krankenhauspharmazie 1999; 20: 138-44

Seyfarth H, Häusler H. Umgebungskontrollen in Produktionsräumen. Pharm Ind 1996; 58: 1135-46

Seyfarth H. Mikrobiologisches Monitoring zur Überwachung der Hygieneanforderungen des EG-Leitfadens einer Guten Herstellungspraxis für Arzneimittel, Teil 1: Anforderungen. Pharm Ind 1993; 55: 503-8

Steinlen S. Herstellung von Arzneimitteln nach GMP-Richtlinien. Krankenhauspharmazie 1998; 19: 5

Gebrauchsinformation für Fachkreise Cymeven® (Ganciclovir) Dezember 2007

2.2 Ventilation and Air Conditioning Systems

1. A cytostatics laminar air flow hood (LAF) must be used, type tested in accordance with DIN 12980. Cytostatics hoods with an additional HEPA cassette filter stage beneath the work surface are to be preferred.

2. An exhaust air system should be installed as an additional safety measure.

3. If realization of an exhaust air system is not possible for technical reasons, it is mandatory to use an LAF with two HEPA filter stages before the air is returned to the preparation room. If a hood is operated using recirculated air, the air change rate must not exceed 8; all the other requirements of the BuBaV (procedure recognized officially and by the professional association) must be fulfilled.

4. In any case, a ventilation system must be installed that leads adequately conditioned and purified fresh air complying with DIN 1946 into the room for compensating the flow of exhaust air in accordance with TRHS (Technical Rules for Hazardous Substances») 560 and ArbStättV (*Arbeitsstättenverordnung*, Ordinance on Workplace Health and Safety), without impairing the protective function of the cytostatics hood. The velocity of the input air must not exceed 0.2 m/s.

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1. In June 2005, DIN 12980 «Cytostatics Safety Hoods» was published in completely updated form. DIN 12980:2005-06 replaces the previous document DIN 12980:1996-09.

The previous Type V (for making ready for administration) was cancelled, and so were the «other types». DIN 12980 now applies only to safety hoods of the

former Type H (for the preparation of ready-to-administer products) with one or more working apertures below or within the pane. In future, all hoods will have to be tested in accordance with DIN 12980 for their performance relating to product protection and prevention of cross-contamination. Basically, this corresponds to a class II safety hood as defined by DIN-EN 12469:2000 «Performance Criteria for Microbiological Safety Hoods». Although during the most recent DIN committee meetings abolition of the separate norm for cytostatics hoods was intensely discussed, the advantages of an independent norm for cytostatics hoods are obvious. Low-contamination filter replacement of contaminated filters in particular was included as a requirement in DIN 12980. The topic of connection to an exhaust air system as an additional safety measure will now also receive greater attention. In the new edition of DIN 12980:2005-06, Chapter 4 will be called «Designs and Connection to Exhaust Air Systems». The comments in the application sector urgently advise that a cytostatics safety hood is intended to retain airborne particulate contaminants, but is not suitable for removing gaseous substances.

Low-contamination filter replacement is generally realized by means of an additional modular (i.e. consisting of a plurality of elements) HEPA main filter stage beneath the work surface. Each of these filter elements has a relatively small air inlet which is easily sealed before transport. The dirty side is on the inside of the filter elements, with the external surface of the filter elements representing the «clean side». The filter elements are designed to be changed easily and safely. The cassettes fit into the normal cytostatics waste containers so that disposal can take place smoothly (fig. 1). Not all filters may be classified as only slightly contaminated, hence general disposal via the cytostatics bins is required. At the same time, this first HEPA filter stage (assuming its integrity is unimpaired and its installation air-tight) protects the whole of the inside of the hood from particulate contamination. Interventions in the motor room can therefore be made without contamination and this is also possible at the main and exhaust filter stages (fig. 2).

In TRHS 525 («Handling hazardous substances in facilities for human medical care») and in the brochure M620 «Safe handling of cytostatics» by the BGW, the requirement is a safety hood is either tested in accordance with DIN 12980

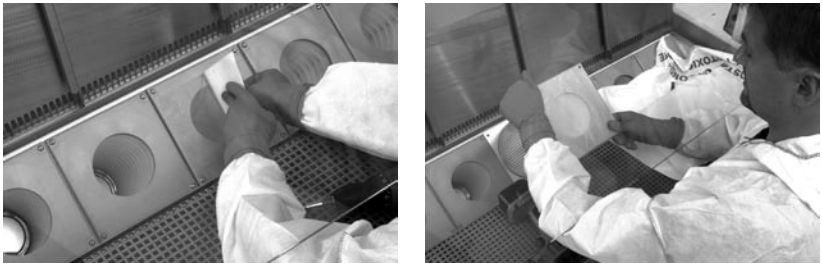


Fig. 1: low-contamination filter replacement of the main filter stage of a cytostatics hood

or provides a level of safety equivalent to that of hoods conforming to DIN 12980. The cytostatics directive of the working group of the highest regional health authority (AOLG), however, stipulates unambiguously that a hood in a new facility must be type tested in accordance with DIN 12980. This official requirement corresponds exactly with the standard which we already proposed at the beginning of 1996 in the first edition of the QuaPOS. It should be possible to continue operating already installed hoods with »equivalent safety technology» with a transition time limit of five years after DIN 12980 comes into force – i.e. until no later than August 2001. The requirement to allow only DIN 12980 type tested hoods to be operated from August 2001 was cancelled by order of the Federal Ministry of Labour on January 15th, 2000.

There is still right of continuance for «possibly still operative microbiological hoods if they are type tested in accordance with DIN 12950 part 10 (replaced by DIN EN 12469 in September 2000), inspected annually and basically guarantee the same degree of safety (onus of proof with the operator)». In case of filter replacement, however, for old 2-filter systems (under no circumstances possible in low-contamination fashion, see fig. 2) the question about safety equivalence will easily be answered in the negative.

With the abolition of the «other designs» according to DIN 12980 a hood with an isolated work area no longer complies with the DIN 12980 standard. No test for product protection or cross-contamination is stipulated for Class III microbiological safety hoods (isolators) conforming to DIN EN 12469. There

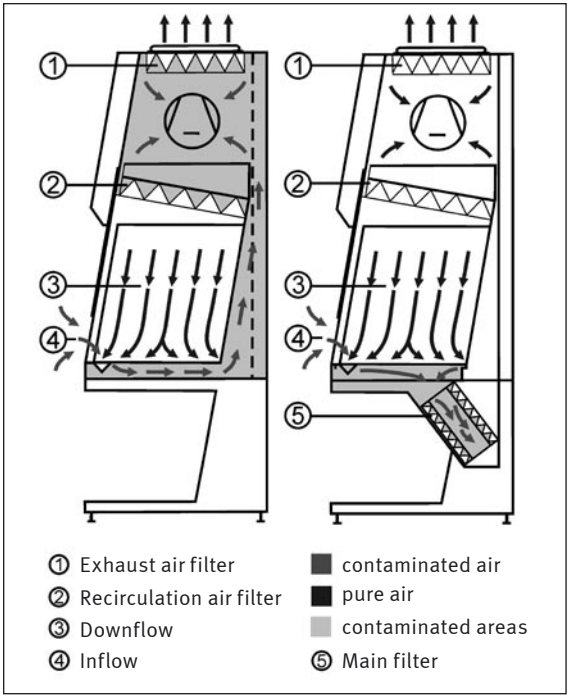


Fig. 2: Comparison between microbiological safety hood (2-filter system) and cytostatics safety hood (3-filter system) with upstream main filter stage immediately beneath the working surface

is no requirement for displacement laminar flow. It is common knowledge that the apparently greater safety provided by an isolator is achieved at the expense of considerable handling difficulties during operation. Apart from the «solved work opening safety problem», all the other safety aspects – such as retention performance at the extracted air filter, exhaust air system and the replacement and disposal of filters – must be evaluated in the same way as for a hood typed tested according to DIN 12980. If the flow- and pressure ratio in the cytostatics laboratory is properly controlled, the safety air stream of a properly operated cytostatics hood will also prevent the release of hazardous substances through its work opening.

Rentention capacity of the hood can be measured in accordance with the DIN norms. However, the handling and the bringing in and out of materials are much simpler for cytostatics hoods (corresponding to class II microbiological

hoods). Under these circumstances hardly any user will still opt for an isolator. Using an isolator (type III microbiological hood without defined requirements for product protection and avoidance of cross-contamination) only because it is not possible to install a class B clean-room as defined in GMP Annex 1 as environment can be described only as the worst «compromise». For safety hoods for processing of CMR drugs it is mandatory that they are, without exception, type tested as cytostatics hoods in accordance with DIN 12980 «Cytostatics hoods» as of June 2005.

For safety reasons, cytostatics hoods with work opening should either run continuously (in standby mode), or the work opening should be closed during longer periods of non-use. In this way it is possible to prevent deposited particles escaping as a result of air movements in the vicinity of the work opening of the hood and contaminating the laboratory.

2. In DIN 12980 it was likewise defined that an exhaust system and an additional upstream HEPA main filter stage are sensible supportive safety measures for safety hoods in which cytotoxic or other highly effective substances are to be processed. The latter applies particularly if, as a result, the first filter stage (cassette filter) can be changed without contamination and disposed of. The requirement for an exhaust air system for the air extracted from the hood is supported by the principle that returning the extracted air is generally not permissible when dealing with carcinogenic hazardous substances. A functioning exhaust air system and an appropriately dimensioned and adapted input air supply, which exerts no negative effects on the safety of the cytostatics hood, must be regarded as the standard. Since it is hardly possible to realize a closed exhaust air system free of reactions and disturbances, the extracted air must be led into the open (e.g. through a chimney stack). In the case of open extraction, the volume of room air drawn in must be approximately 20% greater than the extraction volume of the hood in order to guarantee complete removal of the extracted air. An exhaust air system is also on the safe side in respect of the discussion about gaseous impurities resulting from cytostatics with appropriate vapour pressures, which may pass through the HEPA filter. The installation of active filter stages that also guarantee the separation of gaseous impurities is only necessary and useful if operating in recirculation mode cannot be avoided.

3. An exception to the requirement for an exhaust air system is only possible if this is unreasonable or technically not feasible, and the returned air is purified of carcinogenic substances using methods approved by the professional association or the authorities. However, in the case of air being returned into the preparation room (recirculated air mode) without an exhaust air system, the requirements become more extensive in regard to size and volume for the preparation room. In the case of recirculating air operation of a hood, the AOLG Cytostatics Directive requires that the air change rate (quotient of [extracted air volume of the hood(s) in m^3 per hour]/[net room air volume in m^3]) does not exceed a value of 8.

Thus, for example, a hood with a width of 1.80 m and an extracted air volume of approx. 800 m^3/h may be used in recirculating mode only in a room of at least 100 m^3 net room air volume (6 m × 7 m × 2.5 m = 105 m^3 - 5 m^3 furniture). If the available space is smaller, a correspondingly smaller hood with a lower extracted air volume must be used or an exhaust air system installed.

In respect of liability towards our pharmaceutical staff, at least one additional safety stage must be demanded: either an exhaust air system for air extracted from the hood or an additional HEPA cassette filter stage, which should in any case be present in every cytostatics hood and whose advantages during filter replacement and disposal are obvious. When using a hood with additional HEPA filter stages, it is important during routine measurements that the retention capacity of each filter stage is determined separately – in the case of modular construction also every individual filter cassette. Otherwise, a leak will not become apparent until both filter stages (in front of the exhaust air and in front of the down-flow) become defective. Thus simply purchasing a hood with an additional filter stage is not sufficient; the double safety through the additional filter stage must be regularly verified by means of separate tests.

4. Open ventilation, e.g. through a window, would already be forbidden in a cytostatics laboratory in regard to the GMP requirements; when operating a cytostatics safety hood, this would be classed as negligence. Therefore, a ventilation and air conditioning system must always include an inlet air unit which brings sufficiently conditioned and purified fresh air into the room without impairing the retention capacity of the safety hood. The air velocity

must not exceed 0.2 m/s. If an exhaust air plant is being operated, approximately the same volume of air must be brought into the room as is extracted from it. (Example: 1.80 m hood: 800 m³/h. Air extracted from the hood + 20% = 960 m³/h). Pursuant to the Health and Safety at Work Act (ArbStättV, Arbeitsstä ttenverordnung) the inlet air must contain at least 40 m³ of fresh air (outdoor air) per person and per hour.

At this point the erroneous belief must be corrected that in a laboratory in which a cytostatics hood is being operated in recirculating mode it is only necessary to introduce approximately 40 m³ of fresh air per person per hour, as specified by DIN 1946 and §5 Health and Safety at Work Act. TRHS 560 («Air recirculation when handling carcinogenic hazardous substances») allows an exception from the prohibition of air recirculation in the individual case only if, firstly, the recirculated air is purified of carcinogenic substances and, secondly, the air recirculation constantly meets the requirements in No. 5 of the TRHS 560. This states in §3: «The proportion of recirculating air in the inlet air must not exceed 50 %». This also means, however, that the volume of fresh air brought into the room must be at least as high as the volume of extracted air the safety hood removes from the room. Hoods must therefore not be operated in rooms with lower inlet rates of fresh air. For a hood in recirculation mode with an extracted air volume of 800 m³/h, at least 800 m³/h of inlet air must also be brought into the room, compared to 960 m³/h for exhaust air mode. The outlay for inlet airflow is approximately equal for recirculation and exhaust air operation. *Viewed more closely, therefore, dispensing with an exhaust air system provides no great financial advantage, but simply generates a considerable safety disadvantage*. In the individual case it is essential that the recirculated air mode be approved by the responsible authorities after a hearing by the professional association.

The flow relationships of the ventilation system and the safety hood must be matched to one another and already accounted for in the conception of the room. The inlet air must be purified in accordance with DIN 1946, part 4 «Ventilation and air conditioning systems in hospitals». A prefilter (at least G4 as defined in DIN EN 779: 2003-05) at the outside air inlet, a filter (at least F7 as defined in DIN EN 779: 2003-05) on the pressure side before distribution

into the ventilation network and a HEPA filter (Class H13, separation min. 99.95%) as close to the room as possible should be provided for purifying the inlet air of a cytostatics laboratory.

In accordance with DIN 1946 part 4 and the GMP recommendations, the flow and pressure parameters should likewise be designed for a sterile lab. For hygienic reasons, air should flow from the sterile area to the lower clean-room class areas to keep out germs and particles. In practice this means overpressure in the sterile area which is achieved by the volume of inlet air exceeding that of exhaust air. According to the GMP recommendations, the pressure difference between sterile area and areas of lower clean-room class should amount to 10 – 15 Pa.

DIN 1946 part 7 demands reduced atmospheric pressure for labs where hazardous substances are used in order to protect the environment from contamination originating in the lab.

Ideally, for a cytostatics lab both are required. In fact, this is possible by means of a so-called airlock between the cytostatics area and the lock leading to other areas. This airlock must have considerably higher pressure compared to the preparation room and slightly higher pressure compared to the other areas. Thus, hazardous substances cannot get into the airlock and in particular not to the neighbouring rooms and the environment. At the same time, the increased pressure in the airlock prevents pathogenic germs from entering the preparation area from the neighbouring rooms.

However, in accordance with the current GMP recommendations the decision should always be made in favour of product protection and thus for a preparation room with increased pressure relative to the environment. When a cytostatics hood is being used, GMO criteria demand the ventilation of the containing preparation room to fulfil the criteria of clean-room class B when not operative. Under no circumstances should this demand for clean-room class B for the immediate environment of a cytostatics hood which is run, by design, with reduced pressure relative to the containing manufacturing area be ignored. A constellation with the hood as class A clean-room with reduced pressure, by design, relative to the surrounding class C clean-room preparation area in itself already violates two GMP recommendations (see items 33 and 53

	maximally permissible number of particles per m³			
	non-operative		operative	
class	≥0.5µm	≥5.0µm	≥0.5µm	≥5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	not determined	not determined

in appendix 1 to the EC GMP guidelines). Whether the limits for operation may be kept during the preparation process depends in particular on the staff and the room hygiene, working procedures, quality of the materials entering the area and the air change rate. When adapted to the classification according to DIN EN IOS 14644-1, the particle limits for the individual clean-room classes as published in the current appendix 1 to the EC GMP guidelines allow for somewhat more tolerance for qualification than previously applicable limits, especially for particles with a size of ≥5.0 ìm. Clean-room class B according to GMP corresponds exactly to ISO class 5 when non-operative, to ISO class 7 according to DIN EN ISO 14644-1 when operative.

The DIN EN ISO 14644 series also specifies air change rates (ACRs) for the various clean-room classes. Higher ACRs allow to reduce particle numbers, especially during operative mode. Aseptic work, however, is not correlated with unusually high particles release. Neither is the importance of airborne particles/germs as important for the risk of contamination during aseptic procedures as is the germ load on surfaces, in particular on the gloves of the operator. An ACR of 30 (– 40) should well allow to stay below the limits permissible for a class B clean-room while operative. Also for reasons of energy consumption, ACRs should be kept as low as possible. Well-trained, properly clothed and correctly working staff is the best protection from high particle numbers in operative mode. The most sophisticated clean-room technology is useless if the behaviour of the staff does not meet the requirements.

Inlet-, outlet and exhaust air systems must be dovetailed precisely and designed so that even in the worst case they do not impair the retention capacity of the hood. Such a ventilation system may be designed and implemented only by experienced ventilation engineers.

After installation of modifications to the ventilation or exhaust system, the retention capacity (protection of employees) of the hood under the altered circumstances must be retested on- site. Even moving furniture or rearranging the room necessitates local re-examination on-site.

References:

1. Anforderungen an den Betrieb von Sicherheitswerkbänken mit Luftrückführung für Arbeiten mit krebserzeugenden oder erbgutverändernden Zytostatika – behördlich und berufsgenossenschaftlich anerkanntes Verfahren (BuBaV) nach §36 Abs. 2 GefStoffV, Bundesarbeitsblatt 7-8/1998 S.69
2. ArbStättV, 12. August 2004 (BGBl. I S. 2179), zuletzt geändert durch Artikel 2 des Gesetzes vom 20. Juli 2007 (BGBl. I S. 1595)
3. ASR 5 - Lüftung zu § 5 der Arbeitsstättenverordnung BArbBl. 10/1979 S. 103; 12/1984 S. 85
4. DIN12980, Laboreinrichtungen – Sicherheitswerkbänke für Zytostatika, Juni 2005
5. DIN EN12469, Biotechnik – Leistungskriterien für mikrobiologische Sicherheitswerkbänke Deutsche Fassung EN12469, September 2000
6. DIN EN ISO 14644-1, Reinräume und zugehörige Reinraumbereiche, Teil 1, Klassifizierung der Luftreinheit, Juli 1999
7. DIN 1946 Teil 2, Raumlufttechnik, Gesundheitstechnische Anforderungen, April 1999
8. DIN 1946 Teil 4, Raumlufttechnik, RLT in Krankenhäusern, Juni 2007 - Entwurf
9. DIN 1946 Teil 7, Raumlufttechnik, RLT in Laboratorien, September 2008
10. EG – Leitfaden zur Guten Herstellungspraxis (GMP) Anhang 1, BGBl. I S. 521 vom 26. März 2008
11. M 620, Zytostatika im Gesundheitsdienst, Merkblatt der BGW, Stand: April 2008
12. Quelle der Abbildungen: Firma Berner International
13. TRGS 525 Umgang mit Gefahrstoffen in Einrichtungen zur humanmedizinischen Versorgung, Bundesarbeitsblatt 5/1998; DAZ, Jg. 138 (1998), Nr. 28, S. 2654-2661
14. TRGS 560, Luftrückführung beim Umgang mit krebserzeugenden Gefahrstoffen, Bundesarbeitsblatt, 5/1996
15. Wallhäusers „Praxis der Sterilisation, Desinfektion, Aseptik und Konservierung“, 6. Auflage 2008, Georg Thieme Verlag, Stuttgart ISBN 978-3-13-141121-1
16. Zytostatika Richtlinie der AOLG: Herstellung applikationsfertiger Zytostatikalösungen in Apotheken, DAC/NRF inkl. 23. Erg. 2006 od. Bundesgesundheitsblatt 9 (1998) S. 404-409 od. DAZ, Jg. 138 (1998) Nr.43, S. 4176-4182
17. ISOPP Standards of Practice – Safe Handling of Cytotoxics,J Oncol Pharma Practice 2007 Suppl. 13:1-81

3. Cytostatics Preparation

3.1. Acceptance of Drug Deliveries

Cytostatics deliveries may be accepted only by trained pharmacy staff.

The packages or the sealed cytostatics, respectively, are to be opened at a separate location. The staff is wearing suitable protective equipment.

Noticeable problems such as breakage, contamination etc. must be documented and reported to the manufacturer and to the workplace safety officer. The cause should be identified and eliminated as quickly as possible.

Mag. Inge Zaruba, Eisenstadt

External contamination of cytostatics packages may result from industrial filling or from damage during transport or storage. In studies (1) conducted in European countries with comparable safety standards relating to external contamination of cytostatics packages, these could be detected in every case. Neglect of safety guidelines in handling during receipt of the goods may cause cytostatics to be carrier over in uncontrolled fashion in pure or highly concentrated form. However, this can be essentially avoided by compliance with the safety guidelines and obligatory cleaning.

Acceptance of goods

Cytostatics deliveries should be transported to the cytostatics unpacking site by the supplying company, separate from other products, delivered with unambiguous labelling and unopened.

It is recommended to protect the primary packaging by secondary packaging (plastic sheaths, shrink-wrap foils). This allows to markedly reduce external contamination while at the same time protecting against breakage.

Suppliers taking serious the problem of external contamination and striving to keep their products free from external contamination should be preferred (4).

Unpacking site

This is a specially designated and secured area. The cytostatics deliveries may be opened by appropriately trained staff only. A fume hood above the unpacking site is recommended for protection of the staff.

Unpacking procedure:

1. Put on personal protective equipment (cytostatics gloves: need not be sterile, cytostatics coat, see chapter 3.2 Personal protective equipment)
2. Place a liquid-tight mat and the emergency kit («spill kit») at hand
3. Open the external packaging, remove the shrink-wrap packaging foil
4. Open the secondary packaging (collapsible cardboard box)
5. Visual control of the primary packaging for breakage, fissures and external contamination

If this is in order:

6. 1st step of cleaning the primary packaging with 0.05 M NaOH (wiping method, use lint-free laboratory wiping cloths!) (2)

   2nd step of cleaning using 98% isopropanol (wiping method)
7. Transfer the cytostatic in the primary packaging to the self-contained cytostatics cabinet or cytostatics refrigerator, depending on the storage conditions
8. Properly dispose of the packaging

9. Clean the workplace surface with 0.05 M NaOH, then with 98% isopropanol

If it is not:

6. Put on personal protective equipment for special cases (additionally respiratory protection, protective goggles, overshoes)
7. Dispose of properly in accordance with the Technical Regulations for Hazardous Substances (TRHS 525) and the Ordinance on Hazardous Substances
8. Document and report to the supplier and the responsible safety officer

Storage room

Cytostatics must be stored separately from other storage articles in appropriately marked storage locations (cytostatics safe, locked cytostatics refrigerator). Due to the preceding cleaning process, the cytostatics are stored in the primary packaging. Attention is drawn to the fact that the package insert will be removed together with the secondary packaging. One copy thereof is to be deposited at the storage location (2).

For in-house transport of cytostatics, use suitable breakage-proof and leakage-proof containers (see chapter 3.7: Delivery of cytostatics to the oncological-therapeutic institution).

References:

1. Dr. T. Kiffmeyer, Außenkontamination von Medikamentenverpackungen; Krankenhauspharmazie, 22.Jahrgang, 5/2001,207-212

2. Dr. T. Kiffmeyer, Vorkommen und Beseitigung von Außenkontaminationen bei Primärverpackmitteln", Fortbildungsveranstaltung „Sicherer Umgang mit Zytostatika" IUTA, Duisburg 2007

3.TRGS 525 Umgang mit Gefahrstoffen in Einrichtungen zur humanmedizinischen Versorgung

4., ISOPP, Standards of Practice Safe Handling of Cytotoxics 7.1 J Oncol Pharm Practice 2007,13: 1-81

Acceptance of cytostatics deliveries in the pharmacy (Annex for posting and display)

Cytostatics deliveries may be accepted only by trained pharmacy staff.

After delivery, cytostatics are opened, cleaned and stored at a secured and specially marked location.

1. Transport the deliveries labelled as cytostatics to the cytostatics unpacking site without opening.
2. Put on personal protective equipment (protective coat, cytostatics gloves).
3. Remove secondary packaging on a liquid-tight mat, and dispose of appropriately.
4. Carefully check primary packaging for damage and contamination*.
5. Clean the primary packaging using a 2-step wiping procedure: first 0.05 M NaOH, then 98% isopropanol.
6. Transport to the storage location (cytostatics safe or refrigerator)
7. Properly dispose of the mat and the packaging.
8. Clean the workplace surface with NaOH and isopropanol.

* If the primary packaging is visibly damaged (breakage, fissure, contamination), the cytostatics are duly disposed of in compliance with the relevant regulations on protection and disposal. This incident is to be documented, and a copy is to be forwarded to the manufacturer and the safety officer.

3.2. Personal Protective Equipment

The directives, regulations and guidelines currently in force (*GefStoffV* (hazardous substances regulations), *TRGS* (technical rules for hazardous substances) 525, Cytostatics Directive of the *Länder*, regulations and leaflets of the *BGW / GUV*) stipulate the use of protective equipment by every employee of a cytostatics department deriving from evaluation of the hazards involved. The personal protective equipment must carry the CE mark and must be specified in writing in the hazard evaluation.

In the case of cytostatics preparation, this also applies to those employees who put together the finished drugs for the preparation and package the ready-to-administer solutions.

Personal protective equipment includes:

- **overall or protective gown (possibly in combination with cuffs)**
- **protective gloves**

and in special cases

- **respiratory protective equipment**
- **protective eyewear**
- **overshoes.**

Special cases include:

- **cleaning tasks inside the safety workbench which extend beyond simply wiping the work surface**
- **clearing up spilled cytostatic materials**
- **filter replacement in the safety workbench.**

The personal protective equipment must be adapted to the different requirements and derives from the hazard evaluation.

Gerhard Carstens, Hannover

In order to prevent employees being contaminated with cytostatics, the use of personal protective equipment is the third measure to be taken in addition to organisational measures and the technical equipment.

It must be stressed that organisational measures and technical equipment take priority over personal protective equipment. Thus the technical equipment must be adapted to the state of the art since personal protective equipment, no matter how good, can never compensate for the weak points of obsolete technical equipment. (see Chapter 2.1. Rooms and Equipment).

The basis for a hierarchical design of protective measures is based on the Directive on Protection of Employees from Workplaces Dangers by Carcinogens or Mutagens (*Richtlinie zum Schutz der Arbeitnehmer gegen Gefährdung durch Karzinogene oder Mutagene bei der Arbeit*). Up to five levels of measures can be defined which are to be applied successively. Each turn, the next level shall be applied only if the individual action is not successful or only insufficiently successful.

1. Reduction and replacement

The employer shall reduce workplace use of a carcinogen or mutagens, in particular by replacing it, as far as technologically possible, with substances, preparations or procedures whose use or application, respectively, is less or not dangerous for the health and, if applicable, safety of the employees.

Avoiding dangerous substances and procedures is the safest solution for environment and staff concerned, however hardly implementable at present. Development of therapeutic alternatives in oncology may increase the importance of this measure in the future.

2. Isolation in a self-contained system

If substitution of a carcinogen or mutagen by substances, preparations or procedures whose use or application, respectively, are less or not dangerous for health and safety, the employer shall make provisions for preparing and using the carcinogen or mutagen in a self-contained system.

If hermetic isolation can be guaranteed for the entire duration of the process, it is a reliable protection for staff and environment. Therapeutic requirements strongly limit the use of self-contained systems.

3. Reduction of exposure

If using a self-contained system is technically not feasible, the employer shall have to make provisions that exposure of the employees is reduced to the technically feasible minimum.

3a. Organisational measures

Limitation of the workplace amounts of carcinogens and mutagens, limitation of the number of employees which are or may be exposed, to the feasible minimum, and structuring of procedures.

3b. Technical measures

Structuring of procedures and technical measures with the goal of avoiding or minimizing workplace release of carcinogens or mutagens. Removal of carcinogens at the source, suitable local aspiration system or general ventilation system which are compatible with the required protection of public health and environment.

3c. Personal protective measures

Collective and/or – where no other solution for the avoidance of exposition is possible – individual protective measures.

According to studies by different authors [1 - 3], however, there exists the possibility of contamination in the area outside the workbench despite proper technical equipment. In this connection note must also be taken of works dealing with the outside contamination of primary packaging for cytostatics [4 - 6].

Because of the hazards listed (see Chapter 1.3. Hazard Evaluation), personal protective equipment represents a mandatory measure in respect of minimising the risk of contamination.

Needless to say, this also includes employees who put together the finished drugs for the preparation and package the ready-to-administer solutions, and employees from the sectors cleaning, disposal and transport to the extent that

they handle cytostatics. This derives from the definition of the term *Umgang* (handling) according to *TRGS* 525: handling means preparation including extraction or using. Using includes applying, consuming, storing, keeping, processing and refining, filling, transferring, mixing, removing, destroying and conveying. Handling hazardous substances includes all activities within their danger zone.

When responsibilities of facilities for human healthcare (hospitals, medical practices, pharmacies, etc.) are assigned to outside firms (outsourcing), which is especially common in the transport and cleaning sectors, the safety regulations also apply for the external contractor. The client (e.g. the hospital provider, doctor, pharmacy manager) must inform the contractor (managing director of the external firm) that CMR drugs are being handled in order that it can carry out the instructions properly, with assistance from the client where necessary (see Chapter 1.3. Instruction).

Before the selection and use of personal protective equipment a hazard determination procedure must take place in which not only the kind and scope of the risks at the workplace are ascertained, but also the working conditions and the personal constitution of the person wearing the equipment (*TRGS* 440, ZH 1/700).

In evaluating and selecting personal protective equipment for the aseptic preparation of ready-to-administer cytostatics it is essential that not only aspects of personal protection and wearing comfort are taken into account, but also the requirements of product integrity. The principles of aseptic procedures and the GMP guidelines bear the same weight as the requirements of personal protection.

For the development, production and marketing of personal protective equipment the EU Commission has formulated basic requirements for health protection and safety. Knowledge of the requirements relevant for the oncological sector can be of assistance in selection and use:

Ergonomics

Personal protective equipment must allow the user to perform the work normally and offer the maximum protection appropriate to the risk.

Maximum level of protection

The optimal level of protection is such that to increase it would lead to problems in use and/or to rejection by the user. Personal protective equipment can only fulfil its intended function if it is accepted and used.

Protection classes according to the level of risk

If different levels of intensity of the same risk are to be expected, corresponding protection classes must be defined. Different levels of intensity can refer both to the cytostatics used and to the methods or types of work and duration of exposure.

Suitable starting materials

The starting materials must not exert any harmful influence on the health of the user. This may be relevant in the case of latex gloves.

Appropriate condition of the surface

Parts of an item of personal protective equipment that may come into contact with the user while being worn must not have any sharp edges or points that can cause excessive irritation or injuries. An example would be badly positioned Velcro closures on single-use gowns.

Adaptation to the figure of the user

Personal protective equipment must fit the figure of the user, either by means of suitable adjusting and retaining systems, or by the availability of an adequate range of sizes and/or shapes.

Manufacturer's information brochures

In addition to other information, the brochures must contain instructions for storage, use, cleaning, maintenance, inspection and disinfection. Notes on storage and disinfecting, or the prohibition of disinfection, can, for example, exert a considerable influence on the protective efficacy of single-use gloves.

Personal protective equipment that wraps in the body parts to be protected

Wrapping personal protective equipment must be adequately ventilated as far as possible, or include a method for absorbing perspiration.

Personal protective equipment subject to ageing

If effectiveness can be noticeably impaired as a result of ageing, every individual item of such personal protective equipment must bear the date of manufacture and, if possible, the expiry date. If the manufacturer is unable to provide precise information, it must list all useful information that will enable the user to determine a plausible shelf life based on the actual situation. As an example, it may be assumed that single-use gloves are subject to ageing of this kind.

If modified performance is a result of ageing caused by a cleaning method recommended by the manufacturer, the maximum number of times the personal protective equipment may be cleaned must be stated if possible on every individual item. This may be applicable to multi-use overalls and gowns.

The EU directive is implemented at national level by application of the regulations on safety and health protection in the use of personal protective equipment at work (*PSA-BV*), which in addition to the definition of the area of applicability, also contains basic regulations for provision, use and instruction.

References:

1. Sessink PJ, Van-de-Kerkhof MC, Anzion RB, Noordhoek J, Bos RP.:
2. Environmental contamination and assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed pharmacy technicians: Is skin absorption an important exposure route?, Arch Environ Health. 1994; 49:165-169.
3. Connor TH., Anderson RW., Sessink PJM., Broadfield L., Power LA.: Surface contamination with antineoplastic agents in six cancer treatment centres in Canada and the United States. Am J Health-Syst Pharm 1999;56:1427-32.
4. Pethran A., Schierl R., Schmaus G.: *Wischproben an Arbeitsplätzen mit Zytostatika-Exposition* (Wipe tests on workplaces exposed to cytostatics). Krankenhauspharmazie 2001;22(5):11-5.
5. Hepp R., Gentschew G.: *Untersuchungen zur Außenkontamination der Primärverpackungen von Zytostatika* (Investigation of the outside contamination of primary packaging for cytostatics). Krankenhauspharmazie 1998; 19:22.

6. Delporte JP., Chenoix P., Hubert Ph.: Chemical contamination of the primary packaging of 5-Fluorouracil rtu solutions commercially available on the Belgian market. European Hospital Pharmacy 1999;5:119-21.

7. Favier B., Gilles L., Ardiet C., Latour JF.: External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers. J Oncol Pharm Practice 2003;9:15-20.

General legal principles:

- *TRGS* 525: "Handling hazardous substances in facilities for human medical care", May 1998, *BArBl*. No. 5/98: 99-105
- *TRGS* 440: Ascertainment and evaluation of the danger presented by hazardous substances at the workplace: procedure (ascertainment duty) , March 1999, *BArBl*. No. 3/99
- ZH 1/700: Rules for the use of protective garments, *Hauptverband der gewerblichen Berufsgenossenschaften* (main association of professional bodies) April 1994
- Council directive on the harmonization of legal requirements of the member states for personal protective equipment (9/686/EEC) September 1996
- *Verordnung über Sicherheit und Gesundheitsschutz bei der Benutzung persönlicher Schutzausrüstungen bei der Arbeit* (regulations on safety and health protection in the use of personal protective equipment at work (*PSA-Benutzungsverordnung – PSA-BV*) December 1996, *BGBl*. I 1996: 1841

3.2.1. Overall/Protective Coat

The personal protective equipment covering the body (overall, lab coat) must be closed up to the neck. It has long sleeves with close-fitting cuffs. Particularly exposed sections should be liquid-repellent. For product protection it should be lint-free and at least low-germ.

Gerhard Carstens, Hannover

For the preparation of cytostatics, the «Technical Regulation for Hazardous Substances» TRHS 525 recommends a high-necked coat with long sleeves and close-fitting cuffs. For cleaning work in the safety hood exceeding mere wiping of the workplace surface and also for removal of accidental contaminations produced during preparation or administration (see 4.2: Measures after unintentional release of cytostatics), a liquid-tight protective coat with long sleeves and close-fitting cuffs is required. When replacing the filters of a safety hood, protective coats must be worn which do not need to be liquid-tight.

The Laender cytostatics directive issued in 1998 (Bundesgesundheitsblatt 9/1998) requires – conservatively – «appropriate protective clothing» for protecting the body. It is commented that a combination of a liquid-tight coat high-necked in front with long sleeves and close-fitting cuffs is considered as appropriate clothing for the protection of staff and products.

Discussion: Lab coat versus overall

Bulletin M 620 (Safe handling of cytostatics) by the Professional Association for the Health and Welfare Services (Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege) copies the exact wording of the requirements of the TRHS 525 relating to coats to be worn during preparation, cleaning and removal of inadvertent contaminations. With regard to protective measures during preparation and application, the 04/2008 issue recommends to use for preparation a protective coat and (sterile) gloves and goggles if required.

For application, the bulletin recommends protective gloves and a coat with closed front. With these recommendations, the authors of the bulletin exceed the TRHS 525 which prescribes having at hand an emergency kit («spill kit») only when openly handling cytostatics.

Protective clothing covering the body obviously suggests a coat. This is a garment widely used in health care with various protective functions, available in a variety of qualities and put on without much effort. However, there are also fields of activities and hazards where alternatives must be contemplated. Among these, the preparation area is to be named first. If the requirement for a class A clean-room (sterile hood) in a class B clean-room (manufacturing area) is fulfilled, this standard is more easily complied with by using a combination of overall, boots and hood than with coat, cap and clean-room shoes.

While in the preparation area both variants can lead to acceptable results, in the hazard area a coat is no suitable protective clothing for the removal of unintended contaminations – at least if larger quantities of liquid or solid matter are involved. A long coat protecting the knees of a standing person may become the equivalent of a feather duster or floor cleaning mop when the wearer bends the knees or bows down to remove breakage and contamination. For this reason, a sufficiently large overall is to be demanded at least for spill kits and should be generally contemplated as protective clothing for the cytostatics area (see 4.2 Measures in case of inadvertent release of cytostatics).

Discussion: Single-use material versus reusable products

Protective clothing is available both for single use and for multi-use. For deciding this basic question, the aspects of personal protection and of product protection should be considered first.

If collecting potentially contaminated multi-use clothing is implemented safely, the cleaning procedures remove potential contaminations without leaving any residues and any hazards to the laundry staff are excluded, then with regard to personal protection multi-use clothing is equivalent to single-use clothing.

Product protection can be guaranteed independent of reusability. The EC GMP guidelines require the area wherein the cytostatics hood is installed to be a class

B clean-room and the protective and work clothing to be used to be sterilized. (see 2.1: Rooms and equipment). In spite of this, in Germany cytostatics preparation areas are being operated which do not fulfil these requirements. In areas of clean-room class C and worse, product protection by protective clothing is a minor issue. In such installations, however, it should at least be made sure that body parts extended into the hood (class A clean-room) are covered with sterilized and low-particle protective clothing. If required, this can be guaranteed by using suitable sleeve cuffs.

Apart from the aspects of personal and product protection, aspects to be considered in selection comprise wearing comfort, thrift and ecological footprint.

The importance of wearing comfort is summarized by Harrison & Kloos: «Selecting the best protective clothing material from this group» (of materials investigated) «will not guarantee protection if the manufacturers do not wear the protective clothing» [1]. Economic consideration must, of course, consider total costs, which may for reusable protective clothing also include control and instruction sessions. Assessment of the environmental footprint is expected to be more difficult, since this must consider not only the contamination caused by the preparation procedure itself but also that which is due to cleaning and disposal. Assessment requires precise knowledge of the processes involved. The price is not very helpful since it rather reflects the market situation than environmental costs.

Discussion: Wearing time

In contrast to protective gloves, for protective clothing there are only very limited recommendations pertaining to wearing time. TRHS 525 stipulates that the protective equipment worn during preparation of CMR drugs must be exchanged immediately upon contamination or damage. Additionally, the Laender directives demand that personal equipment is to be taken off upon leaving the cytostatics area. This may imply several hours of wearing time.

A potential personal risk is posed by unnoticed contamination of protective clothing, resulting in direct danger to the wearer if the contamination permeates

the protective clothing. In addition, carry-over of the contamination jeopardizes other persons. The problem of spreading also plays an important role if work in the manufacturing area is interrupted for a shorter (minutes to hours) or longer (hours to days) period of time. The coats or overalls – tainted with unnoticed contamination – may cause spreading of the contamination to other objects and areas both during putting on and taking off and during storage. From the product protection perspective, in compliance with the GMP guidelines reuse without reprocessing (cleaning and sterilization) is not acceptable. When assessing the costs, not only the number of coats or reprocessing steps should be considered but also the effort necessitated by spreading of contaminations or deficiencies in asepsis. Deviations from the state of the art are acceptable only if the same quality can be demonstrated to be guaranteed (see 3.3.1: Validation of aseptic procedures). Furnishing this prove also represents a cost factor which must not be neglected.

The question «liquid-tight or not» is closely linked to wearing time. Even when working in a safety hood, contamination, e. g. with aerosols or drops in the arm, breast, abdomen and thigh are are possible. When unpacking and enriching cytostatics, contamination of the protective clothing may be caused by contamination of the primary packaging, which may dissolved or suspended e. g. by squirting during washing of the hands. In case of breakage, contamination on any scale is possible. These considerations make understandable the desire to wear liquid-tight protective clothing in the manufacturing area as well. However, it is to be considered that liquid-tight, possibly smooth surface of the PPE may cause dripping off of liquid contaminations, resulting in further spreading.. Previously published studies show that commercially available products differ very much in the protection from penetration and permeation of cytostatics solutions they offer [1,2,3]. Unfortunately, wearing comfort and protective efficacy seem to be mutually exclusive [1]. Ideal material for protective clothing comprises an absorbent outside with liquid-tight inside, combining protection from penetration and permeation with high wearing comfort and good breathability. The impossibility of the combination enforces compromises to be made according to the local conditions.

Textile materials

Long-sleeved, high-closing coats, as used as surgical coats in hospitals, or overall made from the same material may be employed. According to Guideline 93/42 EEC such surgical coats are medical products [4] which must comply with the requirements of EN 13795 [5,6,7]. Even though this standard is primarily geared towards prevention of infectious interoperative spreading of germs, the properties thus guaranteed should be expedient for personal and product protection in the manufacturing area as well. This regulation defines, inter alia, requirements relating to penetration of germs, permeation of liquids and release of particles.

Today, the following tissues or laminates are available as textile barrier materials:

Mixed fabrics of polyester and cotton

A tightly intertwined blend of polyester and long-stapled cotton processed to form a dense fabric and additionally treated with fluorocarbon impregnation can achieve a barrier function satisfying standard requirements.

Microfilament fabrics

Yarns for microfilament fabrics are spun from very fine, continuous polyester filaments. They are virtually particle-free and very durable. Rendered liquid-tight by fluorocarbon impregnation, these tissues also satisfy standard requirements.

Textile laminates

In a trilaminate, a microporous membrane is embedded between an upper and a lower layer. The pore size of the membrane can be selected so that an effective barrier against penetration of bacteria and viruses in combination with liquid is provided. This microporous membrane does not impede the passage of water vapour so that natural thermoregulation is provided. In contrast to fluorocarbon-impregnated barrier tissues, a trilaminate is absolutely impenetrable to microbiological germs even at high pressures. As the upper and lower layer consist of polyester filaments, there is practically no release of particles.

If the safety hood used for the manufacture of cytostatics is not installed in a class B clean-room, final sterilization of the coats is dispensable since the coats are, depending on cleaning and drying processes, low-germ due to heat treatment. They are to be completed with sterile (sterilized) cuffs of liquid-repellent material. Here the cuffs of the gloves should be pulled over those of the sleeves to guarantee optimal protection at the borderline between gloves and sleeves. The selection of the cover image of the up-to-date M 620 bulletin by the BGW is beyond all understanding. Here a textile, obviously absorptive sleeve cuff over the protective glove is shown.

For reusable materials, the manufacturers' data relating to cleaning and reprocessing procedures, disinfection and impregnation are to be observed. [8].

For textile barrier materials, currently there are no data available relating to possible permeation of cytostatics.

Single-use coats of liquid-repellent materials

Sterile (sterilized) coats – and cuffs – consisting of polypropylene with and without polyethylene coating are commercially available as single-use articles for the manufacture of cytostatics. They are also available as non-sterile products. Wearing comfort is markedly lower than with textile materials.

Currently, only limited data relating to possible permeation of cytostatics are available [1,2,3] and can be enquired from the manufacturer if needed. Only approved coats and cuffs should be used since materials were presented for evaluation which had an optical resemblance to liquid-repellent materials but completely failed the very first tests.

References:

1. Harrison, Bruce R. MS, Rph, Kloos, Michael D. Pharm D. Penetration and splash protection of six disposable gown materials against fifteen antineoplastic drugs. J Oncology Pharm Practice, 1999;5(2):61-66

2. Laidlaw JL, Connor TH, Theiss JC, Anderson RW, Matney TS. Permeability of Four Disposable Protective-Clothing Materials to Seven Antineoplastic Drugs. Am J Hosp Pharm. 1985;42:2449-2454

3. Connor TH. An Evaluation of the Permeability of Disposable Polypropylene-Based Protective Gowns to a Battery of Cancer Chemotherapy Drugs. Appl. Occup. Environ. Hyg. 1993;8(9):785-789

4. Richtlinie des Rates vom 14. Juni 1993 über Medizinprodukte (93/42/EWG) September 1996

5. Europäische Norm DIN EN 13795 1 Operationsabdecktücher, -mäntel und Reinluftkleidung zur Verwendung als Medizinprodukte, für Patienten, Klinikpersonal und Geräte – Teil 1: Allgemeine Anforderungen für Hersteller, Wiederaufbereiter und Produkte, Februar 2003

6. Europäische Norm DIN EN 13795 2 Operationsabdecktücher, -mäntel und Reinluftkleidung zur Verwendung als Medizinprodukte, für Patienten, Klinikpersonal und Geräte – Teil 2: Die Auswahl und die Entwicklung von gerechten sowie realistischen Testmethoden zur Messung der identifizierten Produktmerkmale, Februar 2005

7. Europäische Norm DIN EN 13795 3 Operationsabdecktücher, -mäntel und Reinluftkleidung zur Verwendung als Medizinprodukte, für Patienten, Klinikpersonal und Geräte – Teil 3: Die Festlegung von Grenzwerten zur Qualifikation von OP-Textilienals Medizinprodukte, August 2006

8. Richtlinie des Rates zur Angleichung der Rechtsvorschriften der Mitgliedsstaaten für persönliche Schutzausrüstung (89/686/EWG) September 1996

3.2.2. Single-Use Gloves for Protection During the Preparation of Cytostatic Solutions

Suitable gloves or glove combinations must be worn; these must be changed at regular intervals and also in the event of contamination.

Dr. Renate Hepp, Gießen

Single-Use Gloves for Protection During Preparation

During the preparation of cytostatics, sterile single-use gloves are used which support aseptic procedures in the sense of product integrity, but simultaneously perform the function of personal protective equipment (PPE).

Sterile, powder-free single-use gloves must be used during the preparation of cytostatics. They must be sterile in order not to endanger the aseptic procedures for preparing cytostatics solutions and they must be powder-free in order not to increase the particle loading in the preparation area. According to *TRGS* (technical rules for hazardous substances) 540 latex gloves must be powder-free and low in allergens [1].

In order to meet standards of personal protection and product integrity during the preparation of cytostatics the gloves must be tear resistant, must fit well with tightly sealing sleeve bands and must provide a good grip.

A further requirement is that damage (faults, holes, tears) must be detectable before, during and after using the gloves. The use of coloured gloves or glove combinations ensures that damage can be detected more quickly and with greater certainty [2, 3]. Gloves must meet standards that guarantee a specific imperviousness [4, 5, 6].

Before using the gloves the wearer must make certain that their macroscopic properties reliably protect person and product from contamination.

The protective function of the glove against the cytostatics used in the preparation (commercial preparations) must be tested. When selecting gloves account should be taken of the quality standards set by DIN EN 374 [3].

Gloves must be stored in a way that does not impair their quality.

Gloves as Barriers against Cytostatics

Protective Aim and Impairing Influences

Gloves used in the area of cytostatics preparation are an important part of the personal protective equipment (PPE) and in the majority of cases also serve to protect the integrity of the product being prepared. The ideal protective glove is impervious to harmful substances. In reality this ideal is not achieved completely.

The harmful substance can pass through the material of the glove by penetration or permeation. These processes are defined as follows (DIN EN 374-1):

Penetration: The movement of a chemical or a microorganism through porous material, seams, pinholes or other defects in the material of the protective glove at a non-molecular level.

Permeation: The process by which a chemical passes through the material of a protective glove at the molecular level. Permeation involves the following steps:

1. Molecules of the chemical applied are taken up by the (outer) surface of the material.

2. These molecules diffuse in the material.

3. The molecules are given off by the opposite (inner) surface of the material.

What methods are used to test the retaining power of the gloves used?

Single-use gloves are normally used during work with cytostatics. These are, for example, surgical gloves and nursing gloves that have been tested in accordance with the standard DIN EN 455 “Medical gloves for single use”. The intended use of these gloves is in the medical sector for protecting patient and wearer from contamination [4].

Gloves tested in accordance with DIN EN 374 are also used for handling cytostatics. Gloves complying with this standard serve for "Protection against chemicals and microorganisms" and are only intended to protect the wearer from these influences.

Test for freedom from holes in accordance with DIN EN 455

"Medical gloves for single use" are tested for freedom from holes.

The method used is a water retention test for ascertaining the existence of holes. Single-use gloves tested according to Point 5.1 must fulfil the required standard for freedom from holes with an AQL of 1.5.

The AQL (acceptable quality level) is part of a statistical inspection system that was developed by standards authorities, manufacturers and users for testing the quality standard of a product. One important factor is the number of samples to be tested, which decisively influences the evaluation of product quality. That means: the lower the AQL value, the "better" the product, and the higher the number of random samples, the "greater" the probability of finding batch sizes from production that do not meet the standard [7].

For further information on AQL (Use, applicability, definition of AQL values) see DIN ISO 28590-1 [8].

Test for penetration in accordance with DIN EN 374

"Protective gloves against chemicals and microorganisms" (DIN EN 374) are subjected to a penetration test in order to determine their freedom from holes.

The inspection method to be used for resistance against penetration is the air leak test Point 5.2 or the water leak test Point 5.3.

In respect of the required standard for resistance against penetration by this type of glove, DIN EN 374-1 differentiates between three performance levels (Class 1 - 3) with corresponding AQLs (0.65 / 1.5 / 4.0).

DIN EN 420 "General standards for gloves", Point 7.3 "Information and instructions for use" requires the glove manufacturer to state the performance class achieved [9].

Test for permeation of the test chemicals in accordance with DIN EN 374

"Protective gloves against chemicals and microorganisms" (DIN EN 374) are also subjected to a permeation test.

For each test chemical the protective glove/test chemical combinations are classified according to the breakthrough time during which the glove prevents permeation. The protection index below is based on the breakthrough time (Table 1) measured during constant contact with the test chemical under normal laboratory conditions, as described in DIN EN 374-3. The actual duration of protection at the workplace can deviate considerably from this protection index.

Table 1: Protection index against permeation

Measured breakthrough time	Protection index
› 10 min	Class 1
› 30 min	Class 2
› 60 min	Class 3
› 120 min	Class 4
› 240 min	Class 5
› 480 min	Class 6

The breakthrough time is defined as the time that elapses between the first application of the test chemical on the surface of the material of a protective glove material and the subsequent appearance on the other side of the material, measured as described in the standard (DIN 374-3).

It is important to point out that the breakthrough is regarded as having occurred as soon as the permeation rate of the test chemical through the glove material amounts to 1 µg min^{-1} cm^{-2} . As long as the permeation rate is lower than this, the glove is regarded as safe for handling the (liquid) test chemical. The tests are performed at a standard test temperature of (23 ± 1) °C.

Studies on the Permeation of Cytostatics through Protective Gloves

Gloves used in the preparation of cytostatics should in addition be tested for their resistance to permeation of the cytostatics being handled (commercial preparations) to the extent that this is not included in the tests performed on the basis of their intended use (e.g. surgical gloves).

Most of the studies in this connection were carried out by interested work groups using non standardised methods.

Permeability experiments on surgical gloves of latex and polyvinyl chloride (PVC) have shown that latex gloves provide better protection than PVC gloves against most cytostatics [10]. Because of these results, its wearing comfort and its material properties, the latex glove has been preferred in the preparation of cytostatics. However, since the latex proteins contained in the glove can lead to allergies in some users, gloves made from other materials also had to be tested with regard to their suitability for handling cytostatics.

Numerous permeation experiments were performed on commercially available latex gloves (material thickness approximately 0.2 - 0.4 mm) and also on glove combinations (two thinner latex surgical gloves worn one over the other) [2, 11, 12, 13, 14]. Rapid permeation of carmustine and/or thiopeta is frequently reported for single-layer latex protective gloves. Mitoxantron is mentioned in this connection to a lesser extent [2, 10, 11, 12, 13, 15]. In experiments using the model substance carmustine and four other cytostatic agents, combinations of two latex surgical gloves proved to be better barriers, or even completely reliable, in their retention power [6, 12].

In a study using ifosfamide, latex gloves with a lower wall thickness (approx. 0.24 mm) provided better protection against the cytostatic than latex gloves of thicker material (0.33 mm) [16]. Compared with the protective gloves commercially available in Germany, a double surgical glove system (two thin hydrogel polymer-coated latex gloves worn one over the other) even provided very good protection against carmustine and proved to be superior to a single glove of the same kind in the test with further cytostatics [17, 18, 19]. Permeation of thiopeta through the material of hydrogel polymer coated latex

gloves was also faster than for other cytostatics. A double glove provided the best protection [19].

In tests over three hours with 5 cytostatics, neoprene gloves fulfilled the breakthrough criteria of DIN EN 374-3; the cyclophosphamide measurements were sensitive to interference by the glove material [20, 21, 22]. With regard to their retaining power against the cytostatics tested, neoprene gloves performed as well or better than non powdered single and double surgical gloves containing latex (referred to thiopeta) [19].

No permeation through nitrile gloves was detected for the 11 cytostatics tested using a conductometric method under the experimental conditions of the ASTM American standard. Although alcohol was detected in the acceptor medium during the test with carmustine, there was no increase in conductivity. Since it is possible, however, that the substance dissolved in ethanol permeated together with the ethanol, the authors recommend that this be subjected to further investigation [23, 24].

Recent studies have been performed using methods analogous to those of DIN EN 374. In an investigation of 15 cytostatics the resistance of selected gloves against these cytostatics was tested over a period of 3 hours. The cytostatics selected were either new or known to be critical. Most of the cytostatics showed no or only slight permeation. The measured permeation rate over 3 h lay at ≤ 0.2 nmol min^{-1} cm^{-2}. The carmustine permeation rate for single layer latex gloves was up to 11 times this value [15].

In a second investigation the commercial cytostatics preparations of one drug manufacturer were tested for permeability through different single-use protective gloves of diverse materials. Here too, the measured permeation rates over a period of 3 h were below 1 µg min^{-1} cm^{---2} [25].

Special Notes on Latex Gloves

Latex Allergy

During the years between 1980 and 1990 there was a dramatic increase in early reaction type allergies towards natural latex products, mostly caused by gloves. Health service employees are one of the groups at risk [26]. One theory for the

increase in the allergy rate is the rapid rise in the use of gloves since 1987 [27]. In addition, the increased demand and the cost pressure in the past has resulted in cheaper production methods and therefore to products with a higher protein fraction being launched on the market [27, 28]. In the meantime the frequency of latex allergies among employees in the medical sector has risen to 17% [29]. The immediate or Type 1 allergies, which represent the majority, are triggered by latex proteins. However, late or Type 4 allergies (6 - 48 hours after allergen contact) also occur, triggered by additives used in the manufacturing process as vulcanisation accelerators, especially substances of the thiuram group [30].

Powdered gloves present a particular allergy risk since the latex proteins bound to the powder enter the air as soon as a package is torn open and can result in irritation of the eyes and the respiratory passages. This may cause conjunctival reddening, running nose, coughing and bronchial asthma. Severe general symptoms - even as far as anaphylactic shock - are possible. The first fatalities have already been reported [30].

Avoidance of Latex Allergies

Primary prevention: The following recommendations are among the protective measures suggested [30, 31, 32, 33]:

- Use of non powdered latex gloves with low protein concentration (if possible < 30 µg per g glove)
- Use of thiuram free gloves in order to reduce the risk of allergic contact eczema
- Consistent skin protection scheme (a skin protection plan must be prepared: *TRGS* 525 3.6 (4), *TRGS* 540 4.4 (3)).

Secondary prevention: Persons allergic to latex may only use latex free gloves. They must avoid any contact with products containing latex.

Statutory Requirements for Handling Latex Gloves

The handling of latex gloves is covered by the *Gefahrstoffverordnung* (hazardous substances regulations) [34] (which were issued on the basis of the *Chemikaliengesetz* (chemicals act) [35]) since they belong to those products

from which hazardous substances may be released during use [36]. Because of their sensitizing properties, latex proteins are hazardous substances in the sense of the chemicals act.

In the USA labelling of medical devices containing latex has been compulsory since 1997 [30]. In the course of harmonisation of international standards, based on the biological evaluation of gloves made from natural rubber latex, mandatory labelling was also included in EN 455-3 [4]. This requires that latex gloves be declared with the statement: "(This product) contains natural rubber latex which may trigger allergies".

Pursuant to the handling requirements of the hazardous substances regulations the employer has a duty to determine whether hazardous substances are being handled in its enterprise (duty to investigate [37]). The manufacturer or supplier must pass on product information if this is requested by the employer [38] (e.g. the protein content of the gloves). The employer is subject to the so-called duty to substitute [39]. This means that it must determine whether products with a lower risk are available, whether it may be reasonably demanded of it that it use these products, and whether substitution with these products is necessary for the life and health of the employees. (If this applies, it may provide only such gloves as are appropriate) [30].

Since the use of latex gloves is regarded as handling hazardous substances, the gloves must be included in the hazardous substances list which the employee must maintain in accordance with the hazardous substances regulations [40]. The working rules prepared for the preparation area must also cover latex gloves. The employees must be given instruction on handling these products at least once a year [41], See also Chapter 1.3. "Hazard Evaluation, Working Rules and Instruction".

Handling Gloves During Preparation

Is it reasonable to disinfect gloves that are not or no longer sterile?

In permeation tests different formulations of the cytostatic vincristine demonstrated very diverse permeation properties. One commercial preparation contained benzyl alcohol, which caused the cytostatic to penetrate through

the glove material very rapidly. In contrast, no permeation was observed for an aqueous solution with the same concentration [19].

The safety of protective gloves is tested according to the conditions defined in studies. These do not take into account the use of disinfecting agents.

The disinfecting agent (e.g. alcohol, tenside, aldehyde) can interact both with the glove material and with the cytostatic. This can lead to unpredictable influences on the protective efficacy of the glove.

For these reasons the use of disinfecting agents for disinfecting gloves used during cytostatics preparation does not appear to be sensible at the present time.

When must protective gloves be worn?

Protective gloves must basically be worn for all types of work during which a contamination by active substances cannot be excluded, e.g. already while unpacking and when preparing infusion bottles with dry substances and cytostatic solutions from ready drugs [42, 43, 44, 45]. It is not necessary to wear sterile, single-use gloves in every case.

In this connection the fact should be considered that examination gloves, which are frequently worn for unpacking the preparations, have been the subject of far fewer permeation tests than surgical gloves. Examination gloves, however, are generally made of thinner material.

Intervals for Changing Gloves

According to leaflet M 620 protective gloves should be changed every 30 minutes, regardless of visible contamination or damage, in order to avoid invisible damage or taking up invisible contamination [3].

Rapid penetration of carmustine and thiopeta has been demonstrated for single layer protective gloves made of latex [2, 10, 11, 12, 13, 15]. Changing soon after the preparation (e.g. performed towards the end of a changing interval), the use of more suitable gloves, or a double glove system is advisable. For thiopeta neoprene gloves are better than latex gloves [19]. A breakthrough time of < 10 minutes through latex gloves has also been described for mitoxantrone [13],

though more recent findings report that no permeation through different glove materials was observed for up to 3 hours [15, 46].

Double glove systems are strongly recommended because of their more than additive protective effect and their "double floor", whereby the outer glove must be changed regularly (and the entire combination when handling critical substances).

In respect of cross-contamination in the working surroundings, a changing interval of 30 minutes also means an interruption in the distribution of cytostatics in the work room. Investigations from the field of occupational medicine reveal that it is still always possible for primary packaging to be contaminated with commercial preparations [45]. Unfortunately commercial preparations with low-contamination or contamination free packaging are not universally available.

As soon as this situation improves and the user is provided experimental results with appropriately low detection thresholds proving that gloves guarantee reliable protection against the commercial preparations being handled, it will be possible to consider longer wearing times for gloves.

Storing Gloves

Gloves must be stored in accordance with the manufacturer's recommendations. These are generally: cool and dry (between 5 and 30 °C). No weight should rest on the gloves during storage as this can result in cracks forming at the folds. The requirements of DIN 58 953 Part 7 (8.2 "Storage duration of sterile goods") must be met [47].

Discussion

Numerous requirements are set for single-use gloves worn during the preparation of cytostatics solutions; these requirements may differ depending on the preparation facility and the user. The employer is legally obligated to provide "effective protective garments with appropriate wearing properties" [1, 48, 49].

The following criteria should be taken into account when selecting gloves:

- material properties (tear resistance, thickness, uniform thickness)
- size and fit

- safety during use (grip)
- retaining power for cytostatics
- tested for freedom from holes (in accordance with DIN EN 455 or DIN EN 374)
- detectability of any damage
- health of the personnel (including low allergenic potential in the case of latex gloves, alternative material for allergic persons).

Many commercially available (single-use) protective gloves are tested for freedom from holes (penetration) according to DIN EN 455 or DIN EN 374 and guarantee high quality in respect of the perfection of their material (defects, holes). However, hardly any gloves are available that have been tested for permeation of cytostatics according to DIN EN 374-3 [50].

Investigations of the permeation of cytostatics through glove materials are predominantly the result of the initiative of different work groups.

Up to now there has been no standard against which "cytostatics protective gloves" could be tested. In this respect the following aspects would need to be considered:

Cytostatics form a heterogeneous group of substances and even different formulations of the same substance can have very different permeation characteristics [19]. A single molecule of a cytostatic agent may damage the genome of an individual. As the actual acceptor medium, the skin has lipophilic properties. Especially the wearing of gloves for long periods results in occlusion, warming and perspiring, leading to many substances being taken up more readily by the skin. The body temperature is approximately 37 °C.

It is a fact that most of the investigations to date were not carried out using standardised methods; they have in common that the chemicals being tested (normally stock solutions of commercial preparations) are applied to one side (outside) of a sample of glove material and an acceptor medium on the other side (inside) of the glove material takes up the permeated substance. The cytostatics

are quantitatively analysed using a variety of analytical procedures. Generally, the time is given after which the first detectable quantities of the cytostatic appear in the acceptor medium, or periods of time are measured during which no substance is detectable. In recent years more and more studies have been performed based on the permeation test of DIN EN 374 [15, 19, 20, 25].

The detection threshold of the analytical method used in the test is of decisive importance for evaluating the protective efficacy of gloves. In every publication up to now, it has only been possible to make statements within the context of the experimental conditions used and the detection threshold achieved for the cytostatics. More sensitive analytical methods could result in shorter breakthrough times for cytostatics in the future.

Studies performed up to now have delivered significant information for the evaluation of single-use gloves for the preparation of cytostatics. The retaining power of gloves does not depend on the material thickness alone [16]. The double glove provides particularly effective protection [51]. Results gathered for one type of glove cannot be transferred to a different type of glove made of the same material. This applies not only for products from the same manufacturer (e.g. examination gloves and surgical gloves) but also for products from different manufacturers (e.g. surgical gloves from different firms). Stretching does not in every case affect the resistance of a glove against permeation [52].

In recent years one work group has methodically carried out a wide range of glove tests using the same methods with the result that directly comparable data are now available concerning the permeation of commercial cytostatic preparations through the materials of different brands of glove.

These were obtained analogously to the methods of DIN EN 374 and must also be evaluated from the aspect of the respective definition of breakthrough [15, 19, 20, 21, 25]. In every case the permeation rates of the cytostatics through the glove material over a period of 3 hours were below 1 µg min^{-1} cm^{-2} so that, in the sense of this standard, they are regarded as safe for handling the (liquid) test chemical. In some cases, however, cytostatics were detected in different concentrations in the acceptor medium. Users must interpret the studies ex-

actly and take such results into account when selecting the glove "suitable" for their purpose.

A welcome development is the initiative of one manufacturer in having the suitability of different single-use gloves tested for handling its cytostatic preparations [25]. Other manufacturers are urged to follow this lead and provide such test data for their products in order to facilitate the user's search for a single-use glove suitable for the preparation of cytostatics.

When searching, it is important to realise that a glove manufacturer may only declare its product in accordance with one standard, even if it has been tested in accordance with two standards (e.g. according to DIN EN 455 and DIN EN 374). It is therefore always worth asking whether the gloves have been subjected to tests extending beyond the declared standard.

References:

1) *TRGS* 540, 4.4 (2) – *Sensibilisierende Stoffe* (Sensitizing substances); status (2000-02)

2) Krammer, B. et al.: *OP-Doppelhandschuh als Schutzhandschuh in der Zytostatika-Herstellung*, (Double surgical glove as protective glove in cytostatics preparation), Krankenhauspharmazie 1997; 18:422-425

3) *Sichere Handhabung von Zytostatika* (Safe handling of cytostatics), Leaflet M620, pub. *BGW* (professional association for the health service and social services); status 2000-04. *Handhabung von Zytostatika* (Handling cytostatics), Leaflet *GUV* (statutory accident insurance) 28.3; status 1999-01

4) DIN EN 455, "Medical gloves for single use"; status 2001-01

5) DIN EN 374, "Protective gloves against chemicals and microorganisms"; status 1994-04.

6) DIN EN ISO 6529, "Protective garments - protection against chemicals - determining the resistance of protective garment materials against the permeation of liquids and gases" (ISO 6529:2001); German version EN ISO 6529; status 2001

7) Kralj, N.: *Sicherheitstechnische und immunologische Prävention berufsbedingter Hepatitis-B-Virusinfektionen (unter besonderer Berücksichtigung des Einsatzes persönlicher Schutzausrüstungen)* (Technical and immunological prevention of occupational hepatitis B virus infections (with emphasis on personal protective equipment), doctoral thesis, Wuppertal 1999; ISBN 3-9807531-0-7

8) DIN ISO 2859-1, "Sampling procedures for inspection by attributes - Part 1. Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection"; identical with ISO 2859-1:1989; status:1993-04

9) DIN EN 420, "General standards for gloves"; status 1994-06

10) Laidlaw, J. L. et al.: Permeability of latex and polyvinyl chloride gloves to twenty antineoplasic drugs, Am J Hosp Pharm 1984; 41:2618-2623

11) Dinter-Heidorn, H. et al.: Comparative study on protective gloves for handling cytotoxic medicines: a model study with carmustine. Pharmaceut Weekblad Scient ed 1992;14(4):180-184

12) Usselmann, B. et al.: Permeability of protective gloves to carmustine solution. In: Radziwill, R. et al. eds. Safe handling of medicines - a challenge for theory and practice, Proceedings of the 22nd European Symposium of Clinical Pharmacy, Heidelberg, 1993; 163-166

13) Mader, R. M. et al.: Permeability of latex membranes to anti-cancer drugs, Int J Pharmaceut 1991; 68:151-156

14) Connor, T. H.: Permeability testing of glove materials for use with cancer chemotherapy drugs. Oncology 1995; 52:256-259

15) Klein M. et al.: Permeation of cytotoxic formulations through swatches from selected medical gloves. Am J Health-Syst Pharm 2003; 60:1006-1011

16) Corlett, S. A. et al.: Permeation of Ifosfamide through gloves and cadaver skin. The Pharmaceutical Journal, Oktober 1991

17) Krammer, B. et al.: Permeability of protective gloves to carmustine solution (Poster). Third European Conference of Cancer Care and Pharmacoepidemiology, Linz (1996)

18) Krammer, B. et al.: *Eignung von hydrogelpolymerinnenbeschichteten Handschuhen für die Zytostatikazubereitung* (Suitability of hydrogel polymer coated gloves for the preparation of cytostatics) (Poster). 26th Scientific Congress, *Bundesverband Deutscher Krankenhausapotheker* (federal association of German hospital pharmacists), Dresden (1996)

19) Klein, M. et al.: Protection offered by selected medical gloves made of either Latex or a synthetic elastomer against exposure to nine cytotoxic agents. European Hospital Pharmacy, 1999, 5(4):152-158

20) Klein, M. et al.: Permeation of five antineoplastic substances through a latex-free glove material. Poster zum ISOPP VI in Washington DC, USA, März 25-29 1998

21) DIN EN 374, *Schutzhandschuhe gegen Chemikalien und Mikroorganismen,Teil 3: Bestimmung des Widerstandes gegen Permeation von Chemikalien* (Protective gloves against chemicals and microorganisms, Part 3: Determination of the resistance against permeation by chemicals); status 1994-04

22) Rau, S. et al. : *Latexfreier OP-Handschuh Biogel Neotech im Permeationstest gegen Zytostatika* (Biogel Neotech latex free surgical glove in the permeation test against cytostatics. Handout to the poster, ADKA Congress, Hannover 14.-17.05.1998

23) The American Society for Testing and Materials. Standard Test Method for Resistance of Protective Clothing Materials to Permeation by Liquids or Gases. Philadelphia: American Society for Testing and Materials. 1985 and 1991. ASTM method F739-85.

24) Gross, E. R. et al.: An Evaluation of nitrile gloves as an alternative to natural rubber latex for handling chemotherapeutic agents. J Oncol Pharm Practice1998; Vol 4, No 3:165-168

25) Klein, M. et al. : *Permeation von Zytostatika der Firma OncoHexal durch Einmal-Schutzhandschuhe* (Permeation of cytostatics from the firm OncoHexal through single-use protective gloves) 2003, in print

26) Bauer, X.: *Struktur und klinische Relevanz des Naturlatex-Hauptallergens Hevein* (Structure and clinical relevance of the main natural latex allergen hevein). Deutsches Ärzteblatt 1997; 94:B-1194-B-1196

27) Senst, B. L. et al.: Latex allergy. Am J Health-Syst Pharm 1997;54:1071-1075

28) Evers, H.-D.: *Latexallergie – Gibt es einen Ausweg?* (Latex allergy - is there a solution?) Deutsche Apothekerzeitung 1998:138;1988-1989

29) Przybilla B. et al.: *Gefährdung durch Naturlatexallergie* (Danger from natural latex allergy), Deutsches Ärzteblatt 1997; 94:B-583-B-585

30) *Latexallergien im Gesundheitswesen* (Latex allergies in the health service), status February 1997, North Rhein- Westphalia regional institute for safety at work, Ulenbergstrasse 127-131, 40225 Düsseldorf

31) *Unfallkasse* (accident insurance provider) Hessen, *Hessische Ausführungsbehörde für Unfallversicherung,* Opernplatz 14, 60313 Frankfurt/M.: *Allergiegefahr durch Latex-Einmalhandschuhe* (Allergy danger from single use latex gloves), GUV 38.9; Stand 1999-10

32) *TRGS* (Technical rules for hazardous substances) 525, 3.6 (4) "Hygienic protective measures at work"; status 1998-05

33) TRGS 540, 4.4 (3) "Sensitising substances", status 2000-02

34) Publication of the new regulations for protection against hazardous substances (*Gefahrstoffverordnung - GefStoffV*); status 2003-05

35) Law for protection against hazardous substances (*Chemikaliengesetz* (chemicals act) - *ChemG*) ; status 2002-06

36) s. 19 (2) and s. 3a *Chemikaliengesetz*

37) s. 16 (1) *Gefahrstoffverordnung*

38) s. 16 (3) *Gefahrstoffverordnung*

39) s. 16 (2) *Gefahrstoffverordnung*

40) s. 16 (3a) *Gefahrstoffverordnung*

41) s. 20 *Gefahrstoffverordnung*

42) Tombrink, A., PTA 1994;8(3):253-254

43) Vaitiekunas, H., 2. *Norddeutscher Zytostatika-Workshop* (North German cytostatics workshop) 1994

44) Hepp, R. et al. : *Untersuchung zur Außenkontamination der Primärverpackungen von Zytostatika* (Investigation of outside contamination of the primary packaging of cytostatics), Krankenhauspharmazie 1998; 19:22-27

45) Pethran, A. et al. : *Wischproben an Arbeitsplätzen mit Zytostatika-Exposition* (Wipe samples at workplaces with exposure to cytostatics), Krankenhauspharmazie 2001; 22:11-15

46) Connor, T. H. : Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. Am J Health-Syst Pharm 1999; 59:2450-2453

47) DIN 58953-7, "Sterilisation - provision of sterile materials - Part 7: Applied technology for paper bags and hot- and self-sealing see-through bags and tubes of paper and plastic composite film"; status:1999-08

48) *TRGS* 525, 3.5 (5) – "Personal protective equipment"; status 1998-05

49) "Cytostatics directive of the *Länder*", Deutsche Apotheker Zeitung 1998;138:4122-4138

50) Berner International GmbH, "Cytostatic protective gloves (sterile/non sterile(, inspection according to PPE Directive 89/686/EC, based on DIN EN 374 Part 1-3 tested and certified (latest inspection 2000)

51) Klein, M. et al.: "The cumulative protection provided by a unique double-gloving system", shown at the "4th Congress of the European Association of Hospital Pharmacists" am 17.-19. März 1999 in Nice, France

52) Colligan, S. A. et al.: Permeation of cancer chemotherapeutic drugs through glove materials under static and flexed conditions. Appl Occup Environ Hyg 1990; 5(12):848-852

3.2.3. Respiratory Protection, protective Goggles, Overshoes

In special cases, respiratory protection, protective goggles and overshoes are required to be worn in addition to protective overall/coat and protective gloves in order to avoid exposition and contamination when handling cytostatics. These additional measures are mandatory for tasks such as cleaning the cytostatics hood, when removing cytostatics spills and when replacing the filters of the cytostatics hood.

The respiratory protection to be used is a particle-filtrating half mask according to DIN EN 149.

The protective goggles must offer side protection and are to be worn over any personal aids to vision.

Overshoes must be liquid-repellent and cover the entire foot, if possible.

Gerhard Carstens, Hannover

In the manufacture of cytostatics, respiratory protection for avoiding the risk of inhalation and goggles for eye protection are of minor importance, since in accordance with the applicable guidelines cytostatics must be prepared in a cytostatics hood (see 2.1: Rooms and equipment).

For cleaning work in the safety hood exceeding mere wiping of the workplace surface, for removal of accidental contaminations outside the hood and for exchanging the filters of a safety hood, protective goggles with side protection and a respiratory mask of at least class P2 [1] must be worn in addition to a liquid-repellent coat and protective gloves. When removing unintended contaminations produced during manufacture or application of cytostatics, wearing overshoes is also mandatory (see 4.2 Measures in case of unintended

release of cytostatics) [2]. The employer is obliged to instruct the employees in the safety-compliant use of the personal protective equipment and arrange training courses and provide information material as required [3].

Particle-filtrating half masks

In accordance with DIN EN 149, particle-filtrating half masks can be assigned to one of the classes FFP1, FFP2 and FFP3. A particle-filtrating half mask is a complete respiratory protection device consisting partly or wholly of the filter material [1]. According to DIN EN 143, the filter materials are assigned to one of 3 classes according to their separation capacities: P1 – low separation capacity, P2 – intermediate separation capacity, P3 – high separation capacity. They differ in terms of thickness and tightness. Compared to a P3 mask, a P1 mask is markedly thinner, designed to be more loosely fitting and consequently less airtight. P1 masks must not be used when working with cytostatics. For handling cytostatics, P2 are the minimum required. P2 masks may be used for concentrations amounting to up to 10fold the MAC (Maximum Admissible Concentration) value. As there are no MAC values for cytostatics, the decision to use P2 masks in the hazard area for CMR pharmaceuticals was made arbitrarily. The performance of the P3 masks approved for radioactive substances, viruses and enzymes amounts to threefold that of P2 masks.

P2 and P3 masks are available both in «S» (for solids only) and «SL» (for both solids and liquids) versions. The higher the separation capacity of a particle mask, the higher the respiratory resistance, limiting the wearing comfort of the mask. This is one of the decisive criteria in selecting the mask, since a mask which is not worn or which is worn incorrectly increases the risk.

Particle-filtering half masks cover nose, mouth and chin and are comfortable to wear because of the soft fleece inside. The use of high-performance exhalation valves prevents heat accumulation and facilitates breathing.

P2 and P3 masks are attached to the head using belts in such a way that tight fitting is guaranteed. If the straps are adjustable, the construction must guarantee that they cannot shift during use.

For putting on the mask, the manufacturer's instructions are to be observed to guarantee optimally tight fitting. In the case of persons wearing glasses, insufficiently tight fitting at the root of the nose may cause further impairment by misting over of the glasses. The mask must not restrict field of view and sight [4].

Generally, the mask must be changed when respiratory resistance becomes too great. The same applies to exchangeable particle filters in half masks.

Particle-filtering half masks without exchangeable filter are not intended to be cleaned or disinfected [1]. Such masks must not be worn by more than one person, and generally not longer than eight hours. Half masks temporarily taken off must be protected from soiling, moisture and other impairments.

Protective goggles

Protective goggles must conform to the regulations of DIN EN 166 – Personal Eye Protection; Requirements. So-called mask or basket goggles (Korbbrillen) offer very high safety. According to the regulations for the use of eye and face protection, basket goggles are defined as protective goggles with a basket-shaped framework of soft, elastic material, so that the framework encloses the eye area and closely fits the face [5].

Protective goggles must have a degree of optical neutrality allowing more or less subtle precision work and/or tedious work. They must be protected against misting over and allow concomitant use of spectacles or contact lenses [4].

Basket goggles are available from the usual suppliers of laboratory equipment.

Overshoes

Overshoes are required as a part of the protective equipment for removal of cytostatics contaminations [2]. Therefore they must be included into the cleaning kit, also known as «spill kit», to be used for the removal of spills (see 4.2 Measures in case of unintended release of cytostatics).

Single-use overshoes of liquid-tight, lint-free material are available. It is to be contemplated whether to use either simple and cheap overshoes merely pro-

tecting the soles and a part of the upper side of the feet or overboots which are correspondingly more expensive but offer significantly superior protection.

When selecting overshoes for use in the preparation area, the aspect of product protection must also be considered. For preparation under GMP conditions, area shoes over overshoes are indispensable. Here, too, boots offer a higher degree of protection than overshoes do.

References:

1. BGR 190 April 2004

2. TRGS 525: Umgang mit Gefahrstoffen in Einrichtungen zur humanmedizinischen Versorgung Mai 1998, BArBl. Nr. 5/98: 99-105

3. Verordnung über Sicherheit und Gesundheitsschutz bei der Benutzung persönlicher Schutzausrüstungen bei der Arbeit (PSA- Benutzungsverordnung – PSA-BV) Dezember 1996, BGBl. I 1996: 1841

4. Richtlinie des Rates zur Angleichung der Rechtsvorschriften der Mitgliedsstaaten für persönliche Schutzausrüstung (89/686/EWG) September 1996

5. BGR 192 Februar 2006

3.3. Technical Equipment for the Preparation

3.3.1. Technical Equipment for the Preparation of Cytostatics

In order to guarantee a minimum standard of safety during the preparation of cytostatics, suitable technical equipment must be used that complies with the technical rules for hazardous substances TRHS 525 and the brochures of the professional associations. This equipment must meet the requirements of the Law on Medical Devices (MPG). Appropriateness for the special criteria of cytostatics preparation must also be taken into account. All equipment must be sterile or capable of being disinfected before use. The quality of the devices must be regularly inspected. Proper handling and functionality of technical equipment should be trained regularly using placebo substances.

Beate Predel, Tübingen

Ready-to-administer cytostatics preparations are being increasingly prepared by pharmaceutical staff, whether in the pharmacy workroom for ambulant chemotherapy or centrally in a hospital pharmacy. Since most of the preparations are intended for parenteral administration and are prepared aseptically for individual patients, suitable technical equipment must be used. In order to raise the level of personal protection and product integrity (see chapter 1.2 Persons Involved in Preparation and 3.6 Preparation), all employees must be familiar with how the sterile devices function, and this should be explained by means of practical training where necessary.

Technical Equipment

Preparation of cytostatics requires the following technical equipment:

- 3-layer work mat
- compresses and swabs

- single-use syringes
- cannulas
- cyto kit
- container for discarded cannulas
- waste container
- closure caps for single-use syringes
- filter cannula or filter straw
- transfer needles, transfusion cannulas
- mixing adaptors
- Clave® oncology, DivibaX®, PhaSeal®, Securmix®, Tevadaptor®
- pressure release systems, hydrophobic filters, spikes

3-Layer Work Mat (fig. 1)

A work mat prevents the hood from being contaminated if cytostatics are spilled. The mat consists of three layers. The upper layer is liquid-permeable and lint-free, the middle layer is absorbent (e.g. laminate) and can soak up liquids, and the lower layer is impermeable (e.g. polyethylene). Colour labelling of these products facilitates their special use and disposal. A work mat with a smooth surface enables even small ampoules to stand securely. According to brochure M 620 «Safe handling of cytostatics» by the BGW (professional association for the health service and social services) (04/2008) and in accordance with the Technical Rule for Hazardous Substances (TRHS) 525 «Handling hazardous substances in facilities for human medical care», «care must be taken that the airflow situation of the hood is not impaired by the work mat, i.e. the front air slots of the hood must on no account be covered»

The underlay is replaced if it becomes contaminated or at the end of the work period.

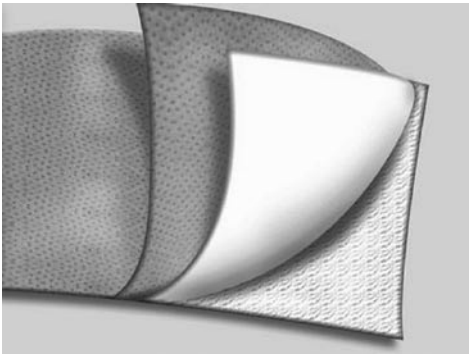


Fig. 1: 3-layer mat

Sterile Compresses and Swabs

In order to prevent contamination caused by the formation of droplets or aerosols, compresses and swabs must be used. Ready-to-administer syringes are carefully and slowly vented using a sterile swab. For microbiological considerations a compress soaked in alcohol is used when opening scored or friable ampoules. The compress also provides protection against injury by cutting.

Single-Use Syringes

Disposable syringes comply with EN ISO 7886-1 «Sterile hypodermic syringes for single use» Part1: Syringes for manual use; Part 2: Syringes for use with power syringe pumps (formerly DIN 13098-2).

The quality of all the materials must meet the requirements of the European pharmacopoeia or ISO 10993-1. The standards for syringes used in the preparation of cytostatics are:

- A clear, appropriate scale which can be easily read. The dosing accuracy must comply with EN ISO 7886. The stated margins of error are maximally 5%, depending on the measured volume and the nominal volume. Luer lock syringes are available in the following sizes: 1, 2, 3 [2,3], 5, 10, 20, 30, 50, 60 and 100 ml [1]. Dosing accuracy is regarded as sufficient if the size of syringe used comes closest to the volume to be measured. According to the recognised rules of pharmacy, the active substance content immediately after preparation should not deviate by more than 5% from the declared amount.
- Luer lock connection (in case of pressure being built up, the syringe cannot detach unintentionally from the cannula).
- Secure and detectable piston stop in order to prevent sudden disconnection.
- Easily moveable piston for safe working (possibly siliconised).
- Piston stop with double sealing ring if possible in order to prevent leakage of solution and to guarantee smooth withdrawal to the maximum volume.

1 www.cardinalhealth.de/alaris, Cardinal Health Germany 318 GmbH; Pascalstraße 2; D- 52499 Baesweiler
2 Z.B. Injekt Luer-Lock; B. Braun Melsungen AG, Sparte Medical Postfach 1120, 34209 Melsungen
3 Z.B. Omnifix® Luer-Lock; B. Braun Melsungen AG, Sparte Medical Postfach 1120, 34209 Melsungen

In the case of two-part syringes[2] the cylinder is made of polypropylene (PP) and the piston rod of polyethylene (PE). Three-part syringes[3] additionally comprise a piston gasket of synthetic rubber (polyisopropene). When preparing cytostatics, care must be taken that solvents or solubilizers do not corrode the rubber. Dark (amber, opaque) syringes and infusion systems must be used for light sensitive substances such as dacarbazine (Fig. 1).

Cannulas (ISO 7846/DIN 13097 Parts 1 – 3)

Cannulas of proven suitability are of stainless V2A steel (iron nickel chromium), with an extremely smooth surface, triple ground and with a finely dosed silicone coating (e.g. polydimethylsiloxane). The diameter and grind of the cannula are crucial for avoiding pieces of rubber being stamped out when inserting the cannula through the septum. In order to avoid stab wounds the protective cap of the cannula must not be replaced (BGW M 620, no recapping).

In order to avoid possible sources of contamination single-use syringes and cannulas should remain connected for disposal (M620).

If a connection must be separated in order to perform the work involved, unprotected cannulas must be unscrewed using a swab and disposed of into a puncture-proof container.

Safe disposal of all contaminated materials is necessary in order to exclude any possibility of danger to third persons. The risk of stab wounds can be reduced by using a syringe block (fig. 3). This is a block with recesses into which the cannula protective cones can be inserted, thus enabling the syringe together with the cannula to be replaced single-handedly from above into the protective cap.

Fig. 3: Syringe block

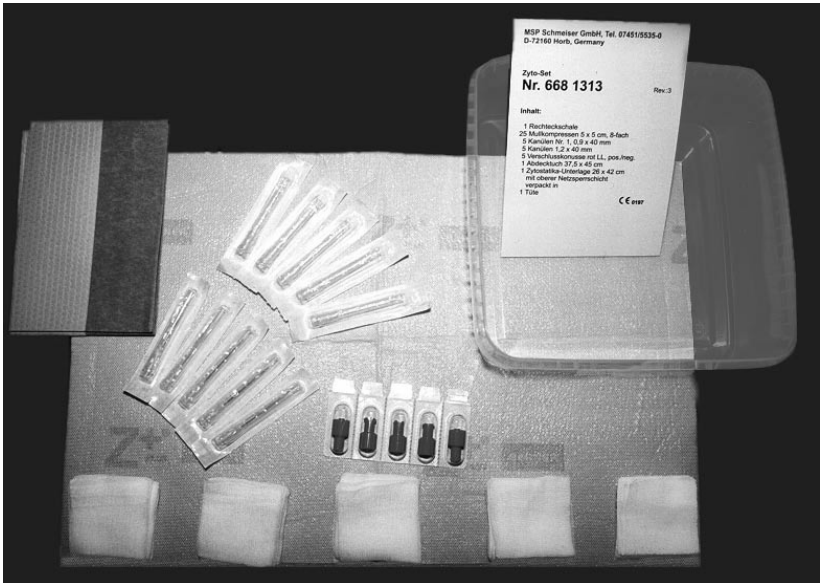


Fig. 4: Cyto Kit

Cyto Kit

The cyto kit contains basic sterile equipment for the daily preparation work. A rectangular dish contains all the items needed, e.g. swabs and compresses, closure caps, cannulas, work mats, suction bags (waste bags with sealing border) etc. The set can be compiled individually (e.g. Cyto Kit Art. 668 2037-01[4]). The entire content is shrink-wrapped into a bag and sterilised by means of ā radiation (fig. 4).

Container for Discarded Cannulas

Since containers for discarded cannulas normally remain in the safety hood for more than one day, they must be puncture-proof, able to be tightly closed and easy to disinfect.

Waste Container

The airflow situation in the hood must not be negatively affected by the waste container, and the size of the container must therefore be chosen carefully.

Slightly contaminated wastes can be collected underneath the safety hood, e.g. in sterile single-use kidney bowls[4]. Heavily contaminated wastes (see chapter 4.1 Disposal of Wastes) must be collected in labelled, sufficiently robust, tightly sealed containers and fed into the disposal process in accordance with the safety measures and in compliance with the legal waste regulations of the respective federal state.

Closure Caps for Single-Use Syringes (Fig. 4b)

Combination stoppers[5] with a double function must be used for closing ready-to-use cytostatics syringes. These consist of polyethylene, have a recessed internal and external luer lock system. Closure caps are produced and type tested according to DIN 58362-S-P.

Filter Needle, Filter Straw with Integrated 5 µm Particle Filter

The use of a filter needle (Sterifix® filter needle – Fig. 5 bottom) or a filter straw[6] (Sterifix® filter straw - Fig. 5 top) is a sensible measure in the case of particle-loaded solutions (e.g. fluorouracil) and with friable ampoules. The 5 µm particle filter is made of nylon, the tube of the filter straw is made of PVC and the filter case of ABS (acrylonitrile butadiene styrene) plastic.

Self-contained System

A self-contained system enables the dry substance or lyophilisate to be dissolved with pressure equalisation and without a risk of aerosol release. A self-contained system consists of a vial containing the cytostatic, an adapter and a container with solvent or infusion solution.

A self-contained system can be built using the following components: mixing adapter, Clave®-Oncology, DivibaX®, PhaSeal®, Securmix®, Tevadaptor®, transfer needles, transfer cannulas.

Fig. 4b: Combination stoppers

4 Zyto-Set Art. Nr. 668 1313, MSP Schmeiser GmbH Siemensstraße 14, 72160 Horb
5 Z.B. Combi-Stopper®; B. Braun Melsungen AG, Sparte Medical Postfach 1120, 34209 Melsungen

Fig. 5: Filter straw above, filter needle below

Mixing Adapter

By using suitable adapters a self-contained system is obtained which is appropriate for the respective carrier solution systems. In this case the solvent is at the same time also the carrier solution. This is forced under pressure from the bag into the vial containing the cytostatic and then shaken. The dissolved cytostatic is returned to the bag as a result of pressure equalisation. Flexible containers for the carrier solution[7] are also suitable for this. Mixing adapters are of limited use for withdrawing partial amounts because dosing may be inaccurate in such cases.

Clave® oncology (Fig. 10)

In combination with Clave® connectors, CHEMOSET systems prevent formation of aerosols and spilling of liquids. Clave® is a microbiologically and mechanically self-contained connector for all ISO-compliant luer slip and luer lock adaptors with a dead volume as low as 0.06 ml and strong counterpressure resistance. It is compatible with blood and lipid products and chemotherapeutics. It is free of latex and metal and can be used for up to 7 days. Clave® offers significant protection for patients from microbial invasion of catheters and reduces infection rates.

6 Z.B. Sterifix® Filterhalm (4,5 cm, 10 cm Schlauch); B. Braun Medical AG, Postfach 1120, 34209 Melsungen
7 Z.B. Glucose 5 Plasco®, B. Braun Melsungen AG, Postfach 1110, 34209 Melsungen

The SPIROS® syringe adaptor is a self-contained male connector for all commercially available syringes, female connectors and luer lock adaptors. The flow-through rate amounts to 126 ml/min. The SPIROS® syringe adaptor may be activated up to 10 times and is compatible with chemotherapeutics. The dead volume amounts to 0.10 ml. The syringe adaptor offers reliable protection when handling high-risk drugs.

Fig. 10: Clave® oncology

This needle-free, self-contained system consisting of Clave® and SPIROS® reduces the risk of needle injury and of contamination during making ready as well as the patient's risk of infection.

For further information please contact kundenservice.de@hospira.com; HOSPIRA Deutschland GmbH, Tel.: +498006646353; Fax: +498006646345, ICUMED.com

DivibaX (fig. 11)

DivibaX offers a new mixing concept with a unique and pioneering design and provides optimal ease of use. For the first time ever, the T piece allows horizontal use of the vial and guarantees 100% reflux safety. DivibaX® is compatible with all 20 mm ISO bottles. DivibaX® is placed upon the infusion bag and pressed down until the blue safety ring snaps into place. The vial with the dry substance to be dissolved is placed into the green ring and turned round clockwise by 180° until it clicks twice. The vial is locked in the adaptor. The yellow safety lock is removed with the thumb. From the infusion bag, liquid is pressed into the dry substance. Here the vial with the dry substance is pointing down-

Fig. 11: DivibaX®

wards and is shaken to dissolve the dry substance. DivibaX® is turned round so that the vial points upwards, and the whole of the drug is transferred to the bag by pumping several times. The green protective cap is now taken off the DivibaX® and pierced using the infu- sion kit. The infusion is now ready for administration. The vial remains fixated within the self-contained system during administration.

DivibaX® guarantees that infusion solution cannot flow back into the vial. The dead volume in the adaptor is 0.3 ml. DivibaX® protects the user from needle injury and minim-izes the risk of aerosol release.

For further information please see www.promens.com/packaging; Email: sales.langeskov@promens.com

PROMENS MEDICAL PACKAGING A/S INDUSTRIVEJG, DK-5550 LANGESKOV Denmark

PhaSeal®

Another self-contained system is PhaSeal® from Sweden. It consists of a protector, injector and connector and is intended for drug bottles with a closure diameter of 14 or 21 mm. Pressure equalisation is achieved by means of an expansion membrane of double-coated polyamide film, which can accept a maximum volume of 50 ml. This is the protector (Fig. 6 right) of PhaSeal® [11], which effectively prevents aerosol release. The luer injector (Fig. 6 top) contains a specially ground encapsulated cannula, which is locked to the syringe and can only be released after unlocking a safety clamp. The connector (Fig. 6 centre) provides a closed connection between syringe/injector and the intravenous access system of the patient.

Securmix®

Securmix® [9] is another self-contained system available in two versions: Securmix® Flasche (bottle) (Fig. 7 right) has a spike with a plastic tube for attaching to bottles with a rim cap maximally 33 mm in diameter, whereas Securmix® Beutel (bag) (Fig. 7 left) consists of a spike with a cannula for attachment to an infusion bag. Securmix® simultaneously connects the drug to be prepared, the necessary solvent and a syringe. It enables the transfer of exact amounts of

Fig. 6:
right protector with expansion membrane, centre connector, top injector

solvent to the drug and vice versa, and venting of the syringe **without** having to disconnect it. The withdrawal of partial amounts is also possible; it should be kept in mind, however, that the device retains a dead-space volume of 0.13 ml. Two 0.2 µm filters separately vent the channel to the drug and the channel to the solution. The main part of the system is made of polycarbonate, the valve is made of polypropylene, the filter housing of PVC and ABS and the filter fabric of acrylic polymer on nylon fleece.

Tevadaptor®

The Tevadaptor system is a self-contained system for safe preparation and administration of cytostatics. Its TOXI-GUARD double filter minimizes the risk of contamination during the preparation. The double filter system prevents impure air from entering the vial and potential aerosols from contaminating the environment.

The Tevadaptor® system consists of a plurality of components. A bottle and syringe adaptor, a connector set, a spike-port adaptor and a luer lock adaptor. The bottle adaptor (20 mm) has a closed septum and in addition to its 0.2 ìm

8 Carmel Pharma ab, Box 5352, SE-40228 Göteborg, Schweden
9 Hersteller: Eurospital S.p.A., Via Flavia 122, I 34147 Trieste, Italia

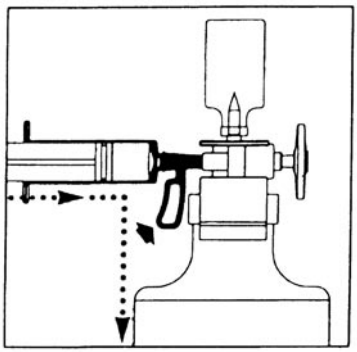


Fig. 7a: Securmix® Flasche (bottle)

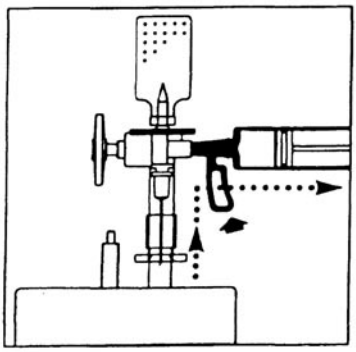


Fig. 7b: Securmix® Beutel (bag)

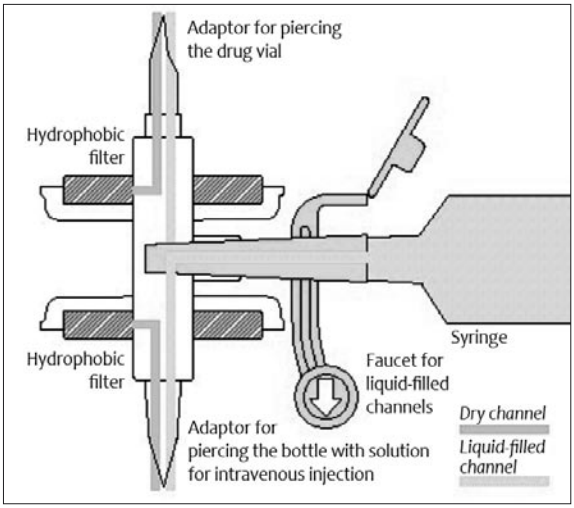


Fig. 7c: technical drawing

filter an additional charcoal filter which can absorb potential aerosols. With the aid of a converter, 13 mm bottles may be used as well.

The syringe adaptor comprises a snap-in mechanism with a protected cannula (19G) with a closed septum (see fig.12d).

Use is straightforward: The bottle adaptor is placed onto the vial, for small bottles the bottle converter is snapped on. The syringe adaptor is connected to the luer

lock syringe, and the infusion bag is pierced with the infusion bag adaptor. The adaptor is closed with a cap and may be used for one working day.

The luer lock adaptor is suitable for bolus injection or for filling pumps. All adaptor components are latex-free and made of ABS plastic (acrylnitrilbutadiene styrene) or DHEP-free (diethylhexyl phtalate) PVC (polyvinyl chloride).

The Tevadaptor® is sterilised by gassing with ETO (ethylene oxide).

Tevadaptor® is a class 1 sterile medical product with a CE-C code (CE0483) and an EAN bar code.

For further information on safe handling please see www.tevadaptor.com or contact info@tevaeu.com

Transfer Set with Plastic Spike, Transfer Needles, Transfer Cannulas

Transfer systems serve to dissolve dry substances by enabling the contents of a solvent bottle to be transferred by gravity into a vial containing the dry substance. The device consists of a two-way cannula or plastic spike with internal pressure equalisation so that no pressure difference arises after removal of the system. According to TRHS, transfer systems are regarded as suitable devices for the preparation of cytostatics, however, only for preparing and emptying drug containers completely. For withdrawing partial amounts the system must be removed from the drug container, and a spike fitted with an appropriate piercing needle must be added. The outside diameter of the plastic spike[10] of approx. 6 mm can be disadvantageous since it may present problems in reclosing the stopper securely (leakiness of the septum).

Selection criteria for transfer systems (M 620 BGW):

- Does the system consist of defined connectors, drug containers, separation elements and an application part?
- Is the system designed for defined application?
- In case of multiple use, are tightness and function maintained?
- Is the system safe against manipulation?

Fig. 12: Tevadaptor®

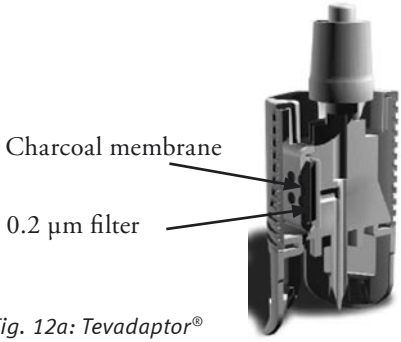
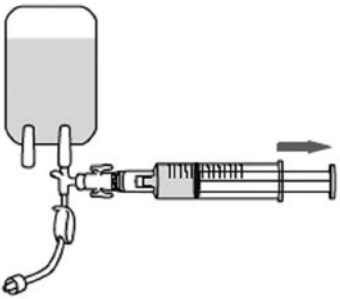
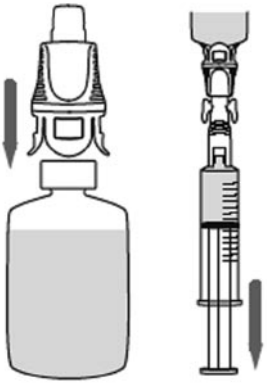


Fig. 12a: Tevadaptor®



b) Connecting syringe and infusion bag



c) Press bottle adaptor onto vial (l.); connect syringe adaptor with solvent bottle (r.)

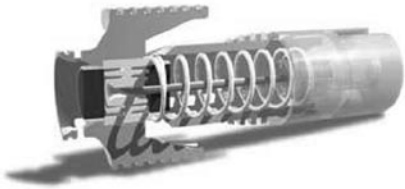


Fig. 12d: Bottle adaptor®

- Are precise operating instructions and approval for a particular drug available?
- Is the manufacturer able to demonstrate practicability by an application study?
- Has a suitable demonstration of the protective effect been furnished?

Pressure Release Systems: Hydrophobic Filters, Spikes

These systems compensate pressure differences which arise during the dissolution process. In the simplest case, a filter cannula [11] (fig. 8) is used with a hydrophobic 0.2 µm filter, which is inserted by piercing through the septum in addition to the injection cannula.

A further possibility for releasing pressure is provided by diverse spike systems, which differ in terms of material, pore size of the filter and thickness and length of the spike. The inflowing air is subjected to sterile filtration. The aerosols potentially formed during the preparation of cytostatics are retained only by a 0.2 µm hydrophobic aerating and venting filter. Thus, the only spikes suitable for the preparation of cytostatics are those with a filter membrane with a pore diameter of 0.2 µm.

Chemoprotect® spikes with integrated hydrophobic 0.2 µm filter and an additional 5 µm liquid filter reliably prevent particle contamination of the solution.

The patented opening and closing mechanism is ideal for frequent administration and obviates the need for a separate closing cap. Dead space amounts to 0.20 ml in Chemoprotect® and 0.28 ml in Chemoprotect®Spike [SWAN].

For further information please contact: www.codan de; CODAN Medizinische Geräte GmbH & Co KG, Grüne Str. 11, D-23738 Lensahn.

The nature of the system means that air bubbles can never be completely avoided during preparation. In the case of conventional spikes, directly injecting back from the syringe into the bottle standing on its head frequently results in leakage of the syringe set because of liquid being forced into the air channel. The Min-

10 Z.B. PPS Transfer-Set; PPS Pharmapack Stute, In der Brückenwiese 4, 53639 Königswinter

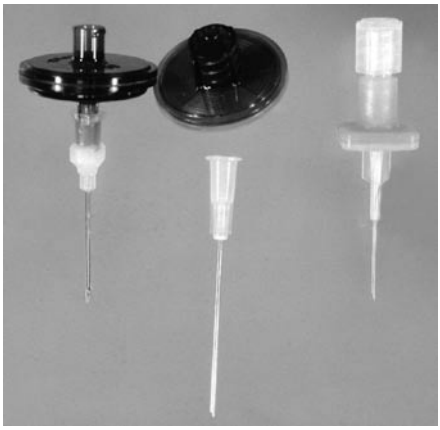


Fig. 8: l. Millex filter cannula, centre hydrophobic filter with separate cannula, r. short filter cannula

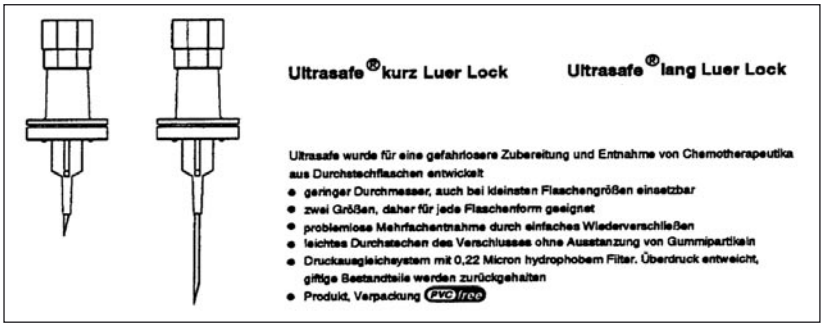


Fig. 8b: Ultrasafe short (l) and long (r.)

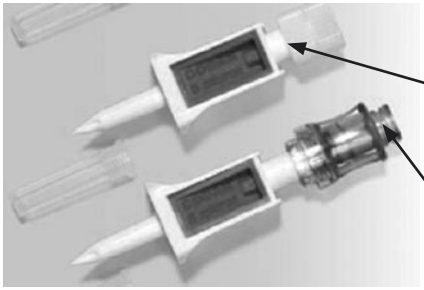


Fig.: Chemoprotect® spikes

Chemoprotect® spike with 0.2 µm filter and additional integrated 5 µm liquid filter

Chemoprotect® spike SWAN

11 Millex®_2, Hauptstraße 87, 65760 Eschborn

iSpike-V-Chemo[4] (Fig. 9b), which has been commercially available since 2002, has the advantage of an integrated valve through which the air bubbles can be easily removed. For the user, this means simple, fast and safe handling.

Regarding materials it must be noted that etoposide may not come into contact with ABS plastic. Filters are made of acrylic copolymers supported by nylon fleece, or of PTFE (polytetrafluoroethylene = Teflon®). These filters are integrated into the spike or mounted on the side. For solutions loaded with particles, a spike with an additional hydrophilic **5 µm particle filter** located in the liquid channel can be used. Spikes are available either with V2A steel cannulas (Fig. 8b[12]) in different lengths and diameters, or with a piercing needle (plastic) (Fig. 9d [13], 9e [14,] which enables faster filling with large volumes but is unsuitable for small bottles.

In the meantime, the Chemo-Mini-Spike Plus® 4 has become available with microtip but without particle filter. The microtip ensures optimal residual emptying of bottles from 3 to 1000 ml. For a spike to be suitable, the diameter of the piercing needle must not impair reclosure of the septum, with the dead-space volume of the spike ideally being as low as possible.

During use, care must be taken that the luer lock negative connection (DIN 13090) of the spike is firmly screwed to the syringe to ensure safe working.

Single piercing with a spike for multiple withdrawal significantly reduces the risk of stamped out pieces of rubber, compared to several piercings with a cannula. The protective cap [e.g. 15] on the spike serves to close the aspiration channel and secures the inside sterility at the same time. For microbiological considerations a limit should be placed on the duration of use. According TRHS 525 pressure release systems must be used during the preparation of cytostatics.

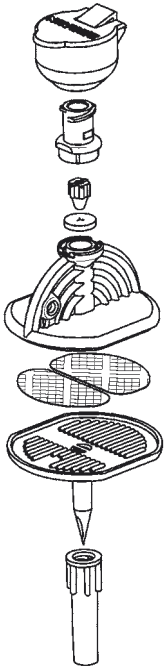


Fig. 9b: Ventilspike Chemo Braun

Fig. 9: Chemospike Braun

Fig. 9c: Extra Spike® AIR SK Chemo

Fig. 9d: Medac spike Chemo

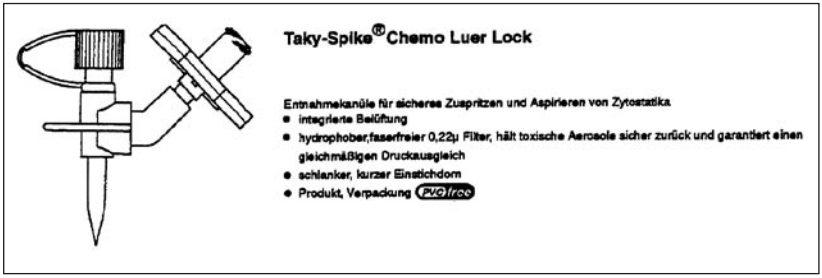


Fig. 9e: Taky spike

Care and Storage

Single-use articles must carry a CE mark and thus meet the requirements of the law on medical devices. Sterile-packaged single-use articles must be stored in dry, dust free rooms and should remain in their original boxes until they are used. The items are kept at a relative humidity of 50 – 60% and a temperature between 10 °C and 25 °C, protected from direct sunlight and moisture. Recommended time limits for the storage of sterile materials for use under normal

aseptic conditions (DIN 58953 Part 7) must be observed and regularly checked. A shorter shelf life may result if the packages are opened. The composite packaging or paper must not be damaged during storage. Outside packaging must not be stored in the sterile area.

Drug-equipment interactions

In order to exclude interactions between drugs and technical equipment, the various materials must be tested individually for their suitability.

The user should always question critically whether the manufacturer can demonstrate the feasibility of his system by an application study, or proof of the protective effect may be furnished using a suitable test method.

All images are reprinted by courtesy of the respective manufacturer.

References

- Barth, J. „Zytostatika-Herstellung in der Apotheke“ 2007, Deutscher Apotheker Verlag, Stuttgart, ISBN 978-3-7692-4433-5
- Baumann, B. „Schutzmaßnahmen beim Umgang mit Zytostatika“ PTA heute, 1999; 11; Nr. 12; S. 1210-1216
- Predel, B.; Barth, J.; Wachsmuth, J. „Zytostatika – Pharmazeutische Grundlagen“ -Materialien für die Weiterbildung, 2003, Deutscher Apotheker Verlag, Stuttgart, ISBN 978-3-7692-3172-4
- „Zytostatika im Gesundheitsdienst“, Informationen zur sicheren Handhabung von Zytostatika, Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege - BGW M 620; 04/2008
- Herstellerangaben der entsprechenden Firmen

12 Z.B. Ultrasafe® kurz (lang) Luer-Lock; Berner International GmbH, Mühlenkamp 6, 25337 Elmshorn
13 Z.B. medac Spike Chemo oder Ultrasafe® medachemo; Vertrieb: Medac Gesellschaft für klinische Spezialgeräte mbH, Fehlandtstraße 3, 20354 Hamburg
14 Z.B. Extra Spike®AIR SK Chemo Chemo; Berner International GmbH, Mühlenkamp 6, 25337 Elmshorn
15 Z.B. Codan Filterspike; CODAN Medizinische Geräte GmbH & Co KG, Postfach 1220, 23735 Lensahn

3.3.1.1. Infusion Pumps for the Administration of Cytostatics

Medical devices may be set up, operated and used only for their intended purpose in accordance with the "law on medical devices" and associated statutory orders, and conforming to accepted technical standards and to working safety and accident prevention legislation.

Thanke Mehrtens, Hannover

1. Types of Infusion Pump

The portable infusion pumps described below are intended for the precise infusion of cytostatics which must be administered slowly and continuously, or in accordance with circadian rhythms, over a period of several hours to days.

Elastomeric pumps

Principle of function: The pump housing contains a balloon of elastic material, which is "pumped up" by being filled with a solution of the cytostatic. The pressure thus generated forces the drug solution out of the balloon and into the infusion tube. The volume delivered is regulated by a flow controller in the infusion tube. Depending on the model, air and particle filters may be integrated in the tube. Because not every pump has an exact level indicator, the end of the infusion can often only be estimated from the level of fluid in the bag. Since every pump has a fixed, pre-set delivery rate (accurate to within +/- 10 - 15 % according to the manufacturer), the duration of the infusion is determined by the filling volume, and the dose of drug by the concentration. In addition, the flow rate is influenced by the temperature (skin or ambient temperature), the viscosity of the solution and the height difference between pump and access (observe manufacturer's instructions). The range of pumps offered by individual manufacturers is wide, so that the right pump can be

chosen for each therapy. Elastomeric pumps may be used only once and must not be refilled or re-sterilised.

Product Examples:
- Easypump (B. Braun / Ribosepharm)
- Intermate / Infusor (Baxter)
- Surefuser (Medac)
- Accufuser (DeltaSelect)

Spring operated infusion pumps

Principle of function: The re-usable infusion pump consists of a housing with an integrated spring drive. The infusion bag (disposable) containing the cytostatic solution is laid in the housing. When the housing is closed, the spring exerts pressure on a plate which, in turn, presses on the infusion bag. The flow rate is regulated by a flow controller in the tube. In addition, air elimination and particle filters are integrated in the tube. A level indicator is provided. The flow rate is influenced by the temperature (skin or ambient temperature), the viscosity of the solution and the height difference between pump and access (observe manufacturer's instructions). The flow rate may deviate from the nominal value by up to +/- 10 %. A wide range of disposable articles with the same filling volume but different delivery rates enables widespread use. Every pump has a serial number and an expiry date. Up to the expiry date, the pump can be used without maintenance and without a safety inspection.

Product Examples:
- Onkoworker (Onkoworks)
- Ultraflow (Fresnius)

Peristaltic pumps

Principle of function: Infusion of the cytostatic solution is controlled by a microprocessor in the head of the battery-driven pump. The solution is placed in disposable material (cassette or bag) which is specific for the pump and which is then connected to it. Different programming possibilities allow continuous, intermittent or circadian infusion, or a bolus administration of one or more solutions. Depending on the manufacturer, different filters are integrated in the disposable material. The pumps are fitted with an alarm function, and frequently

with an electronic memory for monitoring and evaluating the therapeutic data. Safety checks and maintenance tasks must be performed according to the manufacturer's instructions. Infusion accuracy is approx. +/- 5 %.

Product Examples:
- I-Pump (Baxter)
- Multi-Therapie-Infusionspumpe 6060 (Baxter)
- CADD Legacy series (Smiths Medical Deutschland GmbH)
- Graseby Series 9000 (Smiths Medical Deutschland GmbH)
- Melodie Mehrkanalinfusionsspumpe (Logomed)
- Multifuse (B. Braun)
- Pegasus series (Logomed)
- Walkmed 350 (Logomed)

2. Statutory Requirements

The regulations governing the setting up, operation, use and maintenance of medical devices (*Medizinprodukte-Betreiberverordnung, MPBetreibV*) ensure that the medical and technical quality of the medical devices is also maintained for as long as possible after they have been brought into circulation. The regulations consist of 6 sections. In respect of infusion pumps, the first section (area of application and general regulations) and the second section (special regulations for active medical devices) are of relevance. However, not all the pumps described above are subject to the *MPBetriebV* (ask manufacturer). In the following, an attempt will be made to clarify certain parts of the legal text.

General requirements (s. 2 MPBetreibV)

According to the provisions of the *MPBetreibV*, infusion pumps may be set up, operated, used and maintained solely for their intended purpose. This also applies for combinations of different medical devices (pump and single-use material). Thus before buying a particular pump it is important to ascertain whether its intended purpose makes it suitable for the administration of cytostatics and which disposable materials can be used in this case.

Operation and use (s. 2 and 5 MPBetreibV)

Medical devices listed in Appendix 1 to the *MPBetreibV* (e.g. certain types of diffusion pump) must not be put into operation until the manufacturer or

supplier has tested the proper functioning of the device at the location where it will be operated and has given instructions on using the device to a person nominated by the operating authority (s. 5 *MPBetreibV*). All persons using the infusion pump must have the necessary education or skills and practical experience to ensure that they can operate the pump properly, and must also have received instruction in using it from the person nominated by the operating authority. This instruction must be documented.

Before every use of an infusion pump, the respective user must ensure that it is in good condition and functioning properly. Instructions for use, safety information and maintenance instructions must be followed (s. 2 and 5 *MPBetreibV*). The functional description of the pump and the operating instructions must be made available to the user in such a way that they are always accessible (s. 9 *MPBetreibV*). The medical devices book must also be accessible to the user during work time (s. 9 *MPBetreibV*).

Operating authorities are, for example, bodies operating hospitals, owners of medical practices or other in-patient and ambulant health facilities, hospitals or health centres. The operating authority is responsible for ensuring that the relevant provisions of the law on medical devices and the *MPBetreibV* are implemented properly. It creates the organisational requirements for the implementation of the provisions and, within the scope of its organisational authority, is responsible for ensuring that the medical devices are used according to their intended purpose and for the initiation, implementation and monitoring of all mandatory administrative and technical measures, e.g. maintaining inventories, creating the medical devices books and ordering the safety inspections to be carried out.

Before a medical product may be put into operation, the "person nominated by the operating authority" must be instructed in the proper handling, use and operation of the medical product. Only this person may then instruct the users in the proper use of the medical product.

Users are all persons who use the medical product in the course of their work.

Reporting incidents (s. 3 MPBetreibV)

The operating authority or user must immediately report to the *BfArM* (federal institute for medicines and medical devices) any malfunction, any change in the characteristics or performance and any error in the labelling or instructions for use of a medical product which has or could have led to the death or serious deterioration in the health of a patient, an employee or a third party. The *BfArM* passes the report on without delay to the authority responsible for the operating authority and also informs the manufacturer and the authority responsible for the manufacturer.

All users should be appropriately instructed as to whom they can contact in the event of incidents of this kind. The official "Forms for the mandatory reporting of incidents / near-incidents" should also be available there. Such forms are obtainable from the *BfArM* (Bundesinstitut für Arzneimittel und Medizinprodukte, Geschäftsstelle Medizinprodukte, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Tel.: 0228 207-5385, Fax: 0228 207-5300, www.bfarm.de) and the *DIMDI* (Deutsches Institut für medizinische Dokumentation und Information, Weisshausstrasse 36-38a, 50676 Köln, Tel.: 0221 4724-1 or Fax: 0221 4724-444, wsww.dimdi.de).

Maintenance and safety inspections (s. 4 & 6 MPBetreibV)

The statutory requirements of Section 4 and 6 must be observed (which person with which qualifications is permitted to perform which tasks).

The service work (maintenance, including inspection, repair and preparation) and the safety checks to be performed are listed in the instructions for use of the medical product and any enclosed information relating to safety. The intervals at which specific tasks must be performed are also listed here. If this information is missing, contact must be made with the manufacturer or a qualified person with appropriate knowledge. In addition to the time limits for performing safety inspections, the operating authority must also comply with the inspection time limits for the corresponding accident prevention rules (insofar as the requirements are not integrated in the safety inspections) and with the time limits for any calibration checks.

Safety inspections are not mandatory for all infusion pumps. Nonetheless, every pump should be subjected to a regular inspection in accordance with specified criteria in order to ensure timely detection of deficiencies which could endanger patients, employees or third parties. The kinds of inspection and the results must be documented.

Medical devices book (s. 7 MPBetreibV) and inventory (s. 8 MPBetreibV)

For infusion pumps listed in Appendix 1 to the *MPBetreibV*, a medical devices book must be kept and used to record information for identification of the medical product, instructions, safety inspections, malfunctions and reports to the authorities. In addition, the operating authority must maintain an inventory for all active non-implantable medical devices at the respective location, which is used to record information for identification of the medical product, organisational allocations and time limits for safety inspections. The responsible authority can release the operating authority from the duty to maintain an inventory, or from the duty to record specific medical devices in the inventory, if the operating authority can adequately justify this.

The law does not specify which department should maintain these records. An agreement in the hospital with the medical technology department is a reasonable solution.

Keeping of the instructions for use and the medical product books (s. 9 MPBetreibV)

The instructions for use and the information enclosed with the medical product must be kept such that necessary information about the medical product is accessible to the user at all times. The medical devices book must be kept such that the information is accessible to the user during work time. After the medical product has been withdrawn from service, the medical product book must be kept for a further 5 years.

Medical product book and inventory must be shown to the responsible authority on demand.

3. Practical Notes

If it is intended to acquire diffusion pumps for the in-patient sector, prior agreement between the pharmacy and the medical technology department is always useful. Normally, the provisions of the *MPBetreibV* for all the medical technical equipment in the hospital will be implemented by the medical technology department. However, if the pumps (and not just the infusion bags) are filled, issued, emptied, possibly checked for faults and stored in the pharmacy, and if the oncologically involved pharmacist must also instruct the patient on how to use the pump - in the sense of patient-oriented clinical pharmacy -, agreements must be reached about how the *MPBetreibV* should be implemented and these agreements must be documented.

Purchase of the pumps

The following checklist should be gone through when purchasing pumps:

- Does the product meet the requirements of the *MPG*?
- Does the intended purpose of the product conform with its intended use?
- Is the medical product suitable for the intended use in respect of the safety of patients, employees and third parties?
- Is the medical product approved for any intended combination with a different medical product (accessories)?
- Must a medical devices book be created?
- Are safety or calibration inspections necessary? Which, and at what time limits?
- Who will carry out the inspections (in-house technical staff / outside firm)?
- What follow-up costs may be expected?

Instruction

The personnel engaged in cytostatics preparation must receive instruction at regular intervals (see also Chapter 1.3 “Working Rules and Instruction” and Chapter 1.6 “Qualification of the Personnel”). Insofar as this is not already

specified by the *MPBetriebV*, exactly who instructs users and patients and provides them with the necessary written information will depend on how the in-house tasks are allocated.

Preparation procedure

A preparation procedure must be defined for filling the pumps. This must include all the items listed in Chapter 3.6 "Preparation". The respective manufacturer's information on filling (and programming if applicable) must be followed. Any dead-space volume must be taken into account when filling the reservoirs. The preparation procedure must also specify whether the overfilling has already been allowed for in the computer calculation of the filling volume, or whether this overfilling must be calculated in addition by the person carrying out the preparation. Working procedures must be strictly aseptic.

Label

If overfilling is carried out for reasons of the dead-space volume, only the actual administered amount of the cytostatic (i.e. the amount prescribed) must be written on the label.

Delivery of the pumps

Since the breakage security of drug reservoirs for portable infusion pumps is subject to high standards, there is no need for sealing in film. This also applies for spring driven pumps if the infusion bag is delivered in the pump. Some manufacturers recommend packaging the pump in liquid-tight snap-fit bags before these are packed in the bags. Delivery takes place as described in the corresponding chapters 4.5, 4.6 or 4.7.

Waste disposal

The single-use material is disposed of as described in the section "Waste Disposal". Unusually high residual volumes must be documented and the causes determined and remedied (malfunction or wrong use).

References:

1. Law on medical devices (*Medizinproduktegesetz - MPG*) of 2 Aug. 1994

2. First law on amendment of the law on medical devices (1. *MPG-ÄndG*) of 1 Aug. 1998

3. Second law on amendment of the law on medical devices (1. *MPG-ÄndG*) of 1 Aug. 1998

4. Regulations on the setting up, operation and use of medical devices (*Medizinprodukte-Betreiberverordnung - MPBetreibV*) of 29 Jun. 1998

5. Amendment to the *MPBetriebV* of 13 Dec. 2001

6. Product descriptions from the manufacturer

7. AMD Medizintechnik (publisher): *Anwender- und Betreiberpflichten für Medizinprodukte* ("Duties of users and operating authorities for medical devices"), MediVision GmbH, Berchtesgadener Str. 26, 10825 Berlin; IssN 1433-3414

List of Manufacturers

1. Baxter Deutschland GmbH, Bereich Therapiesysteme, Edisonstr. 3-4, 85716 München-Unterschleissheim, Tel: 089 31701-0, Fax: 089 31701-177, www.baxter.de

2. B. Braun Melsungen AG, Carl-Braun-Straße 1, 34212 Melsungen, Tel.: 05661 71-0, Fax: 05661 71-4567, www.bbraun.de

3. Fresenius Kabi Deutschland GmbH, 61346 Bad Homburg Tel.: 06172 686-8135, Fax: 06172 686-5546, www.fresenius.de

4. DeltaSelect GmbH, Hermann-Burkhardt-Straße 3, 72793 Pfullingen, Tel.: 07121-9921-0, Fax: 07121-9921-31, www.accufuser.de

5. Logomed GmbH, Klarenplatz 11, 53578 Windhagen, Tel.: 02645 9531-0, Fax: 02645 9531-31, www.logomed.de

6. medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstraße 6, 22880 Wedel, Tel.: 04103 8006-0, Fax: 04103 8006-100, www.medac.de

7. Onkoworks, Schallbruch 5, 42781 Haan/Rhld., Tel.: 02129-94270, Fax: 02129-942727, www.onkoworks.de

8. ribosepharm GmbH, Berg-am-Laim-Str.127, 81673 München, Tel.: 089-454404, Fax: 089-4544-1130, www.ribosepharm.de

9. Smiths Medical Deutschland GmbH, Hauptstr. 45-47, 85614 Kirchseeon, Tel.: 08091 551-0, Fax: 08091 551-100, www.sims-deutschland.com

3.4. Aseptic Procedures

Aseptic procedures include all the mutually coordinated, necessary steps which – using the best available methods for reducing the number of micro-organisms and the possibility of contamination – contribute to the desired goal, obtaining a sterile product.

3.4.1. Measures for Avoiding Particulate and Microbial Contamination

Detailed planning, preparation and assessment of the entire aseptic production process are of pivotal importance for product quality.

Validation includes evaluation of the entire work process and all aspects of aseptic technique.

Attention is to be paid in particular to:

1. the rooms in respect of cleaning and hygiene

2. the cytostatics safety hood

3. the work materials

4. the starting materials and

5. the aseptic preparation procedure.

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Aseptic technique comprises all the coordinated, necessary procedural steps that lead to a sterile product through utilization of optimal methods to reduce bacteria counts and to avoid contamination.

The maxim under which this section may be gathered is found in the Ph. Eur.: «The aim of aseptic technique is to maintain the sterility of a product assembled from sterilised components.»

To achieve this goal, adequate measures must be taken to prevent particulate and microbial contamination in all production phases.

Basic requirements comprise:

- providing the spatial and technological prerequisites (Chapter 2.1 Rooms and Equipment)
- definition of the persons involved
- analysis of the hygienically relevant processes
- compilation of a cleaning and hygiene plan
- training of staff

The analysis of the hygienically relevant processes should include the items personal protective equipment, hand disinfection, cleaning, and not least, the aseptic working procedure itself. The requirements and characteristics for personal protective equipment are described in Chapter 3.2 (personal protective equipment (PPE)).

All discussed processes must consequently be reflected in an individually adapted hygiene plan which includes the definitions of space, staff and equipment requirements for the respective plants. Adapted to the local situation, the hygiene plan shall comprise such requirements as defined under relevant texts (Ph. Eur., EU GMP Guidelines, DAC section 1.7, PIC/S Guide, TRHS 525, M620, BAK and ADKA guidelines, disinfectant list by the VAH, BGR 230/TRBA 250, ISOPP Standards of Practice). The hygiene plan shall comprise detailed process descriptions.

Especially for larger scale preparations, it may be expedient to define so-called hygiene areas in addition to the clean-room classes with defined maximum values for microbiological contamination and airborne particle numbers as specified in Annex 1 to the EU GMP guidelines. For these areas, locally adapted regimens

have been defined, regulating authorised staff, responsibilities, cleaning agents to be used, cleaning intervals etc. In general, definition of hygiene areas shall be a part of a general hygiene plan for the entire pharmacy.

Cleaning plan

The cleaning plan is an essential part of the hygiene plan. It shall define which persons or groups of persons shall be responsible, and which cleaning measures are to be performed, when, and within which intervals. Moreover, the cleaning plan shall list the types of cleaning agents to be used, where and how to use them, instructions for their dilution, exposure times and effectivity data. The exposure times can be taken from the current up-to-date disinfectant list of the VAH. Diluted disinfectant solutions may be stored only in previously cleaned containers and not for longer periods of time. Filling up partially emptied containers is not permissible. In this context, particular attention must be paid to the development of defined operating procedures. Particular attention is to be paid to potential incompatibilities and possible contamination of the cleaning agents. Alcohols, for example, may contain resistant bacterial spores. Thus, isopropanol 70 % (v/v), for use in the production area, should either be bought as a sterile product or sterilised by filtration through a 0.2 µm filter before use. Filtration of larger volumes in advance for later use is expedient only when properly portioned. NRF 11.27 describes addition of 0.3 % hydrogen peroxide; it is to be kept in mind, however, that sporicidic effects are observed only after very long exposure times.

Materials which release as few particles as possible should be used for cleaning. Single-use products are to be preferred.

All cleaning and disinfection procedures in aseptic preparation areas shall follow detailed descriptions set down in writing. Special importance is assigned to employing skilled persons with an awareness of their responsibility (see Chapter 1.1 Persons handling cytostatics and 1.2 Persons involved in preparation). The cleaning staff should document all cleaning procedures including the date in an appropriate form. All staff should be instructed regularly.

Cleaning/disinfection and decontamination schedule

Safety hood

Before each working session, the safety hood should be cleaned with a detergent and then decontaminated with a suitable agent such as sterile isopropanol. If the safety hood has been switched off after termination of work, a sufficiently long lead time has to elapse prior to beginning cleaning and disinfection. The lead time depends on the technical parameters of the hood; in general, 30 minutes are considered to be sufficient. Wipe disinfection shall include all surfaces of the hood and is always performed from top to bottom, beginning at the rear wall in overlapping strips. The work surface of the hood is the last part to be disinfected. The prescribed exposure times of the disinfectant must be observed.

The safety hood should be decontaminated once a week, and additionally, when any visible contamination or major change (shifting, maintenance etc.) is observed. It must be wiped from top to bottom as described, first using a detergent, then a disinfectant. Interspersing a rinsing step with sterile water may be expedient. [1]

The pan beneath the work surface is also to be cleaned at least once a week with the hood in operational mode.

Because of the risk of damage, accessible or exposed filter surfaces (e. g. the HEPA circulation filter above the hood work space) must not be cleaned. Cleaning of the HEPA filter cover at the interior top side of the working area is a controversial issue. There are no objections, however, to careful cleaning of upstream or downstream guards (e. g. laminators and covers) by wipe disinfection. Because of the structure, attention is to be paid to keeping mechanical stress low during cleaning. Wetting of the filter material is to be avoided since it affects filter integrity and thus filter performance. Here the normative requirements of DIN 12980 (2005) prescribe that «all HEPA filters must be protected from mechanical damage» and that «HEPA filters below, e. g., segmented or perforated work surfaces must be protected from direct absorption of spilled or dripping liquids» (sections 9.3.1 and 9.5.1, respectively).

To date, there is no general consensus with regard to the necessity of a periodic change in disinfectants either. So far, the notion that change might prevent formation of resistance has not been supported in studies [2, 3]. There is reason to believe that reported microbial resistances are more probably caused by incorrect use of disinfectants [4]. Thus, a disinfectant need not be replaced unless problems occur. In any case, the cause of the problem should be investigated.

Most conventional disinfectants are ineffective against bacterial spores. Thus, regular use of a sporicide disinfectant is mandatory. Such sporicides are comparatively more toxic and often corrosive as well. Thus, the ISOPP standard e. g. does not recommend sporicides for everyday routine [1].

Preparation area

All work surfaces are cleaned daily followed by wipe disinfection, the procedures being the same as for the cleaning of the safety hoods. Storage cabinets or shelves and other surfaces accessible for wiping should be cleared for cleaning and disinfection at least once a week. It is recommended to decontaminate with a detergent and then disinfect the external surfaces of the safety hood once a week as well. The preparation area floors must be cleaned and disinfected daily by trained staff. Ceilings and walls should be subjected to a suitable cleaning and disinfection procedure according to the local situation at least once a month.

Cleaning should always start at the hood, progressing towards the locks. The general rules for the use of detergents and disinfectants as described above should be complied with. During their selection, attention should also be paid to compatibility, effectiveness and possible residues.

Hygiene plan for materials

Packaged materials will always be carriers of germs and particles. Separate introduction into the preparation area through material locks is desirable (see Chapter 2.1 Rooms and Equipment). Before introduction, tertiary (cardboard boxes etc.) and, if possible, also secondary packaging materials (foils etc.) should be removed. Storage in the preparation area is discouraged.

The term «materials» is used here to include all sterile single-use articles (syringes, cannulas, spikes, swabs, work mats and gloves) as well as any other working materials such as cytostatics vials, reconstitution buffers and carrier solutions which must be introduced into the safety hood.

Step: Introduction

The materials directly required for preparation (syringes, cannulas, spikes) are introduced into the safety hood directly from their secondary packages («peel package») without them getting into contact with non-sterile hands or other non-sterile objects. Since the packaging of single-use articles may increase particle import and hence the risk of contamination, they should not be entered into class A clean-rooms.

The exact «throwing in» technique is diversely judged. One method is to tear open the packaging directly in front of the air curtain and to «throw» the contents into the hood upon a sterile mat without touching them. Others favour assisted introduction of the opened package from which the preparing staff then withdraw the contents. The second approach is much easier to implement in particular with large volumes of carrier solutions or with infusion bags with fixed secondary packaging. In any case, the introduction of objects causes a disturbance of laminar air flow and should be kept as low as possible. It is also not clear how quickly laminar air flow is re-established.

Other materials such as swabs and absorbent mats are introduced into the hood as described above. For reasons of workplace safety (to prevent spread of contamination), swabs may be used only once. The work mat is the surface used most frequently during preparation. In case of visible contamination, the mat must be replaced immediately. [5, 6]

The term «starting materials» refers to the preparation's components, the cytostatics vials, solvent bottles and carrier solutions (in glass bottles or other containers without sterile packaging) that have to be introduced into the safety hood. Carrier solutions with sterile packaging are likewise «thrown in» or introduced as described above. All other non-sterile starting materials are disinfected before introduction.

Currently available disinfection methods for the starting materials comprise spraying or wiping with disinfectant solutions, or immersion therein. Because of rapid evaporation, it is questionable whether after spraying or wiping with a disinfectant solution a sufficient exposure time is guaranteed. A study has shown that wipe disinfection of stoppers is a suitable disinfection method only for low germ numbers [7]. According to the manufacturer's specifications, certain plastic vials are sterile under the tear flap and do not require disinfection. [8]

A suggested method for disinfection of a vial is to use an immersion bath. However, this method poses a potential risk of contamination by cytostatics residues that are washed off the outside of the vial and then remain in the immersion liquid. Moreover, this procedure is not a recognized method.

In order to ascertain which of the methods named above are suitable and expedient for the prevention of contamination, further studies are necessary. Currently, it must be concluded that immersion, wiping and spraying procedures alike have disadvantages. Moreover the question is sometimes raised whether disinfection before introduction of the starting materials is needed at all. However, several publications have demonstrated the importance of a preceding disinfection step [9, 10]. There is general agreement that drug particles adhering to cytostatics vials can generally be removed only by mechanical decontamination.

As a rule, because of the risk of spreading contamination, the introducing staff must be instructed to regularly change their gloves. Like other relevant texts, the current ISOPP standards recommend the changing of gloves every 30 minutes.

Using leftovers

The use of leftover cytostatics solutions, i.e. vials containing residues of agents, is an essential economic factor in central cytostatics production and waste minimization. However, the utilisation of leftover solution poses high demands on validation. In case cooled storage is prescribed, the cytostatics vials are withdrawn from the sterile area of the hood and taken to an environment of a lower clean-room class. The guideline of the German Association of Pharmacists

(BAK) assigns a manufacturing procedure that includes utilisation of leftover solution to risk class 3, high risk [11].

The issue of suitable sealing of these vials is still controversial. The following approaches are followed:

- Spikes are removed, and the cytostatics vials are sealed within the hood using sterile adhesive tape.
- Spikes are sealed (with sterile adhesive tape) and left in the cytostatics vials.
- Cannulas are extracted prior to storage; upon reutilisation, the vials are pierced again.

For safety reasons, when withdrawing cannulas or spikes prior to storage, maximum caution is advised, because of the risk of aerosol formation. According to TRHS 252, formation of aerosols must be avoided [6]. The danger of bacterial contamination when leaving the spike in place is sometimes considered as being greater than the danger of inadvertent release of cytostatics.

In a paper describing the disinfection of hands and work surfaces, the authors found that injection vials with the cannulas left in place, whether covered or not, were more liable to contamination than vials where sampling was done by using withdrawing cannulas or by inserting a new cannula each time. However, this work was not performed under clean-room conditions [12]. The tightness of chlorobutyl or bromobutyl rubber stoppers, once they have been pierced, has not been fully studied so far.

The question which disinfection method might be suitable for vials that are introduced into the hood a second time has not been clearly answered either, since one does not know whether or how much of the disinfectant can enter

the vial through the pierced stopper or closure, and what the real consequences of wetting the spike filter may be.

Clearly, utilisation of leftover solutions is a critical point in aseptic manufacture. Microbial contamination has a multiplicative effect.

The shelf lives of leftover solutions are derived from the chemical-physical stability of the individual stock solutions and from the results of microbiological validation of the working steps. The American pharmacopoeia comprises the monograph 797 (USP 797) which has defined new standards and focuses strongly on practical aspects concerning shelf lives. Depending on the preparation procedure, risk classes have been introduced which define the risk of microbiological contamination of aseptically prepared solutions. The lowest risk class, for example, assumes use of sterile pharmaceutical products and single-use materials. Here preparation is supposed to be done with a small number of manipulation steps, usually in a self-contained system. The use of leftover solutions results in a «high risk» classification. Given chemical-physical stability, the shelf lives of the prepared products are determined with regard to the individual risk class and in compliance with the mandatory quality assurance guidelines.

It should be possible to transfer these to leftover stock solutions.

Aseptic preparation work flow

Only the appropriate combination of individual work and organisation steps can guarantee aseptic work. This combination is best achieved by comprehensive hygiene management. From the point of view of hygiene, the work flow may be divided into the processes set-up, actual preparation and clearing-up.

The set-up process comprises several steps such as dressing, defining the scope of the work and providing the materials.

Dressing is essentially defined by workplace safety requirements. The minimum requirements for aseptic work comprise the wearing of sterile gloves which reliably cover the sleeve cuffs of the work coat. Wearing surgical caps reduces particle import and must therefore be mandated. Shoes worn in preparation areas

should be sterilisable and dedicated to use in the clean room only. Overshoes increase particle import into the preparation areas. To reduce particle import, low-particle coats or rather clean-room overalls should be worn.

The necessary single-use articles and starting materials are placed ready in the immediate vicinity of the safety hood. Prior to introduction into the hood, they are disinfected as described above.

Preparation includes introduction of the materials and equipment into the hood and the processes of dissolving, drawing-up, filling and decanting. Sterile materials are thrown or handed into the hood in such a way that contact with non-sterile objects can be excluded.

All dissolving, drawing-up, filling and decanting procedures should be performed according to a scheme. Any unnecessary connections are to be avoided. The syringe adapter should always be connected directly with the counterpart (spike, cannula or other injection aid). Contact with other parts or objects should be avoided.

Hand disinfection

In the hospital, hands with their resident and transient microbial population represent the most frequent source of infections and the most frequent transmission route for germs. Thus hand disinfection is infection prophylaxis and an important measure for preventing contamination, in particular in aseptic technique. Therefore, before entering the clean side of the lock of a clean room and before procedures, such as the preparation of infusion solutions where the risk of contamination is great, hygienic disinfection of the hands is mandatory. This must be done using a CEN-standardized rubbing technique on the dry skin shortly after washing the hands [13].

The disinfected and gloved hands must remain under the hood during the preparation process. Secondary disinfection of gloves may reduce permeation tightness and is therefore to be discouraged for reasons of workplace safety.

Clearing-up includes cleaning the workplace and storing the leftover solutions that are to be re-utilised.

The preparation staff themselves have to clean the workplace after each work period. Suitable cleaning procedures as well as the agents to be used are to be defined in the hygiene plan.

The stainless steel surfaces of the hood can be cleaned using a disinfectant tested according to the «Guidelines for testing chemical disinfectants» and recommended by the VAH (VAH disinfectant list) as described above. A disinfectant recommended by the manufacturer of the hood should be preferred. If an alcoholic disinfectant is used to clean the front pane, it should be sterilised by filtration. Ethanol should be used at a concentration of 80 % (v/v), isopropanol at 70 % (v/v).

Cytostatics leftover vials to be stored in the refrigerator are sealed as described above. Placing them into a closable, sterilised container prior to removing them from the working area of the hood is an idea to avoid classification as «high risk» preparation according to the German Association of Pharmacists (BAK)

guideline and USP 797. Leftovers to be stored at room temperature may remain in a sterilisable container within the hood after the end of work, appropriate light protection should be provided. The expiry dates fixed accordingly in writing are to be complied with.

References

[1] ISOPP Standards of Practice: J Oncol Pharm Pract 2007; 13 Suppl: 1-81

[2] Akers MJ, More C Microbiological monitorig of pharmaceutical cleanrooms: The need for pragmatism, J Adv Appl Contam Control 1998, 1: 23-30

[3] Kopis EM Rotation of disinfectants to combact microbial resistance, CleanRooms 1996, 10: 48-50

[4] Kopis EM Regulators put cleanroom sanitizing agents under the microscope, CleanRooms Supplement 1999

[5] Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege, Zytostatika im Gesundheitsdienst, 04/2008 http://www.bgw-online.de/internet/generator/Inhalt/OnlineInhalt/Medientypen/bgw_20themen/M620__Zytostatika__im__Gesundheitsdienst.html (Dezember 2008)

[6] TRGS 525: Umgang mit Gefahrstoffen in Einrichtungen zur humanmedizinischen Versorgung. Stand: Mai 1998 http://baua.de (Rubrik Themen von A-Z/Gefahrstoffe/TRGS

[7] Semenitz E, Lass-Flörl C, Speer G, Dierich M Mikrobiologisches Monitoring bei der Zytostatika-Zubereitung, Krankenhauspharmazie 2001, 22 [8]: 377-382

[8] B. Braun Melsungen AG. Infusiontherapie-Video online http://streaming.aesculap.de/MediaService/tdi1_dt_256k.asf (Dezember 2008)

[9] Langer U, Krämer I GMP in der Krankenhausapotheke, Krankenhauspharmazie 2000, 21 [3]: 89-99

[10] Baumann, L., Maurer, J., Retrospektive Revalidierung – Der Schlüssel zur mikrobiologischen Validierung der aseptischen Herstellung, Krankenhauspharmazie 2003, 24: 471-479.

[11] Leitlinie der Bundesapothekerkammer und Kommentar zur Leitlinie Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential, Stand 25.11.2008

[12] Alles G, Selenka F Die mikrobielle Kontamination von Durchstichampullen bei mehrfacher Entnahme, Hygiene und Medizin 1989, 14:355-358

[13] Standard-Einreibemethode für die hygienische Händedesinfektion gem. CEN EN 1500 http://www.cen.eu/cennorm/homepage.htm

3.4.2. Aseptic Technique Validation

Cytostatics preparation in a cytostatics hood is an aseptic drug preparation process that must be validated.

The requirements of the Ph. Eur. for parenteralia are to be complied with.

Simulations prepared in lieu of the product are to be tested for the absence of reproduction-competent germs, using appropriate microbiological procedures. A testing plan must be compiled. Number and frequency depend on the possibilities of the individual pharmacy.

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In their guidelines, the authorities, professional associations and organisations demand the validation of pharmaceutical processes that influence product quality, and also qualification of the areas, equipment and devices used.

Validation furnishes documented proof that procedures, processes, work flows or systems fulfil previously defined requirements in practical use. Qualification tests and documents that rooms, devices, equipment and materials serving to implement the processes possess the functions and abilities previously defined, it includes operational qualification as well.

Why microbiological validation?

In Chapter 5.1.1 «Methods for the production of sterile preparations, the Ph. Eur. defines: «Sterility is the absence of viable microorganisms. Sterility of a product cannot be guaranteed by testing; sterility must be guaranteed by using a suitable and validated preparation process.»

With regard to preparation under aseptic conditions, the Ph. Eur defines, also in Chapter 5.1.1., in section «Preparation under aseptic conditions»: «It is the goal

of preparation under aseptic conditions to maintain sterility of a preparation obtained from sterile components […]. In order to maintain sterility during preparation, the following points – among others – must be paid particular attention to: environment, staff, critical surfaces, transfer steps. Validation of the procedure comprises suitable testing of the points listed above.»

Microbiological validation of aseptic procedures is of particular importance because sterilisation in the final container followed by a «test for sterility» is immanently impossible in the individual aseptic preparation of parenteral drugs. Even though «testing for sterility» is basically required for all parenterals, for the preparation of ready-to-administer parenterals it may be replaced with complete validation and continuous monitoring of the preparation environment, which is likewise recognised by the authorities as parametric approval of individually manufactured products. For personalized preparations, parametric approval is permissible even without prior approval of the process. The comment on Ph. Eur. 2.6.1 «Sterility testing» states: «Today the notion that a test for sterility is the only way for the authorities to verify sterility of a sample no longer applies. If there is doubt about the sterility of a product, it is much more informative to examine the manufacturer's process and validation data than to test for sterility.» This wording implies the absolute necessity for comprehensive validation and continuous monitoring of the surroundings to provide adequate security in case of forensic issues relating to the microbiological safety of the aseptic manufacturing process used with parametric approval of the individual preparations.

The following items require characterisation with regard to their microbiological safety:

- Rooms
- Cytostatics safety hood (LAF)
- Staff
- Aseptic working procedures
- Equipment quality
- Quality of the starting materials

Excellent and detailed information on implementation can be found in the EC GMP guideline and the appended Annex 1.

Compliance with these GMP guidelines, in particular when using validated procedures for critical preparation steps, is expressly mandated by the Ph. Eur. for the preparation of sterile pharmaceutical products. Further suggestions are found in the quality assurance guideline «Aseptic preparation and testing of ready-to-administer parenterals with toxic potential» published by the German Association of Pharmacists (*Bundesapothekerkammer*, BAK) and the USP monograph 797 «Pharmaceutical Compounding – Sterile Preparations».

The rooms and their characteristics have already been described in QuaPOS Chapter 2.1 «Rooms and Equipment». Preparation proper is to be performed under a cytostatics hood (see Chapter 2.2 «Ventilation and Air Conditioning Systems»). The hood as a class A clean-room, the surrounding preparation area and the annexed locks and rooms including the ventilation system must be qualified appropriately with regard to particle numbers (for maximum allowable values please see Chapter 2.2). When using a cytostatics hood, in accordance with the EC GMP recommendations, the ventilation of the surrounding preparation area must be designed to fulfil the criteria of a clean-room class B under non-operating conditions. Under no circumstances should this clean-room class B requirement on the immediate surroundings of a cytostatics hood, which is run, by design, with reduced pressure relative to the containing manufacturing area, be ignored. A constellation with the hood as class A clean-room with reduced pressure, by design, relative to the surrounding class C clean-room preparation area in itself already violates two GMP recommendations (see items 33 and 53 in appendix 1 to the EC GMP guidelines).

Whether the threshold values under operating conditions as defined in Chapter 2.2 can be kept during the preparation process depends in particular on the staff and room hygiene, working procedures, quality of the materials entering the area, and air exchange rate. When adapted to the classification according to DIN EN IOS 14644-1, the particle limits for the individual clean-room classes as published in the current appendix 1 to the EC GMP guidelines allow for somewhat more tolerance for qualification than previously applicable limits,

especially for particles with a size of ≥5.0 ìm. GMP clean-room class B now corresponds exactly to ISO class 5 under non-operating conditions, to ISO class 7 according to DIN EN ISO 14644-1 under operating conditions.

During aseptic preparation of cytostatics products for individual patients starting from ready-made pharmaceutical products, the procedure itself barely produces any particles or dusts – in contrast to sterile preparation starting from solids which are transferred openly. The risk that airborne particles may enter the product during this type of manufacture is to be considered as not very critical due to the self-contained system. Almost all routine activities during purely aseptic processing of cytostatics can be assigned to risk classes 1 and 2 (low and medium risk) according to the German Association of Pharmacists guideline. Using cytostatics leftovers which have been stored outside a class A clean-room for more than one hour results in classification as risk class 3 (high risk). Thus, combining risk classification with differing requirements on the preparation area (as in earlier guidelines) is very problematic. The basic classification of cytostatics preparation as low-risk preparation, as it is frequently propagated, is not in keep with valid definitions. **Therefore microbiological validation and monitoring during aseptic preparation is of especially high importance.**

Apart from the method for active collection of airborne germs which should be carried out for qualification purposes upon commissioning, after major changes such as change of the inlet air filters, and at least once a year, the determination of the number of airborne germs using sedimentation plates (CASO agar, Ø 90 mm) is suitable and recommended as a semi-quantitative method for routine monitoring of air quality. To this end, the agar plates, with the lid taken off, are allowed to stand open as described in Annex 1 to the EC GMP guideline and then incubated for 2 – 3 days at 30 – 35 °C. The quality of the disinfection of surfaces and gloves can be controlled using contact plates with a diameter of 55 mm (CASO agar with disinhibitor).

Table 1	Recommended maximum values for microbiological contamination [a] Source: Annex 1 to the EC GMP guideline			
Class	Air sample CFU / m³	Sedimentation plates (Ø 90 mm) CFU / 4 h [b]	contact plates (Ø 55 mm) CFU / plate	Glove imprint (5 fingers) CFU / glove
A	‹ 1	‹ 1	‹ 1	‹ 1
B	10	5	5	5
C	100	50	25	not determined
D	200	100	50	not determined

[a] These are mean values.

[b] Individual sedimentation plates may be exposed for less than 4 hours.

CFU = Colony-Forming Units.

Equipment and Starting Materials

All equipment to be used directly in the preparation area of the cytostatics hood must be either sterile single-use articles or materials that have been sterilized or at least disinfected before introduction into the hood.

As the 2000 paper by Langer & Krämer has shown, waiving of previous disinfection of cytostatics vials or introduction of labels leads to a loss of clean-room class A, in particular at the gloves of the preparing person: «Touching primary packages of ready-made cytostatics products, which have not been disinfected, necessarily lead to microbial contamination of the gloves.» In spite of these findings, for reasons of workplace safety, previous disinfection still is not performed generally, and in view of drug safety (!) non-sterile labels continue to be introduced into the hood. In 2003, Baumann & Maurer showed that disinfection of cytostatics vials may also be compatible with workplace safety, namely by preventing spreading of washed-off cytostatics residues. In order to safely remove potential outer cytostatics contaminations, the vials, placed for disinfection on a sterile compress which in turn has been placed on a previously rolled up waste bag on a tray, are doused with spore-free isopropanol 70%. After an exposure time of 30 seconds, the vials are taken up using another

sterile compress, wiped and handed into the hood to the preparing person. In addition, the preparations are labelled outside the hood. These two measures contribute to compliance with the upper limit of <1 CFU for the average of the 5-finger contact tests during the microbiological qualification and thus to maintain clean room class A in the hood.

Utilisation of leftovers is common practice in cytostatics preparation. However, according to the definitions in the German Association of Pharmacists guideline and the USP monograph 797, this results in classification of the preparation as «high risk» if previously sterile starting materials have been exposed to clean-room conditions inferior to ISO class 5 (clean-room class A) for more than one hour after puncture.

Microbiological validation and close monitoring of the environmental conditions is absolutely mandatory and recommended in case of regular utilisation of leftover solutions.

Considerations concerning type, frequency and scope of microbiological validation

According to the EC GMP guideline and various national guidelines, validation of the aseptic processes must include process simulation with nutrient broths. Routine preparation steps should be simulated as far as possible and comprise all critical consecutive stages. All procedures which are known to occur during aseptic preparation, as well as worst case scenarios, must be reproduced. Primary validation should be done with three subsequent simulation runs. Validation is then repeated in regular intervals, taking into account insights gained in the meantime, and after any significant change in procedures or equipment. Normally, process simulations must be repeated twice a year (according to GMP). WHO and USP define a contamination [microorganism count to particle count] rate of 1 : 1000 for aseptically produced parenterals as the upper permissible limit. Validation of batch-based preparation, customary in industrial production, cannot be applied to individual aseptic preparation of parenterals, since essentially each individual preparation represents a batch of its own. Hence the preparation process as such must be validated. However, for statistical significance, the verification of absence of contamination requires

a very large number of bottling operations (transfer steps). Several standards demand dimensions of 1000 – 3000 nutrient broth bottling operations (transfer steps). Because of the lack of statistical significance, one-time, sporadic or discontinuous validation measures, as they are sometimes practised in pharmacies, do not allow valid statements about the safety of the work flow. With dummy bottling of pure base solutions, practised in many places, contaminations may no longer be detectable at the time of evaluation, since the germs may be killed by starvation. On the other hand, because of the necessary subsequent manipulations, microbiological examination of the dummy bags is associated with a barely estimable risk of contamination. In tests using the membrane filter method according to Ph. Eur., contaminations of up to 1 % caused by the examining laboratory are to be expected, rendering the evaluation of the preparation process itself impossible (0.1 % demanded by the WHO). Direct injection of base solution into growth media – even to media with double concentration – may alter the medium so much that false negatives may occur here as well. In general, during such a procedure – if stipulated at all – only a small number of transfer steps per base solution bottling are performed. Use of base solutions of cytostatics leftovers for validation is strictly disapproved of due to the high number of imponderables and the potential hazard to the testing staff.

The advantage of simulated preparation solely with nutrient broth is that the preparation process can be evaluated in detail. The bags thus prepared can be incubated after filling and handling, and the result can be read out directly (clear = no bacterial growth / turbid = bacterial growth). The need for additional manipulations by third parties (test lab) is thus obviated and the resulting risk of contamination is overcome. The nutrient broth conforms to all specifications of the manufacturer relating to microbial growth, even after all manipulations during preparation simulation with media (see below). Due to the stepwise filling, including the subsequent manipulations, these nutrient broth simulations are test solutions according to the direct filling method (nutrient broth into nutrient broth) which are suitable for «testing for sterility» as defined in Ph. Eur.

As nutrient broth, soybean peptone – casein peptone broth as defined in Ph. Eur. is used. This is a universal medium for the growth of both aerobic bacteria and fungi.

The validation procedure according to the German Association of Pharmacists guideline comment has provided for a person-related competence validation followed by revalidation of the preparation process «if there have been any significant changes, but at least once a year for activities belonging to risk group 1 or 2». For activities of risk group 3 (utilisation of leftovers), revalidation should take place twice a year, in conformance with the GMP recommendation. However, such periodic validation schemes lack daily production filling routines which allow evaluation of the entire production period. The comment on Chapter 5.1.1 of the Ph. Eur. states: «Of course, aseptic conditions must be completely validated. However, validation […] based on bottling of nutrient broth, using the example of several error-free filling operations, only shows that the process is basically mastered. Extrapolation to other process days is possible by analogy only […]. Rather, continuous monitoring of the surroundings must ensure that the aseptic procedures are mastered anew in and during each individual filling process.» Thus, controls should be performed on every production day, and environmental conditions should likewise be controlled continuously. Control of the preparation surroundings only once a term is not enough. Weekly repeated controls comply better with the GMP requirements for aseptic preparation processes, which require «frequent controls, e. g. using sedimentation and contact plates». But how can the validation gap be closed most easily without infinitely increasing the resulting workload?

According to the Pharmaceutics Inspections Convention (PIC), well-established preparation processes may be validated restropectively using collected data from the (more recent) past.

Once qualification of the preparation areas and equipment and primary validation of the preparation process have been performed, this kind of data collection is particularly well suited for revalidation of the cytostatics preparation process, because the prerequisites for evaluation of retrospective data are fulfilled.

«Retrospective microbiological revalidation» might become the key for general performance of microbiological process validation of aseptically manufactured parenterals in pharmacies.

The great advantage of retrospective evaluation of collected microbiological data from nutrient broth simulations made on every production day is that the cumulative effort of a periodic validation carried out on a certain test day is distributed over the whole preparation period and thus amounts to no more than approximately 5 minutes per day. In addition, this fulfils the requirement for checking microbiological safety of preparation on every production day.

«After all, you look right and left every time before you cross a busy street, not only once a year!»

Exemplary preparation simulation with nutrient broth

Simulation of preparation using nutrient broth provides important final information on whether the staff working in a selected preparation environment can reproducibly prepare sterile products following the prescribed working procedures.

When preparing cytostatics, volumes are regularly metered out of vials via spikes, using smaller (e. g. 10 ml) and larger (e. g. 50 ml) syringes. The solutions remain either directly as a bolus in these syringes, or they are injected into other infusion containers (e. g. infusion bags). All these possible handling steps must be copied during simulation of the preparation. The maximum possible number of transfer steps in the given preparation area as well as integration of all critical preparation steps require special attention in the nutrient broth preparation simulation.

For work flow description of a whole preparation simulation with nutrients including all manipulations see Fig. 1.

Under production conditions, five bottles à 100 ml of casein peptone / soybean peptone solution are introduced into the hood and provided with spikes. A 50 ml single-use syringe is used to withdraw 25 ml of the broth through a spike, then a cannula is placed upon the syringe, and the broth is injected through the septum into an empty bag. The cannula is disconnected and parked in

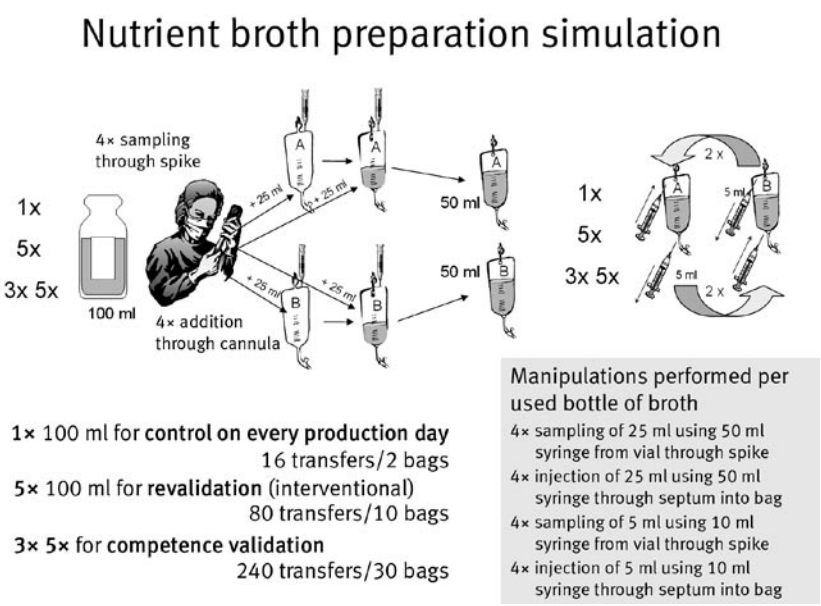

Fig. 1: Nutrient broth preparation simulation

the cannula sheath placed upon a syringe block. Another portion of 25 ml is withdrawn from the broth bottle and injected into the same bag through the septum using a cannula as described above. Using a felt pen, the first bag is labelled «1A» with a mark and date. Using the same 50 ml syringe and the same cannula, the second bag of the bag pair is likewise filled with two portions of 25 ml as described above. This bag is labelled «1B» with a mark and date.

From each of the other four bottles, according to the procedure described above, four further pairs of bags are produced in turn, using fresh 50 ml syringes and cannulas each time. These bags are labelled 2A/2B, 3A/3B, 4A/4B and 5A/5B, respectively. Each bag is labelled with a mark and date.

Each pair of bags (1A/1B to 5A/5B) is subjected to eight further manipulations in turn, using a fresh 10 ml syringe and a fresh cannula each time:

From bag A, 5 ml of broth are withdrawn through the septum and injected into B. The entire procedure is then repeated once again:

Pierce A – withdraw 5 ml – transfer to B – extract cannula from the septum of B – pierce B – withdraw 5 ml – transfer to A – extract cannula from the septum of A.

Microbiological competence validation

After having successfully completed the learning phase and training of the aseptic working procedures, all new staff must perform a simulated preparation with three complete nutrient broth preparation simulations (3 × 5 broth bottles à 100 ml) for initial competence validation (primary validation) purposes. Competence validation also becomes necessary when interventional revalidation (see below) could not be performed successfully. During competence validation, a total of 3 × 80 = 240 transfer steps are performed. The bags are considered as bottling products according to the direct filling method, and they are incubated for at least 14 days. Incubation at 30 – 35 °C is recommended for the detection of bacteria; a temperature of 20 – 25 C is ideal for the growth of fungi. The German Association of Pharmacists guideline recommends incubation at 30 – 35 °C for the full 14 day period. If two temperatures are used for incubation of the broth bottling products, the bags should be incubated for at least 7 days at both temperatures (USP). Subsequently, microbial growth is checked (turbidity). If microbial growth is detected in any bag, the complete competence validation must be repeated all over again. Only successful completion of a complete competence validation (no microbial growth detected in any of the 30 bags) is considered as proof that the preparation process is mastered (Fig. 2). The person concerned shall perform the competence validation at the end of a working day as the introducing worker in aseptic preparation. This procedure ensures that the validation has considered a state of stress including fatigue and impaired concentration.

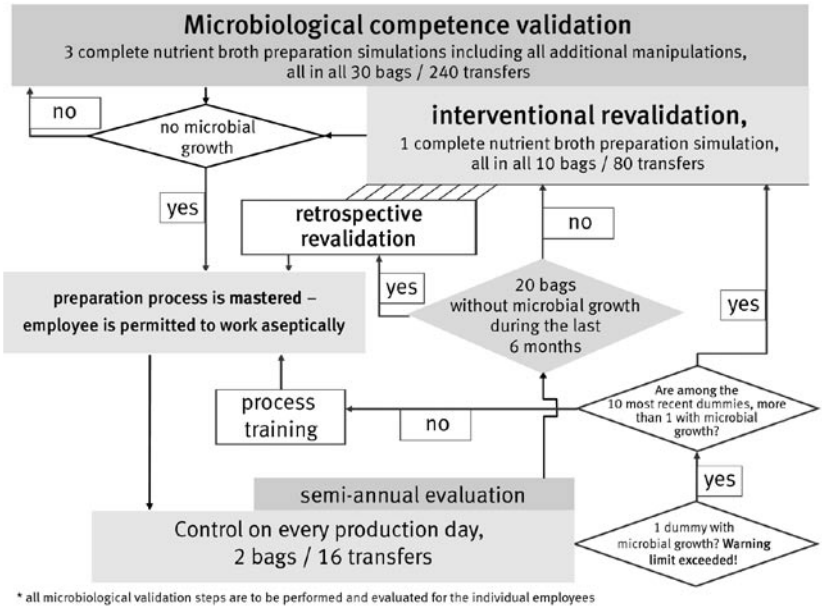

Fig.. 2 Flow chart for microbiological validation of aseptic manufacture

Microbiological revalidation

The preparing staff must regularly furnish proof that working procedures and processes are still mastered and are being performed precisely. To this end, a revalidation is required semi-annually. Reasonable doubts about proper performance of the aseptic preparation process may justify revalidation, in particular when during daily microbial process control or in the 5-finger contact tests the contamination rate increases. This is called *interventional revalidation*. Here the nutrient broth preparation simulation is performed once on five bottles, including all manipulations. If the revalidation is not concluded successfully, competence validation (see above) is mandatory. Just like competence validation, revalidation is performed at the end of a working day in aseptic preparation.

Retrospective microbiological revalidation

Periodic revalidation with nutrient broth preparation simulation may be waived if during the previous six months the persons concerned have produced a total of 10 daily microbiological control bag pairs (i.e. a total of 20 bags) without microbial growth. In this case, the persons are considered as revalidated on the basis of these retrospective data and as having mastered the aseptic preparation process.

However, the interventional revalidation described above may not, under any circumstances, be replaced by retrospective considerations.

If a person has not produced 20 control bags during the previous six months, he/she must undergo interventional revalidation.

Continuous microbiological process control

Microbiological process control consists of a) microbiological preparation control, on every production day, if possible, and b) microbiological monitoring of the surroundings:

a) Daily microbiological preparation control

On every production day, microbiological process control is performed. The procedure corresponds exactly to the nutrient broth preparation simulation including all manipulations, with the exception that only one bottle (100 ml) of nutrient broth is used, from which one pair of bags is made. The bags from daily microbiological control are examined for microbial growth after 14 days of incubation. As the procedure is the same for the daily preparation as for the competence validation and revalidation, conclusions may be drawn relating to the microbial quality of the entire preparation period. A broader data base including as many preparation days as possible thus exists for validation measures. The derived statements on microbiological safety are more reliable. In daily preparation simulation, as in the above example, 2 bags with 8 broth transfers each are produced during six months on each of approximately 125 working days. The amount of approximately 250 bags with a total of 2000 transfers of broth produced per term during each retrospective revalidation is in the statistically required dimension of several standards, thus allowing

«valid evaluation» of the preparation process. Here zero growth should be the goal (cf. EC GMP Annex 1, #69).

The results of the daily controls are continuously evaluated. Microbial growth in one bag (= warning limit) immediately entails process instruction by the preparation management with special focus on the working methods which require special attention from a microbiological point of view as well as troubleshooting. Exceeding the warning limit also entails examination of the 10 control bags most recently produced by the person concerned. There is justified doubt about mastery of the aseptic preparation process if among these 10 most recent control bags microbial growth is demonstrated in at least 1 control bag (= action limit). In this case, additional interventional revalidation becomes mandatory. The person concerned must not be assigned any tasks in aseptic manufacture prior to successful revalidation.

b) Microbiological monitoring of the surroundings

The basic requirement that contaminations in the production setting must be detected is very difficult to fulfil. According to all experience, interference by the staff presents a much higher risk than potential problems in the cleanroom ventilation. Moreover, microorganisms on surfaces remain stationary, whereas airborne germs are usually removed very quickly by air exchange. Thus, determination of CFU numbers on critical surfaces is of much higher importance than determination of air quality, although many guidelines for microbiological monitoring of critical working areas still focus on monitoring of the outflowing air. When planning microbiological monitoring, care should be taken to concomitantly obtain information on routes of contamination.

Microbiological monitoring of the surroundings comprises examination of air (1), surfaces (2) and staff (3) with various respective methods according to a defined sampling plan.

(1) Sedimentation plates of casein peptone / soybean peptone agar (CASO):

The sedimentation plates are placed horizontally on the measurement points defined for this purpose (cf. Fig. 3, in the present example S1 – S6). The expo-

sition time at all points amounts to 4 hours or is commensurate with working time in case of smaller preparation scales.

(2) Examination of surfaces with contact plates of CASO with disinhibitor (for neutralisation of antimicrobially active substances such as disinfectants):

Microbiological monitoring of the surroundings
1st term of 2008 (25 samples per measuring point)

#	Sampling/measuring point	CFO	class
*A1	floor of lock	34	D
*A2	shelf of lock	12	C
*A3	floor next to fridge	0,40	A
*A4	floor beneath window	0,96	A
*A5	window-sill, middle	0,20	A
*A6	floor before hood	0,72	A
*A7	left next to shrink-wrapping device	0,04	A
*A8	materials lock	0,60	A
*A9	preparation trolley	0,20	A
*A10	working surface of hood	0,00	A
A11	coat of person doing the preparation	1,2	B
A12	gloves of person introducing materials	1,2	B
A13	gloves of person doing the preparation	0,00	A
S1	floor area before lock	8,4	C
S2	left next to shrink-wrapping device	1,5	B
S3	working surface of hood, left	0,04	A
S4	working surface of hood, middle	0,00	A
S5	working surface of hood, right	0,16	A
S6	preparation trolley	13,8	C

* Cleaning and disinfection validation

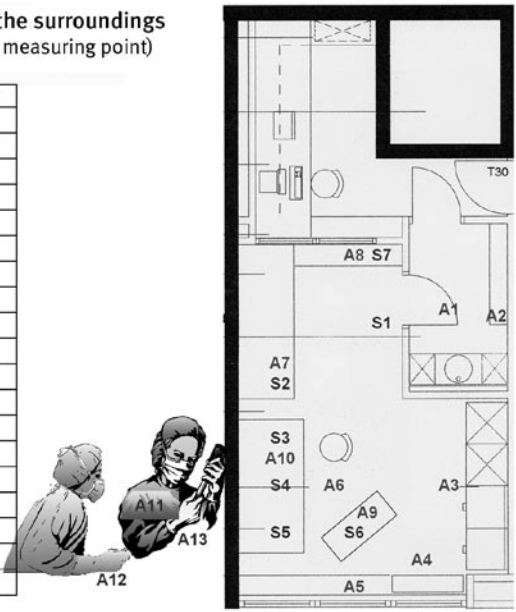

Fig. 3: Microbiological monitoring of the surroundings

Examination of surfaces is done using contact plates at measuring points defined for this purpose (cf. Fig. 3, in the present example A1 – A13). After sampling, the places tested are thoroughly cleaned and disinfected with spore-free isopropanol 70 % and a sterile compress.

(3) Control of staff:

For sampling, the same type of contact plate is used as for the surface checks. Coat sleeves of a preparing employee are principally controlled at the end of a preparation unit (worst conditions) by a contact sample above a glove. Gloves

are «contacted» immediately prior to changing the gloves (generally after 30 minutes) by slightly pressing or rolling the fingertips of all 5 fingers of one hand both of the preparing and the introducing employee onto agar.

The sedimentation and contact plates are incubated at 30 – 35 °C for at least 48 to 72 hours (USP) or in accordance with the instructions by the media manufacturer.

Frequency and scope of the microbiological monitoring of the surroundings

The following tests and frequencies are recommended for monitoring of the surroundings, taking into account previous experience in microbiological validation of aseptic preparation of cytostatics products:

(1) Air control:
→ Count numbers of particles and airborne germs (annually)
→ Sedimentation plates (weekly)

(2) Control of surfaces for validation of cleaning and disinfection:
→ by contact tests (weekly)

(3) Control of staff:
Person introducing the materials:
→ 5-finger glove imprint (weekly)

Person doing the preparation:
→ 5-finger glove imprint (at least weekly; on every production day and of both hands in case germ load frequently exceeds 1 CFU / 5 fingers)
→ contact of a coat sleeve (weekly)

Evaluation of the collected data is done semi-annually to evaluate clean-room quality according to GMP limits. In addition, the values obtained for the term must be subjected to a critical comparison with the data from preceding evaluations.

Each individual measurement, however, should be considered attentively as well. It is recommended to define warning and action limits. For this purpose, the limit values recommended for the clean-room class may be used which at

Table 2: Warning and action limits for consideration of individual values

	Warning and action limits for microbiological contamination					
Class	Sedimentation plates (Ø 90 mm) CFU / 4 h		contact plates (Ø 55 mm) CFU / plate		contact plates (Ø 55 mm) CFU / plate	
	WL	AL	WL	AL	WL	AL
A	1	5	1	5	1	5
B	5	50	5	25	5	25
C	50	100	25	50	not determined	not determined
D	100	200	50	100	not determined	not determined

the same time may also serve as warning limits. For example, the limit value of the immediately inferior clean-room class or repeated or frequent occurrence of values in excess of the warning limit may be defined as action limits. When in individual measurements the warning limit is exceeded, the staff members concerned are informed about this deviation. If the action limits are exceeded, corrective training and error analyses are performed, for example. If these measures do not provide a remedy, the employee concerned must be excluded from preparation until an interventional revalidation has been completed successfully.

In individual aseptic preparation of parenterals, it is mandatory for warning and action limits to relate to individual measurements, since this type of preparation is particularly dominated by intense manual operations by the staff. The warning and action limits may and should be higher than the clean-room values which are compared with the mean values of an entire series of individual measurements (e. g. the average values from the weekly measurements of one term).

Suggestions as made in the most recent edition of the «Wallhäußer» to set the warning limits (WL = 0.5 CFU) and action limits (AL = 0.75) of sedimentation and contact plates as well as of glove imprints below the limit value (LV = <1 CFU) for clean-room class A obviously take mean values into consideration and are thus unsuitable in practice. Is warning or action supposed to be delayed until the mean values for the half-year are obtained, even if higher individual values do occur repeatedly? Moreover, there is the danger that high values obtained from poorly performing individuals or shifts are «averaged out» by the many good results of excellently working staff. For practical application, defining warning and action limits for individual values including steps to be taken in the respective cases is of much more help.

References

1. Baumann, L., Maurer, J., Retrospektive Revalidierung – Der Schlüssel zur mikrobiologischen Validierung der aseptischen Herstellung, Krankenhauspharmazie 2003, **24**: 471-479.

2. Bracher, F. et al., Kommentar zum Europäischen Arzneibuch, Grundwerk mit 29. Aktualisierungslieferung 2008, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart - Govi-Verlag Pharmazeutischer Verlag, Eschborn

3. EG-Leitfaden zur Guten Herstellungspraxis (GMP) Anhang 1, BGBl. I S. 521, 26. März 2008

4. Europäisches Arzneibuch, 5. Ausgabe, Grundwerk 2005 inkl. 8. Nachtrag, 29. Oktober 2007

5. Langer, U., Krämer, I., GMP in der Krankenhausapotheke, Krankenhauspharmazie 2000, **21**: 89ff

6. Kommentar zur BAK-Leitlinie, Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential, Bundesapothekerkammer (BAK), Stand: 25.1.2008

7. M 620, Zytostatika im Gesundheitsdienst, Merkblatt der Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege Hamburg (Hrsg.), Stand: April 2008

8. Schmutz, Chr. W., Zubereitung parenteraler Ernährungsmischungen in der Spitalapotheke – Untersuchungen zur pharmazeutischen Qualität und Stabilität, Dissertation, Pharmakologisches Institut der Universität Bern 1993

9. Seyfarth H., Barnickel H., Validation of Aseptic Filling of Sterile Pharmaceutical Products, Drugs made in Germany 1990, **33**: 58ff

10. United States Pharmacopeia and National Formulary, USP 31 / NF 26 Chapter ‹797› Pharmaceutical Compounding – Sterile Preparations, Rockville, USA 2008

11. United States Pharmacopeia and National Formulary, USP 31 / NF 26 Chapter ‹1116› Microbiological Evaluation of Clean Rooms and other controlled Environments, Rockville, USA 2008

12. Wallhäußer H.-H., Praxis der Sterilisation – Desinfektion – Konservierung, 5. Auflage 1995, Georg Thieme Verlag Stuttgart, New York

13. Wallhäußers „Praxis der Sterilisation, Desinfektion, Aseptik und Konservierung“, 6. Auflage 2008, Georg Thieme Verlag Stuttgart, New York

3.5. Prescription of Ready-to-Administer Cytostatic Solutions

3.5.1. (incl 3.5.2) Prescription Form

Cytostatics are requisitioned by the physician in writing on a prescription form.

The prescription is checked in the pharmacy in accordance with §7 Ordinance on the Operation of Pharmacies (*Apothekenbetriebsordnung*), and the preparation is authorised by the pharmacist responsible.

The prescription must be unambiguous and should include the following information:

- **name and first name and possibly gender of the patient**
- **patient's date of birth and/or admission number**
- **body weight, height and/or body surface area**
- **ward / department / therapeutic unit or section thereof**
- **regimen**
- **cytostatic prescribed (INN)**
- **regular dose and the resulting dosage for the individual patient**
- **dosage adapted according to clinical chemical and pharmacokinetic parameters as target value**
- **correction factor for an indicated dose reduction or dose increase**
- **pharmaceutical form and type**
- **type of carrier solutions**
- **volume of the ready-to-administer solution**
- **required administration time**
- **signature of physician, date.**

Hannelore Kreckel, Gießen, **Dr. Doris Stahl,** Marburg

In accordance with §7 Ordinance on the Operation of Pharmacies, a ready-to-administer cytostatics preparation may be made ready only upon presentation of a written prescription signed by a physician. According to §2 VIII of the Ordinance on the Prescription of Pharmaceutical Products (*Arzneimittelverschreibungsverordnung*, AMVV) a prescription intended for a hospital may be transmitted only via telefax. Within a hospital, electronic data transfer is likewise acceptable if the physician's authentic signature is replaced with a suitable electronic identification procedure (§ 2 VII Ordinance on the Prescription of Pharmaceutical Products).

Prescription data may be transferred online from programs belonging to the ward via an interface to the pharmacy software, or the online transfer of prescription data may already be implemented in the cytostatics preparation programs. In the latter case, the physician will work with a data input module very similar to the module used in the pharmacy. The pharmacy has defined the fields in the input module which must be filled in by the physician to guarantee proper and plausible preparation (name of patient, date of birth, body size and weight, ward name). From these data, body surface and the resulting cytostatics dosage (with the therapy regimen made accessible) are calculated.

The physician will have read-only access to the patients' master data and associated therapies of any patient but no permission to create new master data or change them. After dispatching the prescription, the prescription is sent to the pharmacy and approved by password or deferred for call order.

The minimum data on the prescription form relating to the patient and the individual therapy may be supplemented with further data.

The degree to which these data are copied into the prescription form will depend on whether on the ward the prescription is used as a therapy plan and whether these data are required in the context of pharmaceutical counselling (see chapter 5).

Supplementary information may include:

1. data supplementing the therapy regimen

2. diagnosis, values specific for illness and therapy

3. laboratory parameters

ad 1. Type and designation of therapy regimen

Cycle number

Duration of cytostatics administration

scheduled repetition date if applicable

concomitant medication (type, dosage and duration of administration), e. g.

antiemetic medication

adjuvant medication (analgetics, antidiarrhoics or the like)

pre- and post-purge (type, amount and duration of administration)

These data are required for a plausibility check e. g. with regard to maximum cumulated dosages, always keeping in mind the possibility that the presently competent pharmacy may not know all administered dosages. Likewise, a therapy progression plan may be compiled and made accessible to the therapeutic institution to assist in administration.

A collection of currently used therapy regimens shall be available in the pharmacy. Furthermore, it must be ensured that up-to-date literature on therapy regimens is available.

When the type and volume of the carrier solution have been defined in the therapeutic regimen, they need not be listed on the prescription form. Type and amount of the carrier solution may affect the stability of the drug. Therefore it is recommendable to coordinate this issue with the attending physicians and leave the choice to the discretion of the pharmacy.

ad 2. known secondary diseases, e. g. diabetes mellitus

total medication of the patient

If data on further diseases and on the total medication of the patient are available to the pharmacist, control of the interactions for this particular constellation is possible and reasonable.

ad 3. leukocyte count

thrombocyte count

haemoglobin value

serum creatinine

bilirubin value

GOT

If the laboratory parameters are available to the pharmacist, he/she has the possibility of verifying the plausibility of the prescribed dosage and suggest dosage adaptation if required. This «control function» represents another security aspect, quasi the four-eyes principle in the evaluation of the laboratory parameters. Literature guidelines for dosage reduction should be used for orientation and discussed with the attending physician on the basis of the patient's situation (e. g. curative, palliative).

References:

Schmoll, H.-J.,Höffken, K. Possinger, K. (Hrgs) Kompendium Internistische Onkologie, Teil 1; 2, 3. 4. Auflage. Berlin: Springer-Verlag 2006 ISBN: 978-3-540-20657-6

Senn, H.-J., Drings, P., Glaus, A., Jungi, W.F., Pralle H.B.. Checkliste Onkologie, 5. Aufl. Stuttgart: Thieme Verlag 2001, ISBN 3136855051

Seeber S. Schütte J (Hrgs) Therapiekonzepte Onkologie, Springer Verlag, 5. Auflage 2007

Berger D, Engelhardt R, Mertelsmann R, (Hrgs) Das rote Buch Hämatologie und Internistische Onkologie 3. Auflage 2006, ecomed Medizin, ISBN 978-3-609-51213-6

3.5.3. Cytostatics Dosage in Case of Impaired Renal Function

Cytostatics are drugs with a narrow therapeutic range. An impaired renal function may increase the toxicity of cytostatics and active metabolites through cumulation. Dosage reduction may therefore be necessary for substances which are eliminated renally to a significant extent. The basis for the decision must be the glomerular filtration rate as the parameter of renal function, and the most recent pharmacokinetic and pharmacological knowledge about the cytostatics used.

Tilman Schöning, Heidelberg

Pharmacotherapy always includes knowing about and taking account of the pharmacokinetics and pharmacodynamics of a drug. Since cytostatic agents are drugs with a narrow therapeutic range, reduced elimination associated with higher plasma concentrations may lead to increased toxicity. If the proportion of renal elimination is 30% or more, it may be necessary to adjust the dose. Moreover, some cytostatics themselves cause renal damage, thus increasing the risk still further for patients with an already impaired renal function.

There are certainly still too few pharmacokinetic studies on patients with impaired renal function. Nonetheless, on the basis of general pharmacokinetic and pharmacological principles it may be assumed in the case of moderate to severely impaired renal function (30 - 60 ml/min creatinine clearance) that this will lead to a significant increase in the AUC (area under the plasma concentration - time curve) for a drug with linear pharmacokinetics and 35 - 40% renal elimination [1, 2]. The following recommendations can be derived from known pharmacokinetic, pharmacodynamic and toxicity data:

ALKYLATING CYTOSTATIC AGENTS

N-nitrosourea derivatives

N-nitrosourea derivatives (e.g. carmustine, lomustine, semustine, fotemustine) are metabolised rapidly both enzymatically and non-enzymatically. The metabolites possess cytotoxic activity and are eliminated renally to between 60 and 70 %. Delayed and possibly cumulative bone marrow suppression is the most common dose-limiting factor for nitrosourea derivatives. These cytostatic agents may lead to progressive and irreversible kidney damage. Excretion of the carbomustine metabolites in urine accounts for 30 % of the carmustine dose in 24 hours. 60 - 70 % is detected in the urine as metabolites within 96 hours. In addition to dose adjustment in the case of existing renal impairment, a therapeutic alternative should be considered if the renal impairment is severe.

Bendamustine

Bendamustine is metabolised in the liver to the cytotoxic hydroxy derivative. Both substances are eliminated renally to 50 %. The manufacturer (Ribosepharm) makes recommendations for a GFR < 50 ml/min.

Cyclophosphamide

Cyclophosphamide is excreted via the kidneys but because of the non ionised form of the inactive molecule, tubular re-absorption in the kidney plays an important role. A large proportion of the cyclophosphamide dose is metabolised in the liver. Renal elimination of the intact molecule amounts to 15 % of the creatinine clearance. The more polar, less fat-soluble metabolites are excreted via the kidney to a greater extent. A significantly prolonged retention of active, alkylating metabolites may occur in patients with severe renal insufficiency. Despite this, attempts to demonstrate a connection between severe renal insufficiency and increased myelosuppression have not been successful. The manufacturer (Baxter Oncology) recommends a 50% dose reduction in patients with a GFR < 10 ml/min. [6]

Ifosfamide

Isfosfamide appears to be qualitatively similar to cyclophosphamide. The pharmacokinetics for high bolus doses can be approximately described in terms of a two compartment model; that for fractionated dosage in terms of

a one compartment model. During repeated therapy with 2.4 g/m^2, a plasma half-life of 7 hours was determined with a recovery rate of 73% in the urine. After the single dose the plasma half-life was 15.2 hours. In comparison with cyclophosphamide, of which 90% of the dose is metabolised, ifosfamide is metabolised to only 50%. Large inter-individual differences were observed in pharmacokinetic studies on children. The renal clearance of ifosfamide is approximately double that of cyclophosphamide, i.e. 21.3 compared with 10.7 ml/min after bolus administration and 18.7 compared with 10.7 ml/min for fractionated administration. A prolonged half-life can be expected in the case of overweight patients (> 20% over the ideal weight). This may be connected with an increased distribution volume for such patients. However, the total body clearance for overweight patients was the same at 74 ml/min. Haemorrhagic cystitis is the most marked adverse effect of ifosfamide. Adequate hydration and the administration of sulphhydryl compounds such as mesna (Uromitexan®) reduce this toxicity considerably. The Fanconi syndrome is observed relatively often, especially in children. Patients who have previously been given cisplatin or carboplatin are at greater risk of suffering this side effect. Dose dependent leucopenia is the most important undesirable effect of ifosfamide.

Toxic effects on the CNS may also occur during the therapy. It has been reported that patients with impaired renal function are at greater risk of suffering neurotoxic damage as a result of taking ifosfamide. [7-11]

Melphalan

Melphalan undergoes two-phase elimination with 6 - 8 minutes (α-phase) and 40 - 60 minutes (β-phase). Although the major fraction of the active substance is not eliminated renally, renal elimination still plays an important role. The proportion of melphalan excreted unchanged was 21 - 34%. Bone marrow suppression, which is the most important side effect of melphalan, is higher in patients with renal dysfunction because intravenous administration to such patients leads to an accumulation of the active substance. The dosage should therefore be adjusted for patients with impaired renal function. [12-17]

Dacarbazine

Dacarbazine undergoes microsomal metabolism to 5-aminoimidazole-4-carboxamide and a methyl cation. The substance is excreted renally, 41% unchanged as the inactive parent compound and the rest in the form of metabolites. Hepatic and renal dysfunction lead to a prolonged elimination half-life. A dosage reduction is recommended in the case of impaired renal function. (see Table) [18-20]

PLATINUM COMPLEXES

Carboplatin

Carboplatin is excreted mostly renally. Thus, it has relatively predictable kinetics and can be used in calculated fashion in patients with reduced renal clearance [29, 30]. However, attention is to be paid to myelosuppression, in particular to the thrombocytopenia to be expected, which represents the dosage-limiting side effect of carboplatin. Patient previously subjected to aggressive treatment or with chronic renal insufficiency often exhibit limited haematopoiesis prior to treatment. The molecular mode of action of carboplatin is similar to that of cisplatin. Platinum released from carboplatin has a plasma half life of 90 minutes. The main elimination route of carboplatin is by glomerular filtration and tubular secretion. Only a very small amount, if any, of the active substance is metabolised. Clearance of unbound carboplatin, measured in terms of unbound plasma platinum, is correlated with glomerular filtration. Within 24 hours, 60 – 80% of the administered dosage are eliminated renally. There is a linear correlation between total clearance and AUC of carboplatin and creatinine clearance. Thrombocytopenia is likewise correlated in linear fashion with the AUC of carboplatin. Thus, the dosage of carboplatin is optimally determined in accordance with the AUC to be reached. For AUC-adjusted dosage, Calvert's formula applies [31 – 35]:

Dosage (absolute in mg) = AUC to be reached × (glomerular filtration rate + 25)

AUC to be reached: 2 – 5 in polychemotherapy, 5 – 7 in monotherapy

Cisplatin

30% of the cisplatin is renally eliminated and excreted as free platinum within 24 hours after administration. It displays a 3-phase elimination process with a half-life of 20 minutes in the α-phase, 48 - 70 minutes (β-phase) and 24 hours (δ-phase). The first two phases represent clearance of the free cisplatin and the third phase probably represents the protein bound fraction. 90% of the drug is eliminated renally; less than 10% is excreted via the biliary route. Because of the renal damage it causes, hydration and monitoring of renal function are essential with dose reduction if necessary. [26-28]

Oxaliplatin

Reduced clearance and restriction of the distribution volume has been observed in the case of impaired renal function. In a study involving patients with mild, moderate and severe renal dysfunction, increased toxicity was observed during a monotherapy with oxaliplatin at a creatinine clearance below 20 ml/min. Specialised information therefore contraindicates the use of this substance in patients with severe renal dysfunction (creatinine clearance < 30 ml/min) [48].

ANTIMETABOLITES

Cytarabine

A study showed that serum creatinine values over 1.2 mg/dl were an independent risk factor for the occurrence of neurotoxic symptoms during therapy with high doses of cytarabine. Similar findings were verified in retrospective investigations. Patients with a creatinine clearance below 60 ml/min were especially prone (60-76% of cases) to neurotoxic side effects when treated with high doses of cytarabine. The recommendations in Table 1 apply only for high-dose treatment and not for conventional therapy. [29-33]

Fludarabine

The bone marrow suppressive effect of fludarabine is the dose-limiting side effect of this drug. There is a significant inverse correlation between the granulocyte concentration in the nadir and the AUC of the fludarabine plasma concentration. There is also a correlation between the creatinine clearance and the total clearance for fludarabine. For this reason a dose adjustment is also recommended for this substance in the case of impaired renal function. [34]

Methotrexate

After intravenous administration, methotrexate is distributed over the entire liquid space of the body. Its plasma protein binding is relatively high, amounting to 60 – 70%, and may be affected by other drugs, which may result in a higher portion of free MTX in the plasma. A very large portion of methotrexate is eliminated renally in unmodified form [46] so that limited renal clearance and administration of other drugs excreted via the same route may quickly lead to long-term increases in serum levels followed by severe toxicity reactions [47]. This also applies to accumulation of methotrexate in pathological liquid reservoirs such as ascites effusions or other oedemata. In addition to its nephrotoxicity, methotrexate toxicity is dominated by myelosuppression, mucosal damage and dermatis. During high-dosage therapy in particular, solubility of methotrexate or 7-hydroxy-methotrexate may be exceeded, especially with acid to normal urine pH. This hypothesis is supported by the fact that alkalization of the urine (pH > 7.5) together with sufficient hydration (2.5 – 3 l/m² continuously for 24 hours) suppresses incidence and severity of this side effect. In any case, the patient must possess a sufficient, continuous urine flow. These supportive measures should have begun consequently 12 h before administration of methotrexate and continued until complete elimination. As significant amounts of methotrexate are eliminated renally, in case of limited renal clearance the dosage should be adapted, or other cytostatics should be used if possible [48 – 51].

Pemetrexed

78% of pemetrexed are excreted renally without modification [52]. Protein binding, amounting to 81%, is not affected by impaired renal clearance. Decreasing glomerular filtration rate (GFR) results in reduced plasma and renal clearance of pemetrexed. Patients with a GFR of ≥ 40 ml/min tolerated dosages of 500 mg/m² generally well. However, one patient aged 79 with a GFP of 19 ml/min who had received a dosage of no more than 150 mg/m² died from therapy-related side effects [53]. Moreover, pemetrexed may accumulate in ternary spaces (ascites, effusions). Under these circumstances, use of pemetrexed is not advisable in patients with severely impaired renal clearance.

Pentostatin

Significant amounts of this intravenously administered drug are subject to renal elimination and appear unchanged in the urine. Unfortunately the results of studies published to date are somewhat contradictory. Nonetheless, account should be taken of renal function when setting the dosage. The use of alternatives is especially indicated in the case of severe functional impairment. [39-41]

Raltitrexed

Raltitrexed (Tomudex®) inhibits thymidilate synthetase and is used to treat colorectal carcinoma. In a study on patients with normal and with slight to moderate renal insufficiency (GFR 25-65 ml/min) the AUC and the elimination half-life were doubled. The authors recommend a dose reduction of 50% and prolongation of the interval between doses of 3 to 4 weeks if the GFR lies between 25 and 65 ml/min. If the GFR falls below 25 ml/min raltitrexed should be discontinued. [42]

ANTIBIOTICS WITH CYTOSTATIC ACTIVITY

Bleomycin

Approximately half of the bleomycin administered is excreted renally. A correlation exists between the clearance of bleomycin from plasma and the creatinine clearance. It has been observed that in the case of impaired renal function the plasma half-life of bleomycin is prolonged by a factor of 2.5. If the creatinine clearance is less than 25-35 ml/min, it even increases exponentially. A dose reduction is indicated if the creatinine clearance lies below 40 ml/min. [43-44]

Mitomycin C

Mitomycin C is eliminated renally to less than 20%. Nevertheless, the nephrotoxicity of mitomycin C itself must be taken into account. Thus the possibility of using a different cytostatic agent should be considered for patients with moderate to severe renal dysfunction. The renal function of patients under treatment with mitomycin C should always be monitored on principle.

TOPOISOMERASE INHIBITORS

Etoposide

In the case of this epipodophyllotoxin bone marrow suppression is once again the most prominent adverse affect. If the substance is administered as a continuous infusion, there is a correlation between bone marrow suppression and the plasma concentration in the steady state. Moreover, a correlation exists between the creatinine clearance and the systemic clearance of etoposide. The half-life of etoposide is 7 hours, regardless of the method of administration. Approximately 30% of the dose is eliminated renally. Plasma protein binding in normal patients is very high at 95%. This means a reduced protein binding in patients with lowered serum albumin. The free fraction can fluctuate between 6 and 37%. Because of the above connections between bone marrow toxicity, plasma concentration and systemic and creatinine clearance, the dose should be adjusted appropriately. In addition to the recommendations from Dorr, Sauer gives a formula for calculating the dose [45]:

dose = (standard dose / 2) x [(patient clearance / normal clearance) + 1]

Topotecan

The primary, dosage-limiting toxicity of this topoisomerase I inhibitor is neutropenia. Topotecan is characterised by a lactone ring in balance with a non-active, acyclic organic acid, which balance shifts in favour of the open form under physiological conditions [60]. This is one of the main routes of topotecan clearance. Renal clearance amounts to approx. 30% [61]. In case of moderately to severely impaired renal clearance, topotecan accumulates, potentially necessitating dosage reduction to avoid marked, prolonged neutropenia [62].

References

1. Sauer H: Dosismodifikationen (Dose adjustments) Schmoll HJ, Höffken K, Possinger K. Kompendium Internistische Onkologie (Compendium of oncology for internal medicine) Part 1, 2nd Ed. 1996 Springer-Verlag Berlin Heidelberg New York (ISBN3-540-58370) 14.7 660-74
2. Kintzel PE, Dorr RT. Antitumor Treatment: Anticancer drug renal toxicity and elimination: dosing guidelines for altered function. Cancer Treatment Reviews 1995; 21: 33 - 64

3. Levin VA, Hoffman W, Weinkam RJ. Pharmacokinetics of BCNU in man: a preliminary study of 20 patients. Cancer Treat Rep 1978; 62: 1305-12.

4. DeVita VT, Denham C, Davidson JD, Oliverio VT. The physiologic disposition of the carcinostatic 1, 3-bis (2-chloroethyl)-1-nitrosourea (BCNU) in man and animals. Clin Pharmacol Ther 1967; 8: 566-77

5. Dorr RT, von Hoff DD. Cancer Chemotherapy Handbook,1994, 2nd edition Norwalk, CT, Appleton & Lange Publishers: 270

6. Juma FD, Rogers HJ, Trounce JR. Effect of renal insufficiency on the pharmacokinetics of cyclophosphamide and some of its metabolites. Eur J Pharmacol 1981; 19:443-51

7. Allen LM, Creaven PJ, Nelson, RL . Studies on the human pharmacokinetics of isophosphamide (NSC-109724). Cancer Treat Rep 1976; 60: 451-8.

8. Suarez, A, McDowell H, Niaudet P, Comoy E, Flamant F. Long-term follow-up of ifosfamide renal toxicity in children treated for malignant mesenchymal tumors: an International Society of Pediatric Oncology Report. J Clin Oncol 1991; 9: 2177-82.

9. Pratt CB, Meyer WH, Jenkins JJ, Avery L, McKay CP, Wyatt RJ, Hancock ML. Ifosfamide, Fanconi's syndrome, and rickets. J Clin Oncol; 1991; 9: 1495-9.

10. Moncrieff M, Foot A. Fanconi syndrome after ifosfamide. Cancer Chemother Pharmacol 1989; 23:121-2.

11. Meanwell CA, Blake AE, Kelly KA, Honigsberger L, Blackledge G. Prediction of ifosfamide/mesna associated encephalopathy. Eur J Cancer Clin Oncol 1986; 22:815-9.

12. Cornwell GG 3d, Pajak TF, McIntyre OR, Kochwa S, Dosik H. Influence of renal failure on myelosupressive effects of melphalan: Cancer and Leukemia Group B experience. Cancer Treat Rep 1982; 66: 475-81

13. Reece PA, Hill HS, Green RM, Morris RG, Dale BM, Kotasek D, Sage RE. Renal clearance and protein binding of melphalan in patients with cancer. Cancer Chemother Pharmacol 1988; 22: 348-352.

14. Adair CG, Bridges JM, Desai ZR. Renal function in the elimination of oral melphalan in patients with multiple myeloma. Cancer Chemother Pharmacol 1986; 17: 185-8

15. Albert DS, Chang SY, Chen HS, Moon TE, Evans TL, Furner RL, Himmelstein K, Groos JF. Kinetics of intravenous melphalan. Clin Pharmacol Ther 1979; 26: 73-80.

16. Alberts DS, Chen HS, Benz D, Mason NL. Effect of renal dysfunction in dogs on the disposition and marrow toxicity of melphalan. Br J Cancer 1981; 43: 330-4.

17. Dorr, R T, von Hoff, DD. Cancer Chemotherapy Handbook,1994, 2nd edition Norwalk, CT, Appleton & Lange Publishers; 667

18. Saunders PP, Chao LY. Fate of the ring moiety of 5-(3, 3-dimethyl-1-triazeno) imidazole-4-carboxamide in mammalian cells. Cancer Res 1974; 34: 2464-9.

19. Breithaupt H, Dammann A, Aigner K. Pharmacokinetics of dacarbazine (DTIC) and its metabolite 5-aminoimidazole-4-carboxamide (AIC) following different dose schedules. Cancer Chemother Pharmacol 1982; 9: 103-9

20. Buesa JM. Urrechaga E. Clinical pharmacokinetics of high dose DTIC. Cancer Chemotherap Pharmacol 1991; 28: 475-9

21. Calvert AH, Newell DR, Gumbrall LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judsoni IR, Gore ME, Wiltshaw E. Carboplatin dosage: Prospective evalutation of a simple formula based on renal function. J Clin Oncol 1989; 7: 1748-6.

22. Egorin MJ, van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW, Aisner J. Pharmacokinetics and dosage reduction of cis-diamino (1,1 cyclo-butanedicarboxylato) platinum in patients with impaired renal function. Cancer Res1984; 44: 5432-8.

23. Benett WM, Porter GA. Endogenous creatinine clearance as a clinical measure of glomerular filtration rate. BMJ; 1971 4:84-6

24. Bjornsson TD. Use of serum creatinine concentrations to determine renal function. Clin Pharmacokinet 1979; 4:200-22,

25. Anderson RJ, Gambertoglio JG, Schrier RW. Clinical use of drugs in renal failure Springfield IL, Charles C. Thomas Pub 1976; 15-17.

26. DeConti RC, Toftness BR, Lange RC. Clinical and pharmacological studies with cis diaminedichloroplatinum (II). Cancer Res 1973; 33: 1310-5.

27. van Barneveld PWC, Sleijfer DT, van der Mark TW, Mulder NH, Donker AJM, Meijer S, Schraffordt-Koops H, Sluiter HJ, Peset R. Influence of platinum-induced renal toxicity on bleomycin-induced pulmonary toxicity in patients with disseminated testicular carcinoma. Oncology 1984; 41: 4-7.

28. Reece PA, Stafford I, Russell J, Gill PG. Reduced ability to clear ultrafilterable platinum with repeated courses of cisplatin. J Clin Oncol 1986; 4: 1392-8.

29. Hande KR, Stein RS, McDonough DA, Greco FA, Wolff SN. Effects of high-dose cytarabine. Clin Pharmacol Ther 1982; 31: 669-74.

30. Herzig RH, Lazarus HM, Herzig GP, Coccia FF, Wolff SN. Central nervous system toxicity with high-dose cytosine arabinoside. Semin Oncol 1985; 12: 233-6.

31. Slevin ML, Piall EM, Aherne GW, Harvey VJ, Johnston A, Lister TA. Effect of dose and schedule on pharmacokinetics of high-dose cytosine arabinoside in plasma and cerebrospinal fluid. J Clin Oncol 1983;1: 546-51.

32. Damon LE, Mass R, Linker CA. The association between high-dose cytarabine neurotoxicity and renal insufficiency. J Clin Oncol 1989; 7: 1563-8

33. Hasle H. Cerebral toxicity during cytarabine therapy associated with renal insufficiency. Cancer Chemother Pharmacol 1990; 27: 76-8

34. Hersh MR, Kuhn JG, Phillips JL, Clark G, Ludden TM, von Hoff DD. Pharmacokinetic study of fludarabine phosphate (NSC 312887). Cancer Chemother Pharmacol 1986; 17: 277-80

35. Chabner BA, Young RC. Threshold methotrexate concentration for in vivo inhibition of DNA synthesis in normal and tumorous target tissues. J Clin Invest 1973; 52: 1804-11.

36. Pinedo HM, Chabner BA. Role of drug concentration, duration of exposure and endogenous metabolites in determining methotrexate cytotoxicity. Cancer Treat Rep 1977; 61: 709-15

37. Stoller RG, Hande KR, Jacobs SA, Rosenberg SA, Chabner BA. Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. N Engl J Med 1977; 297: 630-4.

38. Breithaupt H, Kuenzlen E. Pharmacokinetics of methotrexate and 7-hydroxy-methotrexate following infusions of high-dose methotrexate. Cancer Treat Rep 1982; 66: 1733-41

39. Malspeis L, Weinrib AB, Staubus AE, Grever MR, Balcerzak SP, Neidhart JA. Clinical pharmacokinetics of 2'-deoxycoformycin. Cancer Treat Sym 1984; 2: 7-15.

40. Major PP, Agarwal RP, Kufe DW. Clinical pharmacology of deoxycoformycin. Blood 1981; 58: 91-6

41. O'Dwyer,PJ, Wagner B, Leyland Jones B, Wittes RE, Cheson BD, Hoth DF. 2' deoxycoformycin (pentostatin) for lymphoid malignancies. Rational development of a new drug. Ann Intern Med 1988; 108: 733-43

42. Judson I, Maughan T, Beale P, Primose J, Hoskin P, Hanwell J, Berry C, Walker M, Sutcliffe F. Effects of impaired renal function on the pharmacokinetics of raltitrexed (Tomudex ZD1694) Brit J Cancer 1998; 78:1188-93

43. Alberts DS, Chen HSG, Liu R, Himmelstein KJ, Mayersohn M, Perrier D, Gross J, Moon T, Broughton A, Salmon SE. Bleomycin pharmacokinetics in man. I Intravenous administration. Cancer Chemother Pharmacol 1978; 1: 177-81.

44. Evans WE, Yee GC, Crom WR, Pratt CB, Green AA (1982) Clinical pharmacology of bleomycin and cisplatin. Drug Intell Clin Pharm 1982; 16: 448-58

45. Arbuck SG, Douglass HO, Crom WR, Goodwin P, Silk Y, Cooper C, Evans WE. Etoposide pharmacokinetics in patients with normal and abnormal organ function. J Clin Oncol 1986; 4:1690-5

46. Rowinsky EK, Grochow LB, Hendricks CB, Ettinger DS, Forastiere AA, Hurowitz LA, McGuire WP, Sartorius SE, Lubejko BG, Kaufmann SH, Donshower RC. Phase I and pharmacologic study of topotecan: a novel topoisomerase I inhibitor. J Clin Oncol 1992; 19: 647-56

47. Takimoto CH et al. Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a national cancer institute organ dysfunction working group study. J Clin Oncol 2003; 14: 2664-72

Fachinformation (specialised information) Eloxatin®, April 2003

Recommended dose adjustments for renally insufficient patients				
Active substance (INN)	**Reduction to % based on the creatinine clearance of the patients**			
	f	**60 ml/min**	**45 ml/min**	**30 ml/min**
Alkylating agents				
bendamustine	50		75	50(‹10 ml/min)
carmustine	43	80	75	n
lomustine	50	75	70	n
cisplatin	30	75	50	n
carboplatin	66	*	*	*
oxaliplatin				
cyclophosphamide	15			50(‹10 ml/min)
ifosfamide	41	80	75	70
melphalan	34	85	75	70
Antimetabolites				
cytarabine**	80	60	50	n
fludarabine	44	80	75	70
methotrexate	77	65	50	n
pentostatin	65	70	60	n
raltitrexed		50	50	n
Topoisomerase inhibitors				
etoposide	30	85	80	75
topotecan	39	80	75	70
Other				
bleomycin	62	70	60	n
dacarbazine	40	80	75	70
hydroxyurea	35	85	80	75

f = % of the dose excreted as active metabolite or toxic product
n = if possible change over to alternatives
* = dose can be calculated for dosing to desired AUC
** = during high-dose therapy

3.5.3.1. Cytostatics and Dialysis

Tilman Schöning, Heidelberg

If chronic renal insufficiency has reached such an advanced stage that renal excretion fails or is restricted to a minimal residual degree, the kidney function must be replaced by dialysis. In addition, dialysis may be required in the short term in case of acute renal failure or intoxication. Besides the most frequently used haemodialysis process, peritoneal dialysis and haemofiltration may be used but play a minor role in practice. When selecting the approach, the body weight, the amount of excess body water to be removed and the rate of formation of toxic substances in the body must be considered.

Conventional haemodialysis is to be discriminated from the continuous processes which again can be classified into CAVHD (continuous arteriovenous haemodialysis) and CVVHD (continuous venovenous haemodialysis).

Dialysability of drugs is affected by several parameters. On the one hand, it depends on the physical-chemical or pharmacokinetic properties of a substance, on the other hand the type of dialysis, duration of dialysis and blood or dialysate flow rates do have considerable effect on the degree of dialysis. The most important parameters are shown in fig. 1.

For calculating the dosage of drugs it is essential to know the dialysis method. In conventional haemodialysis, dialysable drugs are generally administered after dialysis, whereas in continuous methods the substance loss by dialysis must be known to allow calculation of maintenance dosages, if any should by required. The same applies to conventional haemodialysis after administration of the

drug before or during dialysis [2]. For data relevant for calculating the necessary parameters please refer to the appropriate literature [3]. When calculating the dosage it must not be forgotten that after dialysis a rebound may occur, as it occurs e. g. with ganciclovir. A possible reason for such a rebound is redistribution of the substance from the tissue to the plasma [4].

1. Substance-specific factors

a. Distribution volume (V_d › 2 l/kg not significantly dialysable, V_d ‹ 1 l/kg readily dialysable)
b. Molecular weight (up to a size of 1000 Da without effect, permeable 500 – 5000 Da)
c. Protein binding (substances with protein binding › 80% are generally poorly dialysable)
d. Tissue binding
e. Half-life (substances with a long half-life are generally poorly dialysable)
f. Sterical impediments
g. Water solubility (lipophilic substance tend to be less amenable to dialysis)
h. Plasma clearance of the drug (important if renal elimination exceeds 30%)
i. Type and rate of metabolism

2. Dialysis technology

a. Pore size
b. Pore shape and number
c. Membrane thickness
d. Mechanical deformations
e. Surface, material, thickness and geometry of the membrane
f. Osmotic gradient in peritoneal dialysis

3. Blood and dialysate flow rates

a. Higher blood flow rates accelerate dialysis of small molecules. When blood flow exceeds 300 ml/min, clearance even of small molecules cannot be further increased significantly. In practice, values between 200 and 300 ml/min are aimed at.
b. Higher dialysate flow rates increase the degree of dialysis
c. Flow direction

d. Blood viscosity
e. Thickness of the flowing blood layer
f. Running length of the blood layer

4. Duration of dialysis: The following rules of thumb apply:
a. Minimum dialysis time [min] = body weight [kg] × 4
b. At the end of the dialysis procedure, the urea concentration should be decreased to no more than 37% of the initial value.

Fig. 1: Factors influencing dialysability of substances

When evaluating primary research results, machine type, membrane surface, blood and dialysate flow rates, individual characteristics of the patient and the method for calculation of the dialysis clearance as well as the further factors listed in fig. 1 must be taken into consideration. Variation of dialysis parameters may result in significant differences in the results, which may considerably hamper evaluation of the data. This is not the only reason why therapeutic decisions or dosage recommendations may be made only when the individual situation of the patient is taken into account. Further information on general condition, further organ functions, therapeutic goals and alternatives and pretreatment of the patient are indispensable for making a decision. Evidence for present recommendations is weak, since often only individual studies and case reports are available. Nevertheless, the data presented here should be sufficient as an orientation for the clinical pharmacist in practical consulting.

Bendamustine

About 90% of bendamustine are bound to plasma proteins [5]. It has a relatively high distribution volume and is hence poorly dialysable (approx. 5%). Only some 20% are excreted renally, with the percentage decreasing with deteriorating renal function. Preiss et al. have shown that in renally insufficient patients including patients requiring dialysis but having normal hepatic function there were no significant differences in the pharmacokinetics of bendamustine in

comparison to patients with normal renal function. During two-day treatment with 120 mg/m² each, no therapy-relevant differences in toxicities were found between the two groups. The authors conclude that two-time administration of bendamustine at 120 mg/m² is safe even in patients requiring dialysis as long as hepatic clearance is normal [6].

Busulfane

About 7% of busulfane are bound reversibly, about 32% irreversibly to plasma proteins [7]. Metabolism consists mostly of conjugation with glutathione followed by further oxidation in the liver so that no significant renal elimination of busulfane takes place. Busulfane is readily dialysed [8]. During one-time haemodialysis for 4 hours, clearance of busulfane could be increased by 65%, corresponding to an increase of the daily clearance by 11% [9].

Ballester et al. treated three multiple myeloma patients requiring dialysis with a high dosage regimen of busulfane (4 × 1 mg/kg orally per day for a total of four days) and cyclophosphamide without dosage reduction, followed by autologous stem cell transplantation. Here the patients were dialysed three times a week and showed no particular differences in term of toxicity and response rates when compared to patient with intact kidney function [10].

Carboplatin

Carboplatin is dialysable, but the extent of dialysis depends on the time interval between application and dialysis. Delayed dialysis leads to higher AUC values [11, 12]. Chatelut and Watanabe determined the dosage to be used in dialysis patients using Calvert's formula, setting the GFR to a value of «zero» and defining the desired AUC value as 4 or 5 mg × ml/min. Dialysis was performed not earlier than 16 hours after administration. Dosages of 100 or 125 mg resulted, which led approximately to the desired AUC values between 3.5 and 4.8 mg × ml/min [13, 14]. Therefore carboplatin treatment of dialysis patients should be initiated with a carefully calculated dosage. If protracted thrombocytopenia occurs, the dosage should be adjusted correspondingly for the subsequent administrations. It is recommended to calculate the desired AUC and to perform administration on the interval days of intermittent dialysis [11].

Cisplatin

Because of the very swift onset of plasma protein binding after administration and the high degree of plasma protein binding, amounting to more than 90%, of cisplatin, dialysis is effective only directly after administration [15]. Ribrag et al. demonstrated that administration of cisplatin 30 minutes after begin of a four-hour haemodialysis results in plasma levels and AUCs comparable to those measured in patients with intact renal function after the same dosage [16]. Nevertheless, alternatives are recommended, also because of the narrow time window for effective dialysis and the high toxicity of cisplatin.

Cyclophosphamide

Reduction of renal clearance by 90% may result in an increase of the AUC of the active metabolite 4-hydroxy-cyclophosphamide by 30% [17]. Therefore in patients requiring dialysis the dosage should be reduced. In general, 50% of the normal dosage are recommended [18].

As cyclophosphamide is readily dialysed, in order to avoid a loss of therapeutic efficacy it should be administered after the end of the dialysis process. Subsequent dialysis should be initiated not earlier than 12 hours after administration [19]. It is therefore recommended to perform administration on the interval days of intermittent dialysis.

Docetaxel

The presently approved taxanes docetaxel and paclitaxel are subject to a very low degree of renal excretion (< 10%). Metabolism is mostly hepatic via the cytochrome P 450 system, and excretion via the biliary route. In addition, plasma protein binding of the substances is in excess of 88% [20, 21]. Mencoboni et al. demonstrated that administration of docetaxel before or during haemodialysis does not result in significant changes of the plasma protein–time curve. They conclude that the substance is not dialysed, and that dosage reduction is not necessary in renal insufficiency necessitating dialysis [22] .

Paclitaxel

Paclitaxel clearance is affected only little, if at all, by haemodialysis. Several studies have shown that administration of dosages from 135 to 180 mg/m² leads to dosage-dependent increases of plasma levels and AUC in the dimen-

sions observed in patients with normal renal function [14, 23]. Tomita et al. successfully and safely treated an ovarial cancer patient requiring dialysis with a combination of paclitaxel (150 mg/m²) and cisplatin (30 mg/m²) followed by four-hour haemodialysis (beginning 30 min after administration of cisplatin) [24].

Yet it should be pointed out that it is still not known how the hepatic metabolism reacts to higher dosages. Occurrence of saturation is at least conceivable.

Anthracyclines

Doxorubicin has a very high distribution volume and a relatively long half-life. In addition, there is relatively swift distribution into erythrocytes. After establishment of a dynamic equilibrium of metabolic elimination, this portion of the doxorubicin is no longer available in the short term [25]. Taken together, this explains its poor dialysability. The metabolism of doxorubicin produces the active metabolite doxorubicinol which is mostly formed in the kidney. In case of impaired renal clearance, the hepatic metabolism of doxorubicinol may simultaneously decrease, necessitating caution and possibly a slight dosage reduction in dialysis patients [26].

Whereas epirubicin and idarubicin resemble doxorubicin, daunorubicin seems to have a somewhat higher rate of unmodified renal excretion, amounting to approx. 20% [27, 28]. Therefore the manufacturer recommends a dosage reduction by 50% in case of creatinine clearance below 10 ml/min [29].

Etoposide

Based on the results of several pharmacokinetic studies, dialysability of etoposide must be considered as irrelevant, since its administration under dialysis barely affects pharmacokinetics in patients requiring dialysis [12, 30]. As a rather larger portion of etoposide, amounting to approx. 40 – 60%, is excreted renally over a period of several days, impaired renal function leads to reduced etoposide plasma clearance and increased half-life [31]. However, etoposide is also excreted via the biliary route, where Watanabe et al. see, based on the results of their dosage escalation study, see a possibility for compensation of restricted renal elimination [32]. Nevertheless, for the aforesaid reasons the

dosage of etoposide should be reduced to 60 – 50% when treating patients requiring dialysis.

Gemcitabin

Among 15 patients with moderately impaired renal function (serum creatinine 1.6 – 3.2 mg/dl) receiving reduced dosages of gemcitabin amounting to 850 mg/m² (9 patients) and 650 mg/m² (6 patients), 4 of the patients experienced dosage-limiting side effects which in two patients manifested as severe cutaneous reactions [33].

Kiani et al. showed in one patient that terminal impairment of renal function does not lead to an accumulation of gemcitabin itself. However, according to their results this leads to formation of the probably inactive metabolite dFdU (2',2'-difluorodeoxyuridine), which may result in an up to tenfold AUC increase and possibly toxicity in terminal renal insufficiency. Therefore they recommend administration of the full dosage (1000 mg/m²) and three-hour dialysis which should be performed 6 – 12 h after administration in order to adapt clearance and half-life of dFdU to the values of patients with normal renal function [34].

Irinotecan

Irinotecan is degraded enzymatically in the liver, producing SN-38, a metabolite with 100-1000-times higher cytotoxicity. Both show high plasma protein binding of 65% and 95%, respectively [36]. Approx. 50% of the dosage is excreted unmodified, approx. 30% via the biliary and 20% via the renal route [37]. Strong inter-individual variability of plasma levels after identical dosages, influenced by various parameters such as age or body weight, poses a problem [38]. Two case reports describe the safe weekly administration of irinotecan at a dosage of 50 mg/m² in colorectal carcinoma patients requiring dialysis [35, 39]. It is not known yet whether irinotecan and its metabolite SN-38 can be significantly removed by dialysis, but their pharmacokinetics make this appear rather unlikely. However, the data basis is too imperfect for giving definitive recommendations for the use of irinotecan in patients requiring dialysis.

Melphalan

In case of reduced renal clearance, high dosage therapy (200 mg/m²) followed by autologous blood stem cell transplantation (ABSCT) without melphalan dosage reduction may result in increased toxicity and higher transplantation-associated mortality [40]. Nevertheless, even patients requiring dialysis benefit from such a treatment [41]. Hence, in practice ABSCT is performed in patients with sufficient performance status with a melphalan dosage reduced by 50% [42]. For conventional dosages, Cornwell et al. likewise recommend reduction by 50% [43]. Melphalan is not dialysable, thus it can be administered independently from dialysis times [48].

Methotrexate

Methotrexate plasma levels can be reduced by haemodialysis, in particular with high flux membranes [44]. Other dialysis techniques such as combined haemodialysis, haemoperfusion [45] and peritoneal dialysis [46] were likewise able to remove methotrexate, albeit with varying efficacy. For high efficacy of the dialysis and for avoidance of a second increase in plasma levels (rebound), it is probably essential to keep the delay between the end of the infusion and the begin of dialysis as short as possible [47] in order to prevent extensive distribution of methotrexate into intracellular space and erythrocytes.

Patients requiring dialysis should generally not be treated with methotrexate, since inter- and intra-individual differences in metabolism and excretion may result in rather uncontrollable toxicity.

References:

1. Schoenweiss, G., *Dialyse-Fibel*. 1998, Bad Kissingen: Abakiss Verlag.

2. Rasche, F.M., F. Keller, and D. Czock, *[Chemotherapy in patients with renal failure, dialysis and after transplantation]*. Dtsch Med Wochenschr, 2005. **130**(36): p. 2043-6.

3. Kraehenbuehl, S., *Patienten mit Organerkrankungen*. 2 Aufl. Lehrbuch der Klinischen Pharmazie, Hrsg. U. Jaehde, et al. 2003, Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH.

4. Czock, D. and F.M. Rasche, *New AUC-based method to estimate drug fraction removed by hemodialysis*. Kidney Blood Press Res, 2004. **27**(3): p. 172-6.

5. *Fachinformation Ribomustin®*, April 2006

6. Preiss, R., et al., *Pharmacokinetics and toxicity profile of bendamustine in myeloma patients with end-stage renal disease*. Haematologica, 2003. **4**(Suppl 1): p. Abstract 394.

7. *Fachinformation Busilvex®*, Januar 2006

8. Stein, J., et al., *Accidental busulfan overdose: enhanced drug clearance with hemodialysis in a child with Wiskott-Aldrich syndrome*. Bone Marrow Transplant, 2001. **27**(5): p. 551-3.

9. Ullery, L.L., et al., *Busulfan clearance in renal failure and hemodialysis*. Bone Marrow Transplant, 2000. **25**(2): p. 201-3.

10. Ballester, O.F., et al., *High-dose chemotherapy and autologous peripheral blood stem cell transplantation in patients with multiple myeloma and renal insufficiency*. Bone Marrow Transplant, 1997. **20**(8): p. 653-6.

11. Tomita, M., Y. Aoki, and K. Tanaka, *Effect of haemodialysis on the pharmacokinetics of antineoplastic drugs*. Clin Pharmacokinet, 2004. **43**(8): p. 515-27.

12. Suzuki, S., et al., *Pharmacokinetics of carboplatin and etoposide in a haemodialysis patient with Merkel-cell carcinoma*. Nephrol Dial Transplant, 1997. **12**(1): p. 137-40.

13. Chatelut, E., et al., *Pharmacokinetics of carboplatin in a patient suffering from advanced ovarian carcinoma with hemodialysis-dependent renal insufficiency*. Nephron, 1994. **66**(2): p. 157-61.

14. Watanabe, M., et al., *Paclitaxel and carboplatin combination chemotherapy in a hemodialysis patient with advanced ovarian cancer*. Gynecol Oncol, 2002. **84**(2): p. 335-8.

15. *Fachinformation Cisplatin-GRY®*, Oktober 2002

16. Ribrag, V., et al., *Test dose-guided administration of cisplatin in an anephric patient: a case report*. Ann Oncol, 1993. **4**(8): p. 679-82.

17. Chen, T.L., et al., *Nonlinear pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide in patients with metastatic breast cancer receiving high-dose chemotherapy followed by autologous bone marrow transplantation*. Drug Metab Dispos, 1997. **25**(5): p. 544-51.

18. *Fachinformation Endoxan®*, Januar 2005

19. Haubitz, M., et al., *Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency*. Kidney Int, 2002. **61**(4): p. 1495-501.

20. Clarke, S.J. and L.P. Rivory, *Clinical pharmacokinetics of docetaxel*. Clin Pharmacokinet, 1999. **36**(2): p. 99-114.

21. Rowinsky, E.K., L.A. Cazenave, and R.C. Donehower, *Taxol: a novel investigational antimicrotubule agent*. J Natl Cancer Inst, 1990. **82**(15): p. 1247-59.

22. Mencoboni, M., et al., *Docetaxel pharmacokinetics with pre- and post-dialysis administration in a hemodyalized patient*. Chemotherapy, 2006. **52**(3): p. 147-50.

23. Woo, M.H., et al., *Pharmacokinetics of paclitaxel in an anephric patient*. Cancer Chemother Pharmacol, 1999. **43**(1): p. 92-6.

24. Tomita, M., et al., *Pharmacokinetics of paclitaxel and cisplatin in a hemodialysis patient with recurrent ovarian cancer*. Anticancer Drugs, 2001. **12**(5): p. 485-7.

25. Speth, P.A., Q.G. van Hoesel, and C. Haanen, *Clinical pharmacokinetics of doxorubicin.* Clin Pharmacokinet, 1988. **15**(1): p. 15-31.

26. Yoshida, H., et al., *Pharmacokinetics of doxorubicin and its active metabolite in patients with normal renal function and in patients on hemodialysis.* Cancer Chemother Pharmacol, 1994. **33**(6): p. 450-4.

27. Robert, J. and L. Gianni, *Pharmacokinetics and metabolism of anthracyclines.* Cancer Surv, 1993. **17**: p. 219-52.

28. Eksborg, S., *Pharmacokinetics of anthracyclines.* Acta Oncol, 1989. **28**(6): p. 873-6.

29. *Fachinformation Daunoblastin* Stand März 2004.

30. Holthuis, J.J., et al., *Pharmacokinetic evaluation of increasing dosages of etoposide in a chronic hemodialysis patient.* Cancer Treat Rep, 1985. **69**(11): p. 1279-82.

31. D'Incalci, M., et al., *Pharmacokinetics of etoposide in patients with abnormal renal and hepatic function.* Cancer Res, 1986. **46**(5): p. 2566-71.

32. Watanabe, R., et al., *Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer.* Br J Cancer, 2003. **88**(1): p. 25-30.

33. Venook, A.P., et al., *Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565.* J Clin Oncol, 2000. **18**(14): p. 2780-7.

34. Kiani, A., et al., *Pharmacokinetics of gemcitabine in a patient with end-stage renal disease: effective clearance of its main metabolite by standard hemodialysis treatment.* Cancer Chemother Pharmacol, 2003. **51**(3): p. 266-70.

35. Stemmler, J., et al., *Weekly irinotecan in a patient with metastatic colorectal cancer on hemodialysis due to chronic renal failure.* Onkologie, 2002. **25**(1): p. 60-3.

36. Chabot, G.G., *Clinical pharmacokinetics of irinotecan.* Clin Pharmacokinet, 1997. **33**(4): p. 245-59.

37. *Fachinformation Campto®*, Mai 2006

38. Poujol, S., et al., *Pharmacokinetics and pharmacodynamics of irinotecan and its metabolites from plasma and saliva data in patients with metastatic digestive cancer receiving Folfiri regimen.* Cancer Chemother Pharmacol, 2006. **58**(3): p. 292-305.

39. Budakoglu, B., et al., *Good tolerance of weekly irinotecan in a patient with metastatic colorectal cancer on chronic hemodialysis.* J Chemother, 2005. **17**(4): p. 452-3.

40 Carlson, K., *Melphalan 200 mg/m2 with blood stem cell support as first-line myeloma therapy: impact of glomerular filtration rate on engraftment, transplantation-related toxicity and survival.* Bone Marrow Transplant, 2005. **35**(10): p. 985-90.

41. San Miguel, J.F., et al., *Are myeloma patients with renal failure candidates for autologous stem cell transplantation?* Hematol J, 2000. **1**(1): p. 28-36.

42. *GMMG-HD4-Studienprotokoll.* 2005, German-speaking Multiple Myeloma Group: Heidelberg.

43. Cornwell, G.G., 3rd, et al., *Influence of renal failure on myelosuppressive effects of melphalan: Cancer and Leukemia Group B experience.* Cancer Treat Rep, 1982. **66**(3): p. 475-81.

44. Wall, S.M., et al., *Effective clearance of methotrexate using high-flux hemodialysis membranes.* Am J Kidney Dis, 1996. **28**(6): p. 846-54.

45. Relling, M.V., et al., *Removal of methotrexate, leucovorin, and their metabolites by combined hemodialysis and hemoperfusion.* Cancer, 1988. **62**(5): p. 884-8.

46. Diskin, C.J., et al., *Removal of methotrexate by peritoneal dialysis and hemodialysis in a single patient with end-stage renal disease.* Am J Med Sci, 2006. **332**(3): p. 156-8.

47. Saland, J.M., et al., *Effective removal of methotrexate by high-flux hemodialysis.* Pediatr Nephrol, 2002. **17**(10): p. 825-9.

48. Tricot, G., et al., *Safety of autotransplants with high-dose melphalan in renal failure: a pharmacokinetic and toxicity study.* Clin Cancer Res, 1996. **2**(6): p. 947-52.

3.5.4. Dose Modification in Case of Impaired Hepatic Function

Impaired liver function can exert considerable influence on the hepatic clearance of cytostatics. Limited metabolic clearance leads to slower biotransformation, whether cytochrome P450 dependent or not, whereas a reduced biliary clearance hinders the natural excretion over the bile ducts.

It is known that some cytostatic agents accumulate if hepatic clearance is reduced. The evaluation of laboratory parameters and dose modifications therefore represent an important clinical pharmaceutical service.

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If patients show elevated liver values or changed bilirubin values, the issue must be addressed as to whether and to what extent the dosage of a planned chemotherapy may have to be modified. Particularly when using cytostatics, which have a narrow therapeutic range, failure to modify the dose appropriately can result in severe side effects for the patient. Although a series of recommendations do exist concerning dose modification for patients with impaired liver function (Table 1), it must be borne in mind when consulting such tables that they are based on a much smaller collection of data than are, for example, the recommendations in case of impaired renal function. Information of the kind presented in Table 1 must therefore be interpreted as no more than a guide. The following not only deals more closely with the principle of impaired hepatic function, but also presents an objective discussion of selected classes of active substance.

Table 1: General recommendations for empirical dose reduction of cytostatics eliminated primarily via the hepatic route (see text for further discussions)

Bilirubin elevation	AST (GOT)	Dosage (% of the original dose)
‹ 1.4-fold	‹ 3-fold	100 %
1.5- to 3-fold	3- to 9-fold	75 - 50 %
3- to 5-fold	› 9-fold	50 - 25 %
› 5-fold		individual decision
In case of elevated alkaline phosphatase		50 % dose reduction of vinca alkaloids and podophyllotoxins

Table 2: Normal ranges of different parameters in the case of unimpaired hepatic function

Parameter	Units in µg/L, g/L or U/L	SI units	Conversion factor
Serum bilirubin (total bilirubin)	0.1 - 1 mg/dL	2 - 18 µmol/L	17.1
Direct bilirubin	0 - 0.2 mg/dL	0 - 4 µmol/L	17.1
ALT (SGPT)	0 - 35 U/L	0 - 0.58 µkat/L	0.01667
AST (SGOT)	0 - 35 U/L	0 - 0.58 µkat/L	0.01667
γ-GT	0 - 30 U/L	0 - 0.5 µkat/L	0.01667
Alkaline phosphatase	30 - 120 U/L	0.5 - 2 µmol/L	0.5872
Serum albumin	›3.5 g/dL	›35 g/L	10

Abbreviations: ALT (alanine aminotransferase), AST (aspartate aminotransferase), γ-GT (gamma-glutamyl transferase)

Consequences of impaired hepatic function

Functional disturbances of the liver can lead to a diversity of changes in active substance elimination: if a cholestasis results in biliary elimination being obstructed, a critical cumulation of active substances or their metabolites must

be expected if these are predominantly or entirely eliminated via the biliary route. Important indications of flow impairment are elevated bilirubin values and evidence for increased serum concentrations of enzymes normally localised in the epithelium of the bile duct, such as alkaline phosphatase or gamma-glutamyl transferase (γ-GT).

If there is a massive loss of liver cell mass (for example as a consequence of necrotic changes) associated with a serious decline in cytochrome 450 activity, active substances normally metabolised by enzymes that metabolise foreign substances may accumulate unchanged in the plasma.

If the hepatic dysfunction is associated with restricted albumin synthesis, there will be a significant increase in the freely biologically available, pharmacologically effective fraction of drugs such as etoposide which bind strongly to plasma protein.

Finally, it must also be borne in mind that the use of drugs that are potentially hepatotoxic despite undergoing neither extensive hepatic metabolism nor elimination via the biliary route (e.g. methotrexate) may be expected to cause a critical worsening of the existing liver disease.

Evaluating toxicity becomes somewhat complicated when patients suffering both from severely limited liver function and from ascites are treated with cytostatics (e.g. methotrexate, fludarabine) which can accumulate in the special compartment. In such cases it is helpful to remove water deposits associated with ascites before beginning with the actual therapy.

Changed pharmacokinetic parameters in patients with hepatic dysfunctions

The elimination of active substances through the liver (hepatic clearance) is regulated by three parameters: the flow of blood through the liver (Q), the plasma protein binding (P) and the intrinsic (metabolic) clearance (C):

$$\text{hepatic clearance} = \frac{Q \times P \times C}{Q + P \times C}$$

For active substances subject to a high rate of metabolic clearance the rate of flow through the liver becomes the limiting step for elimination (perfusion-limited clearance). For active substances for which the rate limiting step is the number of interactions taking place per unit time with the enzymes which metabolise foreign substances, clearance proceeds independently of perfusion. In the case of hypoproteinaemia, the above formula shows that the fraction of protein binding can be decisive for the elimination of substances with a high level of binding to plasma proteins.

Severe limitation of the functional reserves of the liver can often not be measured until approximately 30 percent of the normal value has been reached. In this connection the most important methods world-wide are the determination of hepatic clearance using the dyestuff indocyanine green (ICG), which enables the flow of blood through the liver to be quantitatively ascertained, and determination of the galactose elimination capacity, with which the cytoplasmatic liver cell mass can be measured.

Dose reduction on the basis of elevated liver values

Without a doubt, it would be desirable if the routinely measured parameters such as the transaminases, bilirubin or serum albumin could be used directly in defining dose reductions for patients with impaired hepatic function. However, correspondingly changed parameters must be analysed more closely.

Transaminases

The function of the transaminases AST (SGOT) or ALT (SGPT) consists of transferring an amino group from amino-acids to 2-ketoacids such as 2-oxoglutarate or oxalacetate, leading to the formation of the corresponding amino acids such as glutamic acid and aspartic acid. AST (SGOT) can be detected in diverse tissues whereas the activity of ALT (SGPT) is primarily restricted to the liver (Table 2). It is therefore not possible to immediately conclude the existence of hepatobiliary disease on the basis of an isolated elevated AST value since this may also have arisen as the result of an extrahepatic event, e.g. myocardial infarction or rhabdomyolysis. If both enzymes (AST and ALT) are elevated, however, a disease of the liver is more likely.

Alkaline phosphatase and γ-GT

Alkaline phosphatase (AP) catalyses the hydrolysis of different esters of phosphoric acid. The highest levels of activity of this enzyme are normally found in the liver (Table 2), the mucous membrane of the small intestine, the bones, and the placenta in pregnant women. In the liver, the enzyme is primarily expressed in the epithelial cells of the hepatic duct. As a result, obstruction of the bile ducts may lead to elevated AP values as high as 1000 U/L. If at the same time, however, serum bilirubin values are normal, the cause may well be a completely different disease, e.g. a sarcoidosis, a hepatic candidiases or a lymphoma. In the case of parenchymatous liver disease without involvement of the bile ducts, only a moderate elevation of AP is detected in comparison with the transaminases. Since the serum AP value increases naturally after the consumption of food containing fat, it is generally recommended that this be determined while the patient is in the fasting state.

Gamma-glutamyl transferase (γ-GT) is predominantly expressed in the organs kidney, liver (Table 2) and pancreas. Since the highest levels of activity of this enzyme are detectable in the epithelial cells of the intrahepatic bile duct, the level of this enzyme in serum is elevated in the case of a cholestasis.

Albumin

The concentration of albumin in serum is normally at least 35 g/L (Table 2). A fall in this value to below 35 g/L may indicate a disturbance to the synthesis in the liver. However, since on average the half-life of albumin in the serum is approximately three weeks, a hypoalbuminaemia is of no value as an early indication of hepatobiliary disease. If other parameters (e.g. SGOT) do not provide additional evidence of hepatitis, a nephrotic symptom may also be the cause of the hypoalbuminaemia.

Changes in blood coagulation parameters

A severe hepatic dysfunction generally also results in impairment of the vitamin K dependent biosynthetic performance of blood coagulation factors II, VII, IX and X. If the coagulation factors fall below specific minimum values the prothrombin time becomes longer, resulting in smaller and larger haemorrhages. If other parameters indicative of hepatitis (e.g. albumin values) are not elevated,

however, the prolonged prothrombin time can also be the result of insufficient vitamin K synthesis over the intestinal flora, or a malabsorption syndrome.

Evaluation of individual parameters within a hepatobiliary disease

A slight impairment of the hepatic function means AST values still within the normal range (e.g. 28 to 34 U/L) and serum bilirubin between 2.1 and 4 mg/dl. A significant impairment of the hepatic function exists when the AST values are over 200 U/L and the serum bilirubin values are greater than 4 mg/dl (Table 2).

Different liver diseases result in different patterns of modified laboratory parameters, which allow tentative conclusions to be drawn as to the particular disease involved (Table 3). An increase in **total bilirubin** over 1 mg/dl, for example, may be the first indication of a slight obstruction of the bile ducts by a gallstone. Depending on the extent of the obstruction, the serum bilirubin values can reach 6 to 15 mg/dl. In the more detailed analysis a distinction is made between **direct bilirubin** (mainly bilirubin diglucuronide) and **indirect bilirubin** (non-conjugated, protein bound fraction). Normally, approximately 20 percent of the total bilirubin is present as direct bilirubin. The terms "direct"

Table 3: Changes in different liver parameters depending on the type of liver disease

Disease	SGOT	γGT	AP	Serum bilirubin	Quick value
Necrosis	+++++	+	+	= or +	lowered
Adiposis hepatica	+	+++	= or +	=	=
Anicteric cholestasis	= or +	+++	+++	=	=
Icteric cholestasis	+	+++	+++	++	=
Toxic hepatits	+++	++	+	= or +	slightly lowered

Notes: Abbreviations for enzymes: (see Table 2); = : unchanged; + to ++++ = slightly to very strongly elevated

and "indirect" relate to the reactivity towards the reagents used for the quantitative determination. A direct fraction below 20% ("**non-conjugated hyperbilirubinaemia**"), may indicate a hereditary defect in bilirubin glucuronation (e.g. Gilbert syndrome) or an oversaturation of the metabolic capacity (e.g. in association with a haemolysis). In both cases the total bilirubin value can reach (2 -) 6 mg/dl. In such cases, for example when using irinotecan, severe toxicity may result if no dose modification is made. Especially severe cases of hyperbilirubinaemia with values over 15 mg/dl have been reported for patients suffering from sepsis or from acute or chronic graft-versus-host disease (GVHD) after allogenic transplantation.

Recommendations for dose reduction in case of impaired hepatic function using a few selected cytostatics as examples

Anthracyclines

The anthracyclines doxorubicin, daunorubicin, epirubicin and idarubicin are mainly metabolised in the liver. Elimination of the parent substances and the metabolites proceeds predominantly via the biliary route. With the exception of idarubicinol, none of the metabolites formed exhibit any clinically relevant antineoplastic effect. An approximately 3-fold increase in the doxorubicin AUC was observed for patients with 6-fold increases in their bilirubin values. The best pharmacokinetic correlation occurred between the increase in the AST values in association with reduced ICG clearance values, and the decrease in doxorubicin clearance. Hepatic clearance was also slower for the structurally related epirubicin when the bilirubin values were increased by a factor of between 2 and 10.

Up to now the recommendation has been that patients with elevated bilirubin values (1.5 - 3.0 mg/dl) and elevated transaminases (60 - 180 U/L) receive only 50% of the originally planned dose of doxorubicin, epirubicin and mitoxantrone. If the values lie between 3.1 and 5 mg/dl and over 180 U/L, 25% of the planned dose should be given. In the case of daunorubicin the corresponding scope for dose modification is stated to be 75% and 50% since there is the possibility of compensation as a result of the kidneys being able to eliminate somewhat more daunorubicin (in contrast to epirubicin and doxorubicin). It remains difficult

to formulate clear recommendations for idarubicin since the active metabolites also exert an important neoplastic effect. Nonetheless, it is recommended that AML patients over the age of 60 be given 8 mg/m^2 i.v. (instead of 12 mg/m^2) since this dose modification leads to almost the same idarubicinol AUC values as for younger patients.

The pharmacokinetic behaviour of the liposomal compounds (e.g. DaunoXome, Caelyx, Myocet) differs considerably in some respects from that of the conventional anthracyclines. Referring to the use in case of hepatic dysfunction, Hong et al. administered 30 mg/m^2 i.v. pegylated liposomal doxorubicin to a patient with advanced hepatocellular carcinoma. Before treatment the patient's total bilirubin was approximately 3.6 mg/dl; the direct bilirubin was clearly elevated. The AST values were around 20-fold the normal whereas the ALT was barely elevated at all. The disease-related elevated liver values had already been successfully lowered after the first administration. The therapeutic interval was extended to 4 weeks in order to keep bone marrow toxicity as low as possible. The authors describe the therapy as tolerable and very effective. More extensive studies on the use of liposomal anthracyclines in patients with severely limited liver function would therefore be desirable.

Vinca alkaloids

The vinca alkaloids vincristine, vindesin, vinblastine and vinorelbin are extensively metabolised in the liver. Both the metabolites and the unchanged starting materials are eliminated via the gall bladder. In view of this pharmacokinetic behaviour, a corresponding dose reduction in the case of elevated serum bilirubin values is recommended for all members of this group.

The actual dose recommendation are as follows: only 50% of the originally planned dose if the bilirubin values lie between 1.5 and 3.0 mg/dl and the transaminases between 60 - 180 U/L; only 25% of the dose should be given if the bilirubin values are between 3.1 and 5 mg/dl and the transaminases are over 180 U/L.

Taxanes

Similarly to the vinca alkaloids, the taxanes paclitaxel and docetaxel undergo extensive hepatic metabolisation and biliary elimination. Because of the paucity

of study data, paclitaxel should on principle not be used for patients with severely impaired hepatic function; however, its use for patients with moderately elevated serum bilirubin and transaminase values is perfectly possible. Similar observations were also made for the structurally related docetaxel.

There are still no clear recommendations for dose reduction of paclitaxel in patients with elevated bilirubin or AST values. On the basis of results obtained up to now, however, it would appear that patients with slightly impaired hepatic function (e.g. transaminase values below 2.6 to 10 times the normal values and serum bilirubin below 1.25 times normal) can still be treated relatively safely with doses of 175 mg/m^2 paclitaxel. Dosage guidelines for serum bilirubin values higher than this are currently being investigated in studies. In the case of docetaxel it has been observed that the docetaxel clearance was reduced by approximately 30% in patients with AST values over 1.5 times the upper limit of normal and AP values greater than 2.5 times the normal. Up to now it has been recommended that only 75% of the calculated dose be given up to 3.5-fold elevated transaminase values (e.g. < 125 U/L) and up to 6-fold elevated AP values (e.g. < 720 U/L). If these values are exceeded and the bilirubin value is elevated at the same time, it is advised that docetaxel not be used on grounds of lack of relevant results.

Irinotecan

The camptothecin derivative irinotecan (CPT-11) is primarily converted in the liver by carboxylesterase into the highly active metabolite SN-38. SN-38 can be metabolised in the liver to the cytotoxically inactive SN-38 glucuronide (SN-38G). All the compounds named (CPT-11, SN-38 and SN-38G) undergo pronounced biliary elimination. Therefore if the bilirubin and AP values are elevated the CPT clearance decreases exponentially unless an appropriate dose modification is implemented. On the basis of the pharmacokinetic studies of Raymond et al. it therefore appears to be advisable to give patients with bilirubin values between 1.5 and 3 mg/dl a dose of only 200 mg/m^2 i.v. every three weeks instead of the usual 350 mg/m^2.

How difficult appropriate decisions over CPT-11 dose modifications can be is impressively demonstrated in a case report by van Groeningen et al. In the case

of a female patient with serum bilirubin values of 77 µmol/L (89% conjugated) and γ-GT values of 474 U/L given only 100 mg/m^2 instead of the planned 350 mg/m2, the measured concentrations of CPT-11, SN-38 and SN-38G were still too high within 24 hours after CPT-11 infusion. They concluded on the basis of their investigations that as little as 30 mg/m^2 i.v. would probably have been sufficient. For the above reasons, the necessity for using CPT-11 must be very critically considered in the case of patients with impaired biliary elimination. The same applies for the administration of CPT-11 to patients with Gilbert syndrome.

Etoposide and teniposide

Although the topoisomerase II inhibitors etoposide and teniposide are structurally similar, their pharmacokinetic properties are different. Etoposide is not so extensively metabolised, the fraction bound to plasma protein is smaller and it is more rapidly eliminated at the same time as its metabolites via the kidneys and gall bladder.

Different studies have established that at serum bilirubin values between 2 and 12 mg/dl and 3- to 6-fold elevated AST values, conventionally dosed etoposide does not cause any significant change in the pharmacokinetics in the plasma. It is probable that compensation for limited biliary clearance is possible as a result of increased elimination via the kidneys. The studies also demonstrated a very good correlation between the decrease in serum albumin and the fraction of unbound etoposide in the plasma and thus the associated neutropenia. The authors therefore reached the conclusion that dose reduction should primarily be made at albumin values below 35 g/L.

Antimetabolites

Diverse enzymes that are responsible for the metabolic inactivation of the antimetabolites 5-fluorouracil (5-FU), capecitabine or gemcitabine are localised both hepatically and extrahepatically. The resultant metabolites no longer exert any cytotoxic effect. Thus up to now no dose modification has been demanded for 5-FU itself even at a hyperbilirubinaemia of 5 mg/dl. For capecitabine a dose adaptation is made dependent on the levels of transaminases and AP.

Both oral examples, capecitabine and UFT, are contraindicated for patients with severely impaired hepatic function.

For a relatively long time the same applied for gemcitabine. However, studies by Venook et al. have demonstrated that although patients with isolated elevated transaminases (and increased serum creatinine values at the same time) did not require any dose modifications, significant increases in bilirubin and transaminases may be expected in patients with elevated serum bilirubin values who are given gemcitabine without appropriate dose modification. The authors therefore recommend that patients with elevated bilirubin values be administered only 800 mg/m^2 i.v. (instead of 1000 mg/m^2) to start with, that the trend in the above values be monitored, and that the usual dose of 1000 mg/m^2 i.v. per cycle not be administered until tolerance is obviously good.

Trabectedin

Use of trabectedin is frequently accompanied by reversible, acute increase of the ALT and AST transaminases, of serum bilirubin, of alkaline phosphatase and γ-GT.

For this reason, in patients with previous constitutive increases of their values this cytostatic should be used only after a careful risk-benefit analysis. In patients with increased bilirubin levels, use of trabectedin is not recommended. If the ALT, AST and AP values exceed 2.5-fold the upper normal value, instead of 1.5 mg/m² only 1.2 mg/m² should be administered. In subsequent cycles, the dosage can be further reduced to 1.0 mg/m² if the values listed have not normalized but the tumour responds well to the therapy.

Oxazaphosphorines

The oxazaphosphorines cyclophosphamide and ifosfamide are pro-drugs that lead via several steps to the products displaying the actual DNA crosslinking activity. If severely impaired hepatic function is associated with limited capacity of the corresponding cytochrome P450 isoenzyme, a systemically attenuated oxazaphosphorine effect is more likely in this case. An empirical dose reduction would therefore probably result in a reduction of the systemic effect. More extensive results are currently not available.

Summary

Impaired hepatic function can have decisive consequences for pharmaceutical therapy in a number of ways:

- If necrotic changes result in a quantitative decrease in the hepatically localised enzymes responsible for metabolising foreign substances - e.g. the cytochrome P450 isoenzyme, the UDP-glucuronosyl transferases or the glutathione S-transferases -, the active substance administered will be metabolised much more slowly, resulting in a stronger and longer-lasting effect of the drug given.
- A similar phenomenon is also observed if the circulation of the blood through the liver is reduced in the course of the hepatobiliary disease. The issue then becomes especially complicated if an accompanying portal hypertension unfavourably affects the absorption of the active substance from the gastrointestinal tract.
- In the event of a cholestasis, the build-up of bile may limit the elimination of those drugs that are eliminated strictly via the biliary route.
- In the case of an elevated bilirubin concentration in the serum, it must be expected that certain active substances (e.g. methotrexate, etoposide) that bind strongly to plasma protein are forced out of their protein binding and thus contribute to a significant increase in the freely biologically available - i.e. active - fraction.
- The same phenomenon is observed if hypoalbuminaemia occurs in association with a hepatobiliary disease. If in the course of therapeutic drug monitoring (TDM) only the total is measured (i.e. the sum of the protein-bound and non protein-bound fractions), it is perfectly possible that unexpected significant drug side-effects are observed despite the fact that the dose is within the standard therapeutic range (e.g. etoposide). In such cases a more accurate analysis of the non-protein bound fraction can quickly enable conclusions to be drawn about the actual situation.

Although it is currently possible to quantify the individually constitutively existing liver cell mass and the capacity of biliary elimination by means of the

ICG test and the galactose test, there are still a number of open questions in respect of precise determination of the individually available metabolic capacity. The most useful approach would therefore be to administer a test dose of a model substrate for a specific cytochrome P-450 enzyme in order to ascertain the metabolic capacity for a drug that is also converted by this enzyme. Ideas of this kind (e.g. the introduction of a breath test in connection with radioactively labelled erythromycin [ERMBT]) are discussed in the literature repeatedly, but up to now it is not really possible to talk about a practical implementation of this concept, even though it would be possible via ERMBT to predict much more accurately the individual conversion rate for the cytostatics isfosamide, the vinca alkaloids, the podophyllotoxins, irinotecan or the taxanes.

Current practice, and basic prescribing information and package leaflets, usually base a decision for dose modification on changes in the transaminases, bilirubin or albumin values, knowing full well that this decision will hardly bring precision in respect of pharmacokinetics and pharmacodynamics. The hope remains that in the years to come efforts will be intensified towards producing concrete recommendations based on appropriate initial parameters.

Further reading

Bircher J.: Drug dosage in patients with liver disease; in: McIntyre N., Benhamou J.-P., Bircher J.-P., Rizzeto J., Rodes J. (eds): Oxford Textbook of Hepatology; 1388-1400; Oxford University Press 1991

Bruno R., Hille D., Riva A. et al.
Population pharmacokinetics/pharmacodynamics of docetaxel in Phase II studies in patients with cancer
J.Clin.Oncol. 1998; 16; 187-196

Donelli MG., Zucchetti M., Munzone E. et al.
Pharmacokinetics of Anticancer Agents in Patients with Impaired Liver Function
Eur.J.Cancer 1998; 34; 33-46

Gurney H.
How to calculate the dose of chemotherapy
Br.J.Cancer 2002; 86; 1297-1302

Hong R.-L., Tseng Y.-L., Chang F.-H.
Pegylated liposomal doxorubicin in treating a case of advanced hepatocellular carcinoma with severe hepatic dysfunction and pharmacokinetic study
Ann.Oncol. 2000; 11; 349-351

Jonczyk M.
Chemotherapie-induzierte Leberschäden
Med.Welt 1998; 49; 499-500

Lipp H.-P.
Arzneimitteltherapie bei eingeschränkter Leberfunktion: Schwerpunkt Zytostatika
PZ PRISMA, Themenband Zytostatika 1999; 55-64

Raymond E., Boige V., Faivre S. et al.
Dosage Adjustment and Pharmacokinetic Profile of Irinotecan in Cancer Patients with Hepatic Dysfunction
J.Clin.Oncol. 2002; 20; 4303-4312

Rivory LP., Slaviero K., Seale JP. et al.
Optimizing the Erythromycin Breath Test for Use in Cancer Patients
Clin.Cancer Res. 2000; 6; 3480-3485

Stewart CF., Schuetz EG.
Need and Potential for Predictive Tests of Hepatic Metabolism of Anticancer Drugs
Clin.Cancer Res. 2000; 6; 3391-3392

Stewart CF, Arbruck SG., Fleming RA. et al.
Changes in the clearance of total and unbound etoposide in patients with liver dysfunction
J.Clin.Oncol. 1990; 8; 1874-1879

Twelves C., Glynne-Jones R., Cassidy J. et al.
Effect of Hepatic Dysfunction due to Liver Metastases on the Pharmacokinetics of Capecitabine and Its Metabolites
Clin.Cancer Res. 1999; 5; 1696-1702

Van Groeningen CJ., van der Vijgh WJF., Baars JJ. et al.
Altered pharmacokinetics and metabolism of CPT-11 in liver dysfunction: a need for guidelines
Clin.Cancer Res. 2000; 6; 1342-1346

Venook AP., Egorin MJ., Rosner GL. et al.
Phase I and Pharmacokinetic trial of paclitaxel in patients with hepatic dysfunction: Cancer and Leukemia roup B 9264
J.Clin.Oncol. 1998; 16; 1811-1819

Venook AP., Egorin MJ., Rosner GL. et al.
Phase I and Pharmacokinetic Trial of Gemcitabine in Patients with Hepatic or Renal Dysfunction: Cancer and Leukemia Group B 9565
J.Clin.Oncol. 2000; 18; 2780-2787

Wasserman E., Myara A., Lokiec F. et al.
Severe CPT-11 toxicity in patients with Gilbert´s syndrome: two case reports
Ann.Oncol. 1997; 8; 1049-1051

3.5.5. Dosage Adjustment in Case of Changes in Blood Count

The myelosuppressive effect of a cytostatics therapy may be dosage-limiting for the treatment of the patient. Continuous monitoring of the individual patient allows to detect beginning myelosuppression. In the absence of established parameters for estimating the individual capacity for bone marrow regeneration, no standardized recommendations for dosage adjustment can be given. The use of haematopoietic growth factors has extended the range of therapeutic possibilities.

Jürgen Barth, Gießen

One organ parameter among many to be observed in the dosing of anti-neoplastic agents is the blood count or the so-called bone marrow reserve, respectively. However, currently there are no established parameters allowing an estimate for the *individual patient*, also with regard to the regenerative ability of the bone marrow affected by cytostatics (in contrast to, e.g., liver or kidney function, see 3.4.3. Dosage adjustment in patients with reduced hepatic clearance). This is partly due to the possibility that the basic disease may be located in this very organ. The clinician has to rely on more or less close (individual) monitoring (2 – 3× per week after chemotherapy). This is the only way to detect the «real» degree of myelosuppression.

Distinction is to be made between a *curative* and a *palliative* approach to therapy, keeping in mind the (biological) age of patients. Subsequently, *nadir-adapted* dosage modifications are made before the next cycle of therapy. Here it should be pointed out that particularly in curative therapy regimens administration of haematopoietic growth factors such as G- or GM-CSF frequently obviates the need for dosage modification of standard therapies, thus allowing to maintain dosage intensity. *It should be further pointed out that according to*

the most recently reviewed guidelines – in particular for adjuvant therapies – a 20% risk of neutropenic fever is sufficient to justify the use of CSFs in primary prophylaxis (1, 2). High dosage chemotherapy and standard therapy in which dose intensity is increased by shortening the intervals are only possible with growth factor support.

Thus, recommendations for dosage adjustment because of myelosuppression may therefore be considered as *aids to orientation*. In particular in case of existing myelosuppression, in therapy with curative intention continuation of the chemotherapy in combination with the supporting measures mentioned is to be balanced against extension of the intervals.

References

1. Smith TJ (Chair), Khatcheressian J, Lyman GH, Ozer H, et al, 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol. 2006; 24: 1-19.

2. Aapro MS, Cameron DA, Pettengell R, Bohlius J, et al, EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours, Eur J Cancer 2006; 42: 2433-2453.

3.6. Preparation

Preparation is based on the operating instructions (see §20 Ordinance on Hazardous Substances, *Gefahrstoffverordnung*) and is carried out in accordance with manufacturing protocols, incorporating the results of the hazard assessment.

The procedures laid down in the operating instructions and manufacturing protocols are binding. Compliance with them is to by verified regularly.

Dr. Karla Domagk, Cottbus

For preparation of pharmaceutical products in German pharmacies, the Ordinance on the Operation of Pharmacies (*Apothekenbetriebsordnung*) is legally binding. According to §7 of said Ordinance on the Operation of Pharmacies, preparation of ready-to-administer cytostatics solutions for an individual patient constitutes preparation of a pharmaceutical product subject to prescription. §6 I of the Ordinance on the Operation of Pharmacies stipulates that pharmaceutical products are to be prepared and controlled in pharmacies in accordance with established pharmaceutical rules, and that they must have the quality required by the rules of pharmaceutical science. The regulation of §7 II of the Ordinance on the Operation of Pharmacies allows to waive examination only if the quality of the pharmaceutical product is guaranteed by the preparation procedure. Therefore manufacturing instructions for each cytostatic and each mode of application are part and parcel of the validation of the manufacturing process and the quality management system in the preparation of cytostatics.

The guideline «Aseptic preparation and inspection of potentially toxic ready-to-administer parenterals» issued by the German Pharmaceutical Association (*Bundesapothekerkammer*) should be consulted here.

Prior to beginning preparation, the written request signed by the physician must be presented as it forms the basis for verifying the plausibility of the prescription and for approval of the preparation by the pharmacist.

A computer program used in the preparation of individualized ready-to-administer cytostatics solutions guarantees both consistent work and continuous, objective and unambiguous documentation during the preparation process. Using the balance during the entire manufacturing process will not only log the actual amount but also enable determination of the amount of the active ingredient in case of partial taking. If it is not possible to use a balance during preparation, then at least the four-eyes principle must be applied.

For preparation, according to the requirements of TRHS 525 at least the following instruments are to be used: pressure release and and transfer systems (see chapter 3.3.1: Technical instruments for the preparation of cytostatics). In addition, working on a liquid-impermeable mat and bleeding of infusion sets with a carrier solution only are required.

The pharmacist responsible for preparation is obliged to select suitable products for production – in case of doubt concerning the suitability of the products offered for preparation under the individually given conditions in the pharmacy, the purchase has to be refrained from.

3.6.1. Production Specification

A production specification for cytostatic preparations includes the:

- **name of the cytostatic**
- **pharmaceutical form**
- **kind and name of the finished drug to be used**
- **types and names of the medical devices to be used**
- **name of the method for proper preparation**
- **name of the equipment to be used**
- **maximum permissible deviation from the value specified in the requisition**
- **kind of packaging and labelling**
- **information to appear on the label**
- **information on the shelf life of preparations and unopened stock solution**
- **information about special points to be observed when handing over the finished preparation.**

Matthias Klein, Rendsburg

The need for preparation instructions was declared as early as the 1995 Ordinance on Preparation of Ready-to-Administer Cytostatics Solutions by the Ministry of Social Affairs of Lower Saxony. The BAK Guidelines on Preparation and Control of Ready-to-administer Parenterals with Toxic Potential mandate

compilation of a preparation protocol. The comment comprises detailed data on this issue (1).

Production is assigned to one of the risk groups 1 to 3 (low, intermediate, high risk) (1, 2).

Definition of the pharmaceutical products to be used in the preparation instructions prevent mixing-up of during selection of bottles for preparation. Changing the preparation necessitates changing the instructions, also with regard to potentially changes in excipients.

Stipulation of the medical devices and equipment and the description of the method is intended to ensure a uniform quality of preparation. It must be borne in mind, however, that excessively detailed definitions may lead to acceptance problems among the employees.

The maximum permissible deviations from the required value stated in the requisition are legally defined in the specifications of the pharmacopoeias and in the *Füllmengenverordnung* (filling regulations). Although lower limits may be chosen, these are mostly only of economic advantage and not so relevant for therapeutic safety.

Information on the stability and shelf life of the stock solutions, ready-to-administer cytostatic preparations and opened stock solutions must be laid down as part of the production specification. Data from the literature cannot always be used directly. The conditions under which corresponding investigations were carried out may differ considerably from those in the department (concentrations and composition of the solution, material of the container and the medical devices, effect of light, etc.)

Thus information from the literature on chemical and physical stability must be treated only as an indication and should wherever possible be verified by chemical tests performed on the actual product.

The shelf life given in the preparation instructions is the result of the evaluation of chemical-physical stability and microbiological validation. For the shelf life given in the preparation instructions, a source must be given (1).

The preparation instruction must comprise an exemplary label (see chapter 3.6.3 Labelling).

References

1. Leitlinie der Bundesapothekerkammer und Kommentar zur Leitlinie Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential, Stand 25.11.2008

2. The United States Pharmacopoe and National Formulary – USP 31/NR 26 Chapter 797, National Publishing, Philadelphia, PA, 2008

3.6.2. Documentation

The following data are recorded during the preparation and are documented using an appropriate method:

- **time at which the preparation started**
- **batch number of the finished drug and any residues (cytostatics, solvents, carrier solutions)**
- **volumes used of solvents and carrier solutions**
- **name and quantity of the cytostatic used**
- **unusual incidents during the preparations**
- **name of the person carrying out the preparation**

Dr. Karla Domagk, Cottbus

During the preparation of cytostatic solutions the quantities and batch numbers of starting materials used are documented and the date and time at which the preparation started is recorded, in accordance with the requirements of GMP.

Objective and clear documentation is necessary in order that the pharmacist responsible can instruct pharmaceutical personnel to carry out the preparation. In view of current trends in drug liability law, it cannot be excluded that a shift in the burden of proof in individual cases will result in the pharmacist having to prove that he has prepared a specific cytostatic properly. Continuous documentation during the preparation will help to reduce this risk of liability.

If a computer program is not used for this purpose, the preparation process must be documented within the LAF clean room by the person performing the preparation (while maintaining asepticity); alternatively, the individual steps must be documented by a second person outside the LAF during the preparation according to the principle of double checking.

Within the implementation of a quality management system for cytostatics preparation, it is recommended that the batch numbers of the sterile single-use products used are also documented.

3.6.3. Labelling

The label prepared on the basis of the preparation documentation shall comprise at least the following information:

- **name and address of the pharmacy performing the preparation**
- **name and first name of the patient**
- **date of birth and, if applicable, admission number of the patient**
- **ward, department or therapeutic facility**
- **name and quantity of the cytostatic, further active substances**
- **type and volume of carrier solution**
- **method of administration**
- **required time of administration**
- **storage conditions**
- **date of expiry**

Hannelore Kreckel, Gießen

Labelling of the prepared solution must be primarily in accordance with §14 Ordinance on the Operation of Pharmacies (*Apothekenbetriebsordnung*, ApBetrO). Labelling as defined in §6 II Ordinance on the Operation of Pharmacies is an important measure to prevent mix-ups. A unified structure facilitates fast retrieval of relevant data.

For labelling, a clearly legible font is to be printed upon labels which are persistently attached to the product to be labelled and must not affect the product, e.g. by diffusion of adhesives.

Labelling of the cytostatics solution must be done in such a way that the solution can be unambiguously assigned to the patient which they are intended for. As it may well be possible that patients with identical names are lodged on one ward, in addition to the name the date of birth and the number of admission must be listed as identification marks.

If the volume of the ready-for-administration solution is very small, not all relevant data may be placed on the label. In this case, for unambiguous identification and assignment the following information must be provided on the label: Name and first name of the patient, type and dosage of the cytostatic, contents in terms of volume or weight and shelf life. All further information may be provided on a secondary package also including the information named above.

If the ready-for-administration cytostatics solution comprises further active components, these must also be listed in terms of type and amount, and so must all contingent stabilisers, preservatives and other relevant substances which may cause a reaction in the patient.

Because of the limited shelf life of ready-to-administer cytostatics solutions, it is mandatory to state the date until which the preparation may be used (expiry date) and storage conditions. This applies both to stock solutions and to solutions prepared for individual patients.

Providing the desired time point of administration facilitates maintaining the correct temporal sequence of administration in accordance with the polychemotherapy regimens and concomitant supportive medication.

Further data on the label may include:

Transport information

Phone number of manufacturer, contact person

Type of therapy regimen

Documentation generation number

The generation number allows easy retrieval of the production documents in case of questions.

The preparation instructions shall comprise an exemplary label.

References

EG-Leitfaden zur Guten Herstellungspraxis (GMP) Anhang 1, BGBl. I S. 521, 26. März 2008

Leitlinie der Bundesapothekerkammer und Kommentar zur Leitlinie Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential, Stand 25.11.2008

3.7. Delivery of Cytostatics

Cytostatics deliveries must be clearly labelled by the sender.

The packaging must ensure safe transport and unpacking; the consignment must be appropriately labelled.

Technical rules for hazardous substances *TRGS* 525 applies for in-house transport of ready-to-administer cytostatic preparations. These require that the finished preparations be transported in unbreakable, liquid-tight, closeable containers. The transport containers must also carry a warning label such as "Caution Cytostatics".

The return of cytostatics – whether internally or externally – must be agreed with the recipient.

The *Gefahrgutverordnung Straße und Eisenbahn (GGVSE)* (dangerous goods regulations for road and rail) apply in addition for outside transport.

Gerhard Carstens, Hannover and **Hannelore Kreckel,** Gießen

The requirement that cytostatics deliveries be clearly labelled applies for every sender, i.e. not only drug manufacturers and wholesalers but also for pharmacies and, in the event of return, for hospital wards, out-patient clinics and medical practices. The label must consist of an unambiguous, succinct logo and an informative but short text. The logo should preferably be in a striking colour, best of all in a fluorescent colour. Unfortunately it has not yet been possible to persuade the cytostatics manufacturers to agree on a standard logo. The demand that a standard logo be used by manufacturers and suppliers, and possibly also in health service facilities, has lost none of its legitimacy and is worth pursuing further.

For safety reasons cytostatics should be delivered separately from other drugs. In order to achieve this it may be necessary in individual cases to place separate orders with the manufacturer or wholesaler.

The transport packaging must guarantee that breakage cannot occur, that the primary packaging is not contaminated by microorganisms or other particles and that any traces of cytostatic substances adhering to the primary packaging cannot result in contamination of the transport packaging and consequent danger to the persons responsible for unpacking the consignment. For these reasons the transport packaging should comprise a) a liquid-tight enclosure of the primary packaging, b) protection against impact and c) an outer transport container. Additional climatic packaging may also be necessary for the purpose of product integrity. The liquid-tight wrapping of ready-to-administer packages from the cytostatics laboratory of the pharmacy can be implemented either using heat-sealed tube packaging or bags with a MicroSnap closure. Manufacturers should apply liquid-tight wrapping to septum bottles immediately after the production process or a subsequent cleaning step. A few model solutions are already being offered by different manufacturers.

The requirements of s. 31 (2) *Apothekenbetriebsordnung* (pharmacy regulations) concerning the issuing of drugs to wards and other departments of a hospital in suitable, closed containers are extended by *TRGS* 525. These stipulate that the cytostatic solutions prepared be delivered in unbreakable, liquid tight, closed containers, separated from other goods. The containers must carry the inscription "Caution Cytostatics". Closure may be realised by means of a key or a seal. The place where the key to the transport container is kept and and who has authorised access to it must be clearly and unambiguously regulated both in the pharmacy and in the unit performing the oncological therapy. For thermolabile products or those in danger of crystallising out, an insulated box to the same specifications must be used during transport if there is a risk of critical temperatures.

The prepared products are pre-packaged before being placed in the transport container. Filled pumps may in principle be delivered without a bag if the system is secure against leakage. [Additional packaging poses no problem, however,

and is worth considering on formal grounds.] The cytostatics directive of the *AOLG* (association of the highest regional health authorities) requires that the prepared products are sealed in liquid-tight film. During sealing care must be taken that the welded seam does not develop a leak as a result of premature separation of the film. Light protection bags are used for light sensitive substances. Placing in clip-closure bags ensures protection against the leakage of liquids as long as the MicroSnap closure is fitted properly together. Enclosing packaging ensures that any leakage is contained without the transport container being contaminated. For safety reasons the boxes can be lined with absorbent material for binding any solution which does escape.

Deliveries are made directly. The prepared products are handed over punctually to the professional personnel in the department that placed the requisition.

Transport by non-pharmacy personnel is permitted only after these persons have been instructed on the action to take in the event of danger. The time of handing over must be agreed with the persons performing the transport.

An important aid during transport is a mobile telephone, since this enables the transporter to ask for instructions and assistance quickly. There is no need to wear special protective clothing for the transport. During transport in which it is not possible to hold the container, the box should be placed on or in the transport vehicle in such a way that it cannot fall. It may be reasonable to carry a suitably adapted decontamination set during transport over longer distances. As a minimum, however, two pairs of (non sterile) gloves must be kept in the vehicle and regularly inspected and replaced (see Chapter 1.1. Persons Handling Cytostatics,; 1.3. Working Rules and Instruction, Protective Clothing).

The regulations for the transport of dangerous goods by road and rail (*Gefahrgutverordnung Straße und Eisenbahn*, GGVSE) apply in Germany for the transport of CMR substances by road. Although cytostatics preparations count as dangerous goods, they must not be labelled with the UN number 1851, which includes «medicines, liquid, poisonous», but according to ADR «Ready-to-use pharmaceutical products, e.g. cosmetics and medicines, which are prepared for personal use and are packaged in trade or household packages (and) are not subject to the requirements of the ADR/RID.» (ADR – *Accommodation*

des Affaires dangereuses en Route – Zwischenstaatliches Übereinkommen über den Transport von Gefahrstoffen auf der Straße/Eisenbahn (International agreement on the transport of dangerous substances by road/rail) - in the German version GGVSE; RID 2009, Regulations concerning the International Carriage of Dangerous Goods by Rail – *Internationale Ordnung für die Beförderung gefährlicher Güter mit der Eisenbahn*). Thus, ready-to-administer cytostatics do not have to be labelled with a UN#.

For other transports of CMR substances on roads within Germany, the *Gefahrgutverordnung Straße und Eisenbahn (GGVSE)* applies. Cytostatics preparations are considered as hazardous goods and are classified with UN# 1851 as «medicines, liquid, poisonous, not otherwise specified, class 6.1» and belong to packaging class II (toxic) or III (slightly toxic). Furthermore it must be kept in mind that the highest allowable total amount per transport (ADR 1.1.3.6.3) is to be complied with (no more than 333 l), and the maximally allowable amounts per package are to be observed (LQ (limited quantity) exemptions), with an interior packaging of no more than 500 ml and a package volume of no more than 2 l.

The UN# is to be attached to the package within a diamond with an edge length of 10 cm. The UN# may be placed on a sticker attached to the transport containers, or a sheet protector for insertion of the UN# may be attached. If the maximally allowable amounts are exceeded, all ADR requirements must be observed (package must by type-tested, requirements for joint transport must be observed, accident form sheet and transport papers must be handed over...). For packaging group I (highly toxic) there are no LQ exemptions, here extensive requirements would have to be met.

The cytostatics solutions for specific patients are taken to the requisitioning department by an employee of the pharmacy or the transport service and handed over to the professional personnel. If necessary, the preparation can after prior agreement be fetched from the pharmacy by an appropriately instructed employee of the requisitioning department.

The return of problem deliveries (suspected hairline cracks, contamination, etc.) must be made after prior agreement with the addressee, securely packed

in accordance with the general transport criteria and clearly labelled. Deliveries which are clearly broken and seriously leaking are not returned but are disposed of locally after agreement with the supplier. When returning materials from the pharmacy to the manufacturer or wholesaler the use of bags with twist packaging (e.g. Whirl-Pak®) are recommended. The bag, ideally provided by the manufacturer, should have an inscription area where the problem associated with the contents can be described. For safety reasons an appropriate procedure must be stipulated for returns by end users (wards, out-patient departments, medical practices) to the pharmacy performing the preparation. Details must be specified in service rules or delivery agreements.

3.8. Valuation

The costs of preparation are divided between the following areas:

1. Material costs

a) drugs

b) carrier solutions

c) single-use articles

2. Personnel costs

3. Additional charges

For valuation in public German pharmacies account must be taken of the contracts existing between the leading organisations of the statutory health insurance bodies and the pharmacists associations.

Klaus Meier, Soltau; **Michael Marxen** and **Klaus Ruberg,** Wesseling

3.8.1. Material Costs

a) Drugs and b) Carrier solutions

This means both the active substances used and the carrier solutions employed. In this connection particular attention should be directed at the calculation of residual quantities. As long as it is not necessary to assign costs directly to the individual patient, the calculation can be performed according to a general department-related method for apportioning costs.

c) Single-use articles

The costs of the disposable medical articles used in the preparation must be accounted for, as well as the costs for disinfecting and cleaning agents.

3.8.2. Personnel costs

The personnel costs to be charged for a ready-to-administer cytostatic solution are essentially determined by the working time.

The working time can be divided into

a) time needed directly for the preparation, which is determined both by

1. the properties of the substance and also

2. by the pharmaceutical form, and

b) time connected indirectly with the preparation, which arises through the work to be performed on the basis of defined standards of quality. [1]

The recording and classification of the time needed for this necessitates further calculations relating to the hospital as a whole, in order to arrive at generally applicable conclusions. [2]

3.8.3. Additional charges

These are primarily internal accounting items for balancing the budget and fiscal accounting items such as VAT. The internal charges, which are also accounted for in a full calculation of costs, should cover any management costs (overheads).

The times used must be correlated from two aspects:

1. The different number of preparations per year exerts an influence on the costs incurred through setting-up times, even if preparation is performed according to the same criteria.

2. Although a noticeable rationalisation effect occurs with increasing preparation figures, this is subject to restraint through parameters such as work conditions (e.g. number of workplaces) and limits to the flexibility with which the personnel can be deployed.

The following factors can be used for working times and setting-up times. [3]

Table 1:

1.	less than 1000 per year	factor 1.1
2.	1000 to 5000	factor 1.0
3.	5000 to 10,000	factor 0.8
4.	over 10,000	factor 0.6

Principles of staff requirement calculation:

In order to be able to correlate the working times for the individual preparations to the costs incurred, the following principles are available for internal calculations and staff requirement calculations:

In analysing reference figures, these must be fixed taking into account the currently applicable standard hours of work and absence quotas. Reference figures are updated (corrected) not only if standard hours of work are reduced, but also - according to the same principle - when adjusting for absence quotas, especially when accounting for absence quotas for the individual hospital.

Whereas changes in the working time are accounted for by updating reference figures, the "reference values" (minute factors) on which the (recognised) reference figures are based have "normative" character. [4]

It is therefore useful for this analytical method to break down reference figures into their components and to link the "normative" reference values with individual hospital working times.

The percentual starting point for calculating the staff requirement is basically defined by the 1969 reference figures of the *DKG* ("German hospitals association"), updated to the 40-hour week.

The fixed absence quota in the reference figures is derived as follows. The reference figures of the *DKG* for the year 1969 for the nursing service included an absence quota of 15% as "supplement to the effective working time for periods of absence" (supplement method, personnel supplement quota -*PZQ*).

This corresponds to a "deduction from the standard working time" (deduction method, personnel absence quota - *PAQ*) to the amount of 13.04%.[5]

Therefore, the reference basis for the personnel absence quota is either

- the "effective" working time (supplement method) or
- the "standard" or "gross" working time (deduction method).

Today, the "deduction method" in the narrower sense is generally employed. The term personnel absence quota (PAQ) will therefore be used.

In its recommendations of 1974 the *DKG* used the deduction method as the basis, but retained the fixed rate of 15%, which is generally accepted today.

Since the personnel absence quota on which the *DKG* reference figures for 1969 are based do not take any "weekday public holidays" into account, efficiency examinations are implemented in practice such that the standard working time is reduced (depending on the particular *Land*) by 10 or 11 weekday public holidays (gross annual working time) and the absence quota is applied to the reduced basis.[6]

In the case of 11 weekday public holidays, this increases the staff requirement by approximately 4.4%.[7]

The annual working time is calculated as follows:

Table 2:

365.25 calendar days p.a.
- 104.3 weekend days
- 10.0 weekday public holidays
intermediate total = 251.0 annual working days (gross)
x 7.7 hours/day (for a 38.3 hour week)
= 1923.7 hours p.a. (gross)
x 0.8225 for 17.75% absence time[8]
Result = 1590.0 annual working time (net)

Summary

In the past, calculations of working time and costs incurred through the preparation of ready-to-administer cytostatic solutions often did not define a total time value, but work performed on a regular or irregular basis was listed individually in the same way as for the individually accepted time values for preparation in its narrowest sense. The result was that - known to all those responsible - most of the work extending beyond the pure preparation itself was not accounted for in calculating the working times. An isolated viewpoint of this kind does not support the aim of creating a standard basis for calculating pharmaceutical services in central cytostatics preparation. Rather, the danger exists that by ignoring the quality aspects during future negotiations between funding bodies and hospitals or state governments - e.g. in connection with special payments and fixed payments for specific cases - prices will be agreed which do not even partially cover the costs.

On the basis of the available data it may be assumed that:

- the large majority of hospital pharmacies producing ready-to-administer cytostatic solutions centrally belong to the group to which the factor 1 applies (cf. Table 1). For these, the following values apply:

Table 3:

Activity	per Production
Setting-up times	26 minutes
Production	19 minutes
TOTAL	**45 minutes**

- The working time of a full-time employee includes the working time fractions of the participants as follows: 20% pharmacist, 70% pharmacy technician and 10% pharmacy auxiliary staff.
- The net working time of 1590 hours allows that - on the basis of the work documented in the quality standard - one full-time employee can perform 2120 cytostatics preparations per year.

Whatever can be recorded in minutes can also be calculated in terms of money. For the costing of so-called "post-inpatients" or "part-inpatients" we can derive the following:

- An average time of 45 minutes (at factor 1) yields mean preparation costs of 20 euros per administration.
- To this must be added drug and other material costs.
- A fixed price of 30 euros in addition to the drug costs has proved to be a practicable figure within the hospital.

For valuation in the ambulant sector and in public pharmacies account must be taken of the contracts existing between the leading organisations of the statutory health insurance bodies and the *DAV* (German pharmacists association), which deviate from the general conditions of the *AMPreisVO* (directive on drug prices) but is allowed for there in s. 5 (5).

A present the valuation of solutions for parenteral use is regulated in the still valid auxiliary charges 2002 with the extensions of 1 July 2003. Depending on the differences in preparation according to the properties of the substance and the indication the solutions are divided between the groups cytostatics, parenteral nutrition, antibiotic virostatics, solutions for parenteral pain therapy and "miscellaneous". The batch size and work price are calculated depending on the allocation to these groups.

In the case of generic prescriptions, i.e. prescription without proprietary drug name, drugs must be taken from the lower third of the price range, in accordance with the aut-idem rule. According to the *DVA* multiple packs need not be taken into account since each prescription is regarded in isolation.

Prices are based on the purchase price according to the *LAUER-TAXE*. For calculation purposes the respective most economical package size for the total quantity of substance prescribed is used, i.e. if necessary substance per ready-to-administer unit times number of units; this solves the formerly controversial problem of partly used packs. The additional charge according to the *AmPVO* is applied to this purchase price, but to a maximum of 30%. Carrier solutions

are calculated at purchase price plus 30%, pumps, cassettes or other administration aids - which must be prescribed exactly - at purchase price plus 25%. The work price, which covers administration costs such as mask, gloves, spikes, underlays, gowns, disposal and documentation, is set at 19 euros for cytostatics and 15 euros for other solutions such as folic acid. VAT is applied to the total of these individual prices.

At the moment many detail questions are open in respect of the implementation in practice and continual revaluation procedures. Particularly the use of reimports, the general use of multiple packs, the basic use of the cheapest offer whether available or not, and substitution in general are the subject of many appeals against revaluation.

As a result of the planned *GMG* (law on modernisation of the health service) changes are possible in all directions, even as far as the abolition of the auxiliary charges; this means that new valuation rules may be expected to come into force after publication of the QUAPOS 2003.

It must be stated for the record that: The agreed work price in ambulant care is very close to the level calculated by us, even though inclusion of the equipment costs does not appear to be covered completely. It will certainly be possible to compensate for this shortfall by exploiting existing possibilities for economies in work costs. Nonetheless, it is important to take appropriate steps to ensure that the quality of preparation does not suffer in the future and that the aspect of employee protection is awarded due importance:

1. **An accompanying quality control through certification as performed by the *DGOP* for the last three years is an important instrument for the independent standardisation of the pharmacies carrying out the preparation.**
2. **The continuous documentation of the necessary material costs must contribute towards raising the agreed amounts to the necessary level.**
3. **Patient orientation is the most important basis for the preparation of ready-to-administer cytostatics solutions and guarantees that individual requirements are taken into account correctly and appropriate for the therapy.**

1. The so-called setting-up times are divided into: 1. Work arising on an irregular basis, 2. Work necessary for every preparation, 3. Setting-up times arising daily and 4. Documentation and organisation times.

2. In a study performed over a period of 4 years and started by the CYPRO users, average setting-up times of 26 minutes were obtained at factor 1 (presented at the 6th user meeting, Nov. 1995, Flensburg).

3. See (for example): Section 5.1 "Sterile and aseptic preparation" in the "Catalogue of pharmaceutical services in the hospital" (*KaphaLeiKh*) from the "committee for rates and contractual questions" of the *ADKA* (association of German hospital pharmacists); February 1996.

4. "Directives for examining efficiency and economical management of hospitals" (Baden-Württemberg 1984).

5. Effective working time = standard working time x 100/115 = standard working time x (100-13.04)/100 (PAQ = 13.04%).

6. The deduction of weekday public holidays for calculation of the effective annual working time is independent of whether the respective service operates on weekday public holidays.

7. Effective annual working time = standard annual working time x 250/261 x (100 - PAQ)/100. The staff requirement increases by 261/250 = 1.044 (4.4%).

8. This is the average absence time published by auditing firms for the medical technical sector in hospitals, to which the pharmacies are allocated pursuant to budget legislation.

9. In determining the basic prices for the substances a distinction is made between articles with and without a * (asterisk). For articles with no * the INN price is multiplied by the quantity prescribed; for articles with an * the INN price is multiplied by the amount of the smallest divided unit of a pack.

10. The work price covers management costs such as: mask, gloves, spikes, underlays, gowns, disposal, documentation.

3.9. Sources of Information

Any oncology pharmaceutical service is based on facilities for obtaining and distributing information relevant to all issues relating to tumour therapy which must be commensurate with the importance of this interdisciplinary department. Apart from a reference library to be kept supplied with the relevant print media and PC equipment with access to relevant software and digital information, connection to the internet is indispensable for database queries, for use of search engines and following various links, of email and other services.

Standard facilities must also include audio and video material for training.

Silke Braband, Hamburg; **Michael Höckel**, Eisenach

For obtaining information in the field of oncology, it has been found expedient to describe the individual problem of interest as precisely as possible before searching for information. Only then the decision should be made which media are suitable for performing a successful search within acceptable time. It is advisable to document and archive the queries including the answers and the media used. A structured approach allows to retrieve existing knowledge swiftly. Search for information becomes effective and amenable to planning in terms of time only by systematic performance in accordance with an individually defined scheme taking into account the available equipment. Archiving is done in the form of databases for fast retrieval but is also possible using index cards.

In queries relating to clinical syndromes and diagnostics, textbooks in oncology and haematology (1) are the primary sources of information.

For current references, an additional internet search (2) is helpful and allows to provide up-to-date answers. In questions relating to active substances, product

information and knowledge databases (3) with monographs (free or partly non-free) are available; these data are more or less up-to-date, depending on revision status. The date of the most recent revision must be visible and should also be documented during archiving.

For more or most recent information, it will then be necessary to consult the corresponding original papers, literature databases being available to this purpose. In most cases, access to the databases (4) and abstracts via the individual search forms is free. However, obtaining the corresponding original paper often entails costs. The pharmacist may then contact a university library or similarly equipped library in his area and order the required papers. In addition, subscription to a commercial vendor is possible, and/or there is contact with the medical sciences department of a pharmaceutical company. In clinically relevant practice issues, information (e.g. manuals) published by tumour centres (5) and scientifically supported guidelines for diagnosis and therapy (6) can provide a quick overview and thus enable to answer the questions in step with actual practice.

A plethora of sources is available to anybody seeking information, not least as a result of the internet, often culminating into an unmanageable flood of data. Therefore a team should make a selection of media to gain experience on usage. Within the institution, one person should be responsible for regularly updating the required print and non-print media.

Apart from obtaining data, their assessment is a further important aspect in answering queries. Data from the internet should be assessed using a check list. Some operators of information pages control their own information themselves, using a certified catalogue of criteria, thereby guarding quality and reliability of their web pages.

An example of this is recognition of and compliance with the HON (Health on the Net Foundation) code, a hallmark of quality recognisable by the authorised HON logo on the web page (7). This logo is awarded to web sites whose operators recognise and adhere to the eight HON principles. These principles comprise, inter alia, the marking of pages and articles produced by non-experts, compliance with data privacy rules, clear reference to sources, identification of

sponsors and financial independence of the results or products presented. As a matter of principle, the contents of the sites must be supervised by experts.

The «Discern» project (8) represents the first implementation of quality control aspects on the medical internet and offers operating instructions for the assessment of publications found during an individual research. With regard to information for patients and laypersons, a web site (9) is provided by the Medical Quality Assurance Central Office (Ärztliche Zentralstelle Qualitätssicherung, «äzq»).

However, even these hallmarks cannot comprehensively guarantee the quality of the content of the articles. Final assessment and classification of the results in the context of the problem is left to the oncology pharmacist. Very careful examination should be performed, especially before passing on information to physicians, nurses or patients.

(1) Schmoll et al. (2006): «Kompendium Internistische Onkologie». Springer, Berlin and «Standards in Diagnostik und Therapie» (2006) as CD-ROM;

Berger D.P., Engelhardt R., Mertelsmann R. (2006): Das Rote Buch 2006: Hämatologie und Internistische Onkologie. Ecomed, Landsberg/ Lech;

Engelhardt R. et al: Das Blaue Buch 2007-2008 as CD-ROM; Hämatologie und Onkologie – Manuale Tumorzentrum München. Zuckschwerdt, Munich, also available online at http://tumorzentrum-muenchen.de/aerztebereich/manuale.html;

www.onkodin.de, book on haematology, oncology and supportive therapy, freely accessible, with updates.

(2) http://www.oncolink.upenn.edu/ (Medical and Cancer Center, University of Pennsylvania); www.cancer.gov/cancer_information/ (most recent research results compiled from Physician Data Query PDQ);

http://www.nci.nih.gov/cancer_information/pdq/, from the databases of the National Cancer Institute Cancer and data from Cancerlit;

(3) www.fachinfo.de – Fachinformationsservice Deutschland, Satz-Rechenzentrum Berlin and BPI-Service GmbH;

www.documed.ch – Swiss Drug Index;

Micromedexâ Thomson Healthcare, Drugdex Drug Evaluations – a pharmacological full-text data base on drug information and Martindale as pharmacological Standardnachschlagwerk

The Micromedex databases are also available non-free at http://www.micromedex.com/products/ pharmacists/index.html, see also http://www.clinicalpharmacology.com/ and https://www.epocrates.com/; https://www.curehunter.com/public/showTopPage.do

Informations on therapies and active substances, evidence-based

(4) www.medscape.com u.a. for medline search or via www.nlm.nih.gov/ directly to the National Libary of Medicine of the USA and www.nci.nih.gov/ of the National Cancer Institute;

www.dimdi.de – non-free access to various databases

(5) http://www.tumorzentren.de/ – Shared site of the German tumour centres

(6) http://leitlinien.net/ – scientifically founded guidelines for diagnostics and therapy; AWMF guidelines

(7) http://www.hon.ch/, see there for the rules in English

(8) www.discern.de, patient information quality criteria

(9) www.patients-information.de – Information site by the äqz (Medical Centre for Quality in Medicine);

www.inkanet.de – information net by affected persons for patients and family members;

www.krebs-kompass.de – anticancer information;

www.meb.uni-bonn.de/cancernet/deutsch/index. html – German translation of information by the American National Cancer Institute relating to individual forms of cancer for patients.

4. The Pharmacy as Coordination Centre in Cytostatics Therapy

Acting as the pivotal point in cytostatics therapy, the pharmacy implements quality management of the oncological pharmaceutical service, thereby assuming a share of the responsibility for patients and staff in all areas of cytostatics therapy.

The pharmacy records and processes all medically and toxicologically relevant data relating to cytostatics and, if possible, to accompanying and supportive measures as well.

The data presented are evaluated epidemiologically, examined from clinical, pharmacoeconomic and ecological points of view, documented, used for counseling and training of staff.

Annette Heiny, Brunswick

When almost two decades ago in Germany production of individual cytostatics solutions for chemotherapy was begun, it was initially established centrally in dispensaries. At this point of time, few people imagined that in this very field the pharmaceutical sciences would most strikingly exhibit their forward-orientation and power for innovations.

At the latest when manufacture of cytostatics had spread to public pharmacies and ambulant oncological therapy increased, there was opened up a field whose management required a high degree of additional knowledge. It became obvious that simply acquiring the necessary preparative skills and knowledge would not be sufficient.

Verification of cytostatics prescriptions already requires knowledge necessitating consultation of oncological-medical sources of information. This consultation, however, concomitantly also widens the horizon for further issues.

More and more, the pharmacist has developed into an advisor for the physician, the nursing staff and the patient for all issues relating to cytostatics therapy. Because of the constant changes in therapies, he/she has been and will continue to be able to meet this challenge only by ongoing further training and qualification. This has fostered the realization that comprehensive quality management is appropriate in this field.

With all information on products and therapy converging in the pharmacy, it is expedient to have it function as a communication platform delivering services.

Joint reflection on therapy regimens together with the medical staff results in exchange of knowledge relating not only to cytostatics but also to accompanying therapies and application problems and in correlation of individual experiences with general research results. This leads to improvements of quality both in the treatment of patients and in workplace safety for the staff.

The offer to collect all medical and pharmaceutical data relevant to cytostatics therapy and manufacturing safety and to make them accessible at any time to every member of the oncological team enables and optimizes interdisciplinary cooperation.

The patient and the documentation of his/her data have become the focus of events. The possibility to epidemiologically evaluate existing information is perceived as helpful. This information not only contributes to transparency in the development of costs but, above all, to examination of therapy success in a relative way, and they facilitate discussion of the therapeutic goal.

Obtaining and processing meaningful data is a prerequisite for establishing a coordination centre. The use of modern IT based on the complete network integration of the pharmacies with the prescribing physicians and the shared use of suitable IT programs allowing processing and presentation of all relevant data facilitate efficient and comprehensive consulting by the pharmacist.

The pharmacist can and should assume and fulfil the possible tasks to increasingly add substance to the professional image of the oncology pharmaceutical profession.

References:

Bremberg ER, Hinsing C, Nylén U, Ehrson H, Eksborg S, An evaluation of pharmacist contribution to an oncology ward in a Swedish hospital, J Oncol Pharma Practice 2006, 6: 75-81

McLennan DN, Dooley MJ, Brien JE, Beneficial clinical outcomes resulting form pharmacist interventions, J Oncol Pharma Practice 1999, 5: 184-189

Höckel M, Amulatory chemotherapy:- pharmaceutical care as a part of oncology service, J Oncol Pharma Practice 2004, 10: 135-140

4.1. Waste Disposal

The fundamental principles for waste disposal are (in this order of priority):

1. Avoid waste
2. Recycle waste
3. Dispose of waste

Their goals are to:

1. Protect people
2. Protect the environment

Hazardous wastes and objects contaminated with such are collected

- **separately from other wastes**
- **at the place of origin**
- **in suitable, distinctly labelled collection bins.**

Basically, wastes comprising cytostatics require special monitoring («hazardous», «special» or «toxic» waste). For collection, special bins should be used which can be sealed hermetically after filling. Wastes comprising cytostatics are subject to the Ordinance on Intrastate and Interstate Transport of Hazardous Substances on Roads and Railways («Gefahrgutverordnung Straße and Eisenbahn», GGVSE).

Applicable national and regional regulations must be complied with.

Dr. Annette Freidank, Fulda

The goal of controlled disposal is to protect persons and environment while complying with the legal regulations.

Protection of persons means avoidance of contamination with cytostatics, i.e. that cytostatics are absorbed neither transdermally nor via the airways by inhalation of dusts or aerosols.

All persons handling cytostatics are concerned, including, in addition to pharmaceutical staff responsible for preparation, pharmacy staff responsible for purchase, medical staff on wards and in medical practices applying cytostatics, cleaning and maintenance staff and the delivery and collection staff disposing of cytostatics wastes, as well as patients and their family members (see also chapter 1.1: Persons exposed to cytostatics).

The environmental footprint, on the one hand directly caused by cytostatics, but also by emissions produced during transport or incineration, should be kept as low as possible. Whether, for example, slightly contaminated wastes can be disposed of as household waste, or whether considerable transportation routes with subsequent incineration are required, is a question to be individually decided by each producer of waste.

Compliance with all the legal regulations is often difficult, since – in addition to federal laws – the laws and ordinances of the laender and municipalities and of the EU must be observed. If larger amounts of waste are produced, in consequence of the size of the company or institution a waste officer responsible for planning and implementation will generally be required. In case of doubt, inquire with the competent authorities

Legal regulations

According to the Act for Promoting Closed Substance Cycle Waste Management and Ensuring Environmentally Compatible Waste Disposal (Kreislaufwirtschafts- und Abfallgesetz – KrW-/AbfG),

avoidance,
recycling and
disposal of waste

are the fundamentals of waste disposal.

Central preparation of cytostatics contributes to the fundamental principle of avoiding waste, since a lower amount of cytostatics (approx. 13%) must be discarded, and generally single-use articles may also be saved. Drug safety considerations limit the extent to which recycling is possible, but cost considerations also mean that work is organised so that only a minimum of cytostatics must be discarded. Cytostatics which can no longer be used and materials contaminated with cytostatics must be fed into a controlled waste disposal system. Controlled disposal comprises collecting, packaging, preparing, storage, transport, treatment, recycling and disposal of waste until final disposal. The waste producer shall be responsible.

In addition to the Act for Promoting Closed Substance Cycle Waste Management and Ensuring Environmentally Compatible Waste Disposal, the Waste Act, Infection Protection Act, Workplace Safety Act, Chemicals Act and Hazardous Substances Act as well as the regulations and ordinances by the laender and local authorities must be observed.

Below, the current regulations relating to disposal of cytostatics wastes are cited:

TRHS 525 – Technical Rules for Hazardous Substances – Handling Hazardous Substances in Institutions for Human Medical Care (May 1998)

5.7. Disposal

(1) When disposing of CMR drugs, residues thereof and materials contaminated therewith, the waste disposal regulations of the individual bundesland must be complied with.

(2) Being wastes requiring special monitoring , residual substances and residual solutions must be collected – in accordance with the regulations relating to waste – in specially labelled, sufficiently robust, tightly sealable containers and to be fed into the disposal process.

(3) Reusable clothing or alternatively reusable textiles must be changed immediately after contamination, to be collected without further manipulation and to be processed in the laundry.

(4) Information on labelling waste collection and transport containers can be found in the TRHS 201 «Labelling of Wastes for Handling».

(5) Further information on proper handling of wastes in health care can be found in the LAGA (Laender Waste Management Study Group) bulletin «Avoiding and disposing of wastes in public and private health care institutions».

(6) Since contamination of filters cannot be excluded, for reasons of precaution protective measures at least analogous to no. 5.4 par. 2 should be implemented when replacing filters. The protective coat does not have to be liquid-tight.

(7) When purchasing new hoods, make sure that the filters that do not have to be disassembled for disposal.

from: http://www.baua.de/nn_5846/de/Themen-von-A-Z/Gefahrstoffe/TRHS/TRHS-525__content.html?__nnn=true (August 17th, 2008)

Federal Directive on the Preparation of Ready-to-administer Cytostatics Solutions in Pharmacies

Study Group of Senior Medical Officials (September 1998)

7 Disposal

7.1 Separation of cytostatics wastes into wastes which are preferably incinerated as toxic waste, and other wastes which are produced during handling of cytostatics and may be disposed of together with domestic waste is governed by the applicable laws of the individual land (TRHS 525).

7.2 Collection of contaminated wastes (including residues) in sufficiently robust, tightly sealable single-use containers (§ 36 VI 6 Ordinance on Hazardous Substances, Gefahrstoffverordnung).

7.3 Labelling of waste bins in accordance with the Ordinance on Hazardous Substances (§ 36 VI 7 Ordinance on Hazardous Substances; TRHS 201)

7.4 Low-contamination replacement of filters by expert and properly performed, supervised and documented disposal of filter elements. When purchasing new materials, filters must be selected that do not have to be disassembled for disposal (TRHS 525).

7.5 Proper decontamination of obsolete equipment before scrapping.

from Cyran/Rotta, as of August 1st, 2003

Cytostatics in health care – Information on safe handling of cytostatics (order number M620)

Professional Association for the Health and Welfare Services (Berufsgenossenschaft für Gesundheitsdienst and Wohlfahrtspflege)

5.4 Waste disposal

Cytostatics residues and materials contaminated with cytostatics may be produced both during preparation and application.

Thus, during preparation varying amounts of the following are produced:

- residual quantities of concentrated cytostatics solutions (injections)
- residual quantities of diluted solutions (infusions, instillations)
- empties (original containers, syringes)
- manufacturing and preparation implements (hollow needles, swabs, mats, gloves etc.)

During application, the following are usually produced::

- empties (syringes, infusion containers)
- cytostatics residues of injections not completely used up for the patient

- infusion residues in lines, infusion kits, bags and bottles not completely emptied

To avoid unnecessary dangers to staff and third parties from wastes containing cytostatics, already at the point of origin the waste material must be collected (cytostatics hood in the pharmacy, application preparation, treatment room) separately into waste bins and made available for internal transport.

In in-house collection and later transfer to the waste disposal contractor assigned, the legal regulations of the individual land must be observed. The laender focus on the so-called «Guideline on Correct Disposal of Wastes from Health Care Institutions» by the Laender Waste Management Study Group (Länderarbeitsgemeinschaft Abfall, LAGA). The goal of this guideline is – taking into account economic reasonableness – to guarantee safe and correct disposal of waste in a way avoiding, inter alia, environment pollution.

According to this, the following cytostatics-containing wastes in particular must be disposed of as hazardous wastes («toxic wastes»):

- original containers not completely emptied (e. g. cytostatics left after termination of a therapy or not used as intended)
- lapsed CMR drugs in their original packages
- residues of dry substances and broken tablets
- syringe barrels and infusion bottles/bags with clearly visible levels of liquid/residual contents (> 20 ml)
- infusion systems and other materials contaminated with cytostatics (> 20 ml)
- materials evidently contaminated by release of large quantities of liquid or solid matter during preparation or application of the aforesaid drugs (such as mats, highly contaminated personal protective equipment)

These wastes should be collected into waste bin operated by foot pedal or other mechanisms in order to avoid direct contact with the hands/gloves.

The wastes must be transferred to the waste disposal contractor in compliance with the legal regulations pertaining to hazardous substances and workplace safety, stating the legal waste designation «AS 18 01 08* – Cytotoxic and cytostatic wastes», the UN Hazardous Substance number (see below) and the sender, in sealed and undamaged containers. Basically, the hazard sign # 6.1 («skull» symbol) must be attached to the disposal containers.

Waste containers for cytostatics labelled with hazard sign # 6.1 do not require additional labelling according to the Ordinance on Hazardous Substances (hazard symbol T, skull on orange background).

Cytostatics wastes disposed of under the legal waste designation «AS 18 01 08* – Cytotoxic and cytostatic wastes» should be associated with one of the following UN numbers:

- UN 2810 «Toxic organic liquid, not listed elsewhere (n.l.e.)»: suitable for liquid cytostatics residues. For small amounts of liquids, the packaging must conform only to the requirements of packaging class III.
- UN 2811 «Toxic organic solid, n.l.e.»: suitable for solid cytostatics residues (such as broken tablets) and highly contaminated materials.
- UN 3243 «Solids with toxic liquid, n.l.e.»: may be used as an alternative to UN 2810 and UN 2811. It must be guaranteed that the transport container comprises a sufficient amount of binder to directly absorb any possibly released liquid.

In general, the following slightly contaminated wastes are not included into the listed group of hazardous wastes:

- protective sleeve cuffs
- gloves
- respiratory protection masks
- single-use coats
- plastics and paper materials

- swabs
- wiping towels
- empty cytostatics containers after regular use (ampoule bottles, syringes, infusion accessories, infusion containers)
- air filters of safety hoods.

Slightly contaminated cytostatics wastes should be collected in plastic bags already at the location of origin before final disposal, and [the bags] should be sealed. They are disposed of using the official designation «AS 18 01 04 – wastes whose collection and disposal do not pose any special requirements with regard to prevention of infections (such as wound bandages and plaster casts, laundry, single-use clothing, diapers)». Usually they can be disposed of together with hospital waste (previously class B waste). Sharp or peaked objects such as hollow needles, transfer needles, spikes and broken glass must be collected in puncture-proof and safely sealable containers (such as needle drop boxes) at the point of origin of the wastes.

Because of the dilution effect, body fluids and excreta are not to be considered as hazardous. Excreta may be discharged into the sewerage.

General hygiene guidelines for the handling of excreta must be complied with.

In disposing of cytostatics-containing wastes the waste disposal regulation by the county or city must be observed (e.g. with regard to the obligation to offer waste).

from: http://www.bgw-online.de/internet/generator/Inhalt/OnlineInhalt/Medientypen/ bgw_20themen/M620__cytostatics__im__Gesundheitsdienst.html (17.8.2008)

Guideline on Correct Disposal of Wastes from Health Care Institutions, dated January 2002

Laender Waste Management Study Group (LAGA) (January 2002)

These guidelines replaces the 1991 bulletin by the Laender Waste Management Study Group (LAGA) on the avoidance and disposal of wastes from public and private health care institutions. The guidelines are conceived of as recommendations and give practical advice on the disposal of wastes from any health care institutions with the aim of ensuring safe and proper waste disposal. The are compliant with European law.

The two groups relevant for disposal during the handling of cytostatics are the wastes according to waste keys 18 01 04 and 18 01 08, which will be contrasted below:

Disposal in practice

Cytostatics wastes are classified into slightly and heavily contaminated wastes. Assignment to either of the two groups has been considerably simplified by the new LAGA guideline.

For either group, collection separate from other wastes is necessary. Sorting or transferring from one container to another is prohibited. Heavily contaminated wastes must be collected and transported in containers of approved type (Ordinance on Intrastate and Interstate Transport of Hazardous Substances on Roads and Railways (Gefahrgutverordnung Straße and Eisenbahn, GGVSE)) which must fulfil specific standards (disinfectable, water-tight, proof against puncture also by needles, with dispenser, approved type). Less heavily contaminated wastes may be collected in tear-proof, moisture-resistant and impervious containers and be disposed of together with household waste.

Waste code (AS)	
18 01 04	18 01 08*
AVV («Waste Index Directive», Abfallverzeichnis-Verordnung)	
wastes whose collection and disposal do not pose special requirements with regard to infection prevention	cytotoxic and cytostatic drugs
Waste classification (control classification)	
must be controlled during disposal	must be specially controlled during disposal
Waste definition	
Wastes contaminated with blood, secreta or excreta such as wound dressings, plaster dressings, single-use clothing, diapers, single-use articles etc.	CMR drugs according to TRHS 525; wastes consisting of residues or off-specification batches of such drugs or which are visibly contaminated with CMR drugs (heavily contaminated).
EAKV 1996 («old» waste code according to the Ordinance on Introduction of the European Waste Catalogue)	
18 01 04	18 01 05 D1*
LAGA Group (previous LAGA classification as A to E)	
B	D
Places of origin	
entire area of patient care	area of patient care using cytostatics and virustatics (e.g. oncology), pharmacies, medical practices, lab area

Constituents	
Wastes slightly contaminated with cytostatics, such as • swabs, • protective cuffs, gloves, • respiratory protection masks, • single-use coats, • plastics and paper materials, • wiping cloths, • empty cytostatics containers after regular use (ampoule bottles, syringe barrels without needles, etc.) • air filters and other slightly contaminated material from safety hoods	• original containers not completely emptied (e. g. cytostatics left after discontinuation of a therapy or not used as specified) • expired CMR drugs in original packages • residues of dry substances and broken tablets • syringe barrels and infusion bottles/bags with clearly visible levels of liquid/residual contents (› 20 ml) • infusion systems and other materials contaminated with cytostatics (› 20 ml), e.g. pressure release and transfer systems • materials evidently contaminated by release of large quantities of liquid or solid matter during preparation or application of the aforesaid drugs (such as mats, highly contaminated personal protective equipment).
Collection, storage	
Collection in tear-proof, moisture-resistant and impervious containers. Transport only in carefully sealed containers. No transferring to different containers (not even in the central storage area), sorting or pretreatment (unless submitted in pressure container)	In puncture- and breakage-proof single use containers of approved type. No transferring to other containers or sorting! No pre-treatment. Transport and storage only when tightly sealed.

Disposal	
Incineration in approved waste incineration plant (Hausmüllverbrennung, domestic waste incineration) or landfill disposal while still permissible. Containers with major amounts of body fluids may be emptied into the sewerage, observing aspects of hygiene and infection prevention (comply with municipal waste water regulations).	Disposal of wastes requiring special control with certificate of disposal into approved waste incineration plant, e. g. toxic waste incineration (Sonderabfallverbrennung, SAV)

Labelling of containers

The cytostatics waste containers 18 01 08* must be labelled as follows:

Waste code 18 01 08*

UN designation as specified by the Ordinance on Hazardous Substances (see M620)

Waste producer.

For the containers with less heavily contaminated wastes there are no labelling requirements, but nevertheless appropriate labelling is recommended for in-house transport.

Air filters

According to the LAGA guidelines, air filters of safety hoods may be classified as less heavily contaminated wastes. They must be assumed to be contaminated; after careful work, however, their contamination should be only slight. Therefore the filters must no longer be transported, in transport containers of approved type, to a toxic waste incineration facility and burnt there. This obviates the laborious sawing-up of these filters which was necessitate by the transport containers holding no more than 60 l. For transport, impervious and tear-proof sacks of sufficient size may be used.

With regard to workplace safety, the German Hospital Association furthermore recommends having in-house low-contamination filter replacement performed with appropriate safety measures (e.g. encapsulation), trained staff etc.

In new hoods compliant with DIN 12980, the design facilitates replacement of the filter without contamination (see chapter 2.2 Ventilation equipment).

Safety hoods

Cytostatics preparation hoods which are no longer operational are generally slightly contaminated, in the same way as air filters. Whether they must be classified as less strongly contaminated wastes and can be scrapped after cleaning by informed and trained staff, must be decided on a case basis. There are no standardised concepts yet.

Excreta

High concentrations of cytostatics may be excreted over extended periods of time, so excreta will be generally contaminated. Some cytostatics are unstable and rapidly inactivated, other remain detectable for longer periods of time.

It it recommended to flush excreta into the sewerage with plenty of water. Care should be taken to avoid contamination. This means that the cleaning staff on the wards, the patients and, if applicable, their family members must be informed to wear gloves when handling excreta (see chapter 4.9 Handling excreta).

Disposal plan

Although a disposal plan is not mandatory until the quantities of controlled wastes have reached a defined level, the disposal of all cytostatics should be regulated and documented.

The following points must be observed:

- which wastes are produced
- where the wastes originate (at a few centres – distributed over many wards)
- spatial conditions (transport routes, delivery and collection service)

- centralised or distributed disposal (transport of wastes in case of central disposal)
- classification of wastes produced (the more persons are involved, the simpler the classification should be)
- local/municipal regulations
- information and training of the persons involved (how often, who informs whom)

All persons involved should be made to participate from the very beginning (e.g. waste officer, pharmacists, medical staff, hygiene department etc.)

References:

Arbeitsgemeinschaft der leitenden Medizinalbeamtinnen und –beamten der Länder (AGLMB) Herstellung applikationsfertiger Zytostatikalösungen in Apotheken. Deutsche Apotheker Zeitung 1998;138:4176-4182 B

Berufsgenossenschaft für Gesundheits- und Wohlfahrtspflege. Sichere Handhabung von Zytostatika. (BGW), 1998

Carstens G. Handhabung von Zytostatikamüll. Krankenhauspharmazie 1992;13:105-106

Cass Y, Musgrave CCF. Guidelines for the safe handling of excreta contaminated by cytotoxic agents. Am J Hosp Pharm 1992;49:1957-1958

Kaijser GP, Underberg WJM, Beijnen JH. The risks of cytotoxic drugs. II Recommendations for working with cytotoxic drugs. Pharm Weekbl (Sci) 1990;12:228-235

Kraft U. Problematik der Abfallentsorgung in den Krankenhäusern. Das Krankenhaus 1998:683-686 LAGA-Richtlinie (http://www.laga-online.de)

Mehrtens T. Umgang mit Ausscheidungen nach Zytostatika-Therapie. Krankenhauspharmazie. 2000;21:148

Pilz T. Anwendung des europäischen Abfallkataloges. Das Krankenhaus 1998:678-682

Schaaf D. Entsorgung von Arzneimitteln und Zytostatika im Krankenhaus. Krankenhauspharmazie 1990; 11:183184

Schaaf D. Umgang mit Zytostatika. Krankenhauspharmazie 1994:15:588-591

Scherrer M, Daschner F, Strehl E, van Gemmern R. Zytostatika: Umgang und Entsorgung. Krankenhauspharmazie 1997;18:176-178

4.2. Decontamination after Inadvertent Release of Cytostatics

Workplace-related operating instructions must be available for the measures to be taken in case of inadvertent release. It must be based on a danger analysis. These instructions must describe the precise measures from cleaning to disposal in order to prevent damage to persons and environment. It comprises definition and presence of a decontamination kit, also known as spill kit. This spill kit must be accessible in all areas where cytostatics are handled. The pharmacy as central institution can guarantee this.

The spill kit includes:

- operating instructions
- marking material
- single-use overall
- overshoes
- respiratory protection mask (P3)
- 3 pairs of protective gloves
- protective goggles, with side protection and to be worn over personal glasses
- single-use towels
- hazard note
- implements for collecting up broken glass
- waste bags
- form sheet for documenting an accident
- information sign «No entrance»

Removal and disposal of spilled cytostatics may be performed only by properly instructed staff.

For the procedure to be followed after inadvertent release, a danger analysis must be produced, based upon these results operating procedures must be written, and the procedure must be instructed and trained at least once a year.

Ludwig Metz, Burglengenfeld; **Klaus Meier**, Soltau

Danger analysis, operating instructions, instruction and training

All staff handling cytostatics must be instructed orally and on the basis of the operating instructions about potential hazards and suitable protective measures (see chapter 1.3. Danger assessment, operating procedures and instructions). Written workplace-related operating instructions providing unambiguous information on measures in case of damage should be present wherever cytostatics are handled (from incoming goods department to ward and disposal). A previously conducted danger analysis is the basis for the operating instructions. For acquiring the necessary practical skills, performing regular training is expedient and indispensable. Training must be done under realistic conditions, e.g. with protective clothing and collection of a «test contamination», and instructed by competent persons (see chapter 3.2.3 Respiratory protection, protective goggles, overshoes).

Legal basis: TRHS 525, Ordinance on Hazardous Substances, Bulletin M 620

Decontamination procedures mandatory after spill of cytostatics are listed in the TRHS 525 (Technical rules for Hazardous Substances), in the Ordinance on Hazardous Substances § 14 and in the Bulletin M 620.

- Under item 5.5 «Actions upon inadvertent release of CMR (cancerogenic, mutagenic, reproduction-toxic) drugs», TRHS 525 mandates the following:

- (1) Contaminations with spilled CMR drugs (dry substances, broken tablets, preparations) must be removed properly at once, to this end a kit with personal protective equipment must be kept ready. For collecting the substances, single-use towels or pulp may be used. If any dry substance has been spilled, the materials used to collect them must be dampened.
- (2) In skin has been contaminated with CMR drugs, the affected area must immediately be rinsed with plenty of cold, running water.
- (3) Splashes into the eyes must immediately be rinsed thoroughly for at least 10 minutes with plenty of water or isotonic saline. Then an ophthalmologist must be consulted without delay.
- (4) For collecting contaminated broken glass, use appropriate aids and wear an additional pair of protective gloves to guard against mechanical hazards.
- (5) The contaminated surfaces must then be cleaned.
- The Ordinance on Hazardous Substances § 14 describes the information which the operating instructions must contain inter alia.
- In chapter 10.3, the new bulletin M 620 presents examples for operating instructions and comprises valuable information on the handling of cytostatics.

Spill Kit

Spill kits can be compiled individually by the user, or they may be purchased ready for use. The contents should include overall, overshoes, respiratory mask (filter mask for respirable dust P3 (see chapter 3.2.3.1. Respiratory protection)), 3 pairs of protective gloves, suitable protective goggles (with side protection and to be worn over personal glasses (see chapter 3.2.3.2: Protective goggles)), shovel, cardboard box, bag, pen, accident protocol form sheet, hazard sign, paper towels and cable clips. The ESOP (European Society of Oncology Pharmacy) spill kit is recommended.

Spill kits are used for safe removal of smaller amounts of released cytostatics substances or solutions. If larger amounts of CMR substances have been re-

leased, the applicable alarm or disaster plans must be followed. The superior is responsible for correct use of the spill kit.

Clearing of released substances

Decontamination of persons followed by medical care has precedence.

Contaminated areas must be secured immediately, in particular areas which are relatively freely accessible (e.g. on wards, in practices, in the receiving section of pharmacies etc.) to prevent danger by spreading to further persons. Spills must be marked. In case of powdery contaminations, care must be taken that in this area there is no airflow or draft (ventilation, door), For absorbing spilled liquid, use single-use towels with high capacity for the absorption of liquids. For decontamination of powdery cytostatics, wet the towels with water before to prevent dispersing the substance as dust. A hand brush must not be used under any circumstances because of the danger of dispersal by turbulences. For safe collection of broken glass and other sharp objects, a shovel and a cardboard box for holding up or a pair of tongs may be used. All implements used, including the personal protective equipment, are single-use articles and to be disposed of after use.

The contaminated surfaces must be cleaned thoroughly, progressing from the outside to the inside. Studies on decontamination of primary packaging material showed that the following two-step procedure yields the best results: Clean

1. with 0.05 M NaOH solution and

2. with 98% isopropyl alcohol.

Isopropyl alcohol must be handled carefully to avoid danger of explosions [1]. These cleaning agents and additional surfactants must be kept reading in the cytostatics preparation area, plus a sufficient amount of pulp, since the spill kits comprise only basic material.

To guarantee in-depth safety, it is recommended to perform wiping tests after cleaning to document efficacy of the cleaning.

Disposal

All contaminated objects, such as protective clothing, towels, fragments etc. are packaged into the bag (supplied as a part of the spill kit), sealed and then quickly collected in a suitable waste container. The container must be labelled to rule. When selecting the waste containers, the commercially available approved bins should be used which cannot be opened again once they are closed. They are disposed of as wastes requiring special monitoring. Disposal must be conducted in accordance with the regulations and to be supervised by skilled professional staff.

Summary

Removal or decontamination of a spill requires much experience.

The article above describes the basics of the procedure, indicating the legal requirements. In-depth study of the relevant literature is required to perform correct decontamination.

References:

1. Kiffmeyer, T. Dr.: «Vorkommen und Beseitigung von Außenkontaminationen bei Primärpackmitteln» 6. Fortbildungsveranstaltung «Sicherer Umgang mit Zytostatika», IUTA, Duisburg 2002

2. Yodaiken R.E. & Bennett D.: OSHA work-practice guidelines for personnel dealing with cytotoxic drugs. Am J HospPharm 1986;43:1193-1204

3. Scherrer, M., Daschner F. et al., Zytostatika: Umgang und Entsorgung, Krankenhauspharmazie 1997; 4:176-178,

4. Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (BGW) (Hrsg.): BGW-Expertenschrift. Zytostatika im Gesundheitsdienst – Informationen zur sicheren Handhabung von Zytostatika. Hamburg 2008. http://www.bgw-online.de/internet/generator/Inhalt/OnlineInhalt/BGW-Mitteilung/2008/3-2008/Artikel/Service/Zytostatika__Gesundheitsdienst.html

4.3. Extravasation (Paravasation)

Inadvertent escape of cytostatics with vesicant potential into surrounding tissue represents a serious complication of intravenous cytostatics therapy, necessitating immediate treatment.

On all oncological wards and in all therapeutic institutions, instructions for prevention, a catalogue of measures for treatment and a documentation form sheet for the performed treatment and follow-up of any paravasation should be available.

A kit for the immediate treatment of paravasation, adapted to the treatment recommendations, should comprise all materials and drugs required and be placed at an easily accessible location on the ward or in the oncological therapy institution.

Christine Bismarck, Berlin, and **Tilman Schöning**, Heidelberg

Paravasation is a potential complication in intravenous cytostatics therapy. The term «paravasation» denotes inadvertent instillation or escape of a drug solution into perivascular spaces and subcutaneous tissue during administration.

Even low amounts of vesicant drug escaping into perivascular spaces may lead to serious consequences such as severe ulcerations, necroses and pain of the skin. Tissue atrophy with damage to nerves and joints as well limitation of the function of the affected limb may result. Hospitalisation, skin transplants or even amputation may become necessary if treatment is not begun immediately or if the measures taken are ineffective.

Statements relating to the incidence of paravasation are difficult to make. Published data are inhomogeneous and vary from 1 to 6%, with frequency increasing in correlation with individual risk factors such as advanced age of patient, longer-term cytostatics treatment or radiological pre-treatment.

Paravasation may occur even with central access systems (port-a-cath system, venous catheter).

Classification of cytostatics according to the potential to cause necrosis

The cytostatics used in oncological practice differ not only in term of their various mechanisms of action but also of the potential for causing local damage in case of paravasation. It is therefore of crucial importance to know possible local complications which may arise during parenteral application of these substances and to familiarize oneself with measures for prevention and therapy. In the genesis of paravasates, a number of factors such as osmolarity of the solution, specific tissue toxicity of the substance administered, vasospasticity, infusion pressure, tissue pressure and regional anatomic situation play a role. Type and scope of local damage depend on the substance properties of the cytostatic, the excipients and the amount of substance leaked.

With regard to substance properties, differentiation is made between «non-vesicant», «irritant» and «vesicant». Non-vesicants do not cause any local reaction in case of paravasation, and some of them, such as methotrexate or cytarabine, may also be applied subcutaneously or intramuscularly. Irritants such as bendamustine may locally cause reddening and burning pain up to phlebitis. Vesicants such as anthracyclines or vinca alkaloids may be associated with additional development of ulcerations or necroses in case of paravasation. Here, after initial oedematous swelling of the tissue, reddening follows, which turns into a brownish induration over the course of a few days. The ulceration process may last for weeks to months and affect wide areas around the site of paravasation.

The final state may comprise dys- and atrophy, scarring, damage to nerves, muscles, sinews and bones and limitation or loss of function of extremities. Sometimes, skin transplants or even amputations may be required.

Non-vesicant cytostatics

Do not irritate the tissue and lead to paravasates which often remain unnoticed and thus untreated.	
L-asparaginase	ifosfamide
antibodies	interferones
bleomycin	interleukin-2
carboplatin	irinotecan
cladribin	methotrexate
cyclophosphamide	nimustine*
cytarabine	pegaspargase
estramustine	pentostatin
etoposide phosphate*	raltitrexed
fludarabine	topotecan
5-fluorouracil	
goserelin	* final assessment hampered by lack of experience with paravasation

Irritant cytostatics

Cause local pain, burning or atypical inflammation of the vessel up to phlebitis, but no necrosis of the tissue	
bendamustine	etoposide
bortezomib	fotemustine
busulfan	gemcitabine
carmustine	melphalan
cisplatin (‹ 0,4 mg/ml)	streptozocin*
dacarbazine	teniposide
daunorubicin in liposomes	treosulfan*
docetaxel	trimetrexate*[1]
doxorubicin in liposomes*	*final assessment hampered by lack of experience with parava-sation

Vesicant cytostatics

Have necrotising potential	
amsacrin	
cisplatin (›0.4 mg/ml)	mitoxantrone
dactinomycin	oxaliplatin
daunorubicin	paclitaxel
doxorubicin	vinblastine
epirubicin	vincristine
idarubicin	vindesine
mitomycin c	vinorelbine

[1] Do not «soak» the affected area in DMSO but only brush it with the cotton dabber. Too much DMSO increases skin permeability and thus absorption of the cytostatic.

Measures for the prevention and treatment of paravasates

Since randomized trials on the treatment of paravasates are ethically unimaginable, recommendations for prophylaxis and therapy are largely based on empiricism, clinical case reports, guidelines by the drug manufacturers and animal studies. However, because of differing skin structure animal models, e. g. in mice, cannot be readily transferred to humans.

Existing data are frequently contradictory or irreproducible, not least because of insufficient documentation of treatment measures taken. Nevertheless, many authors have published guidelines for prevention and therapy of paravasates. It is up to the pharmacy to review and evaluate the existing data and to produce guidelines for prevention and therapy of cytostatics in the oncological team.

Preventive measures

From this point of view, prevention is of crucial importance. Prior to any therapy, the patient must be informed. Vesicants may be administered only by skilled staff experienced in handling cytostatics. Venous access is pivotal to preventive measures. Cytostatics with a potential for tissue damage should be administered via central access systems such as port-a-cath systems or central venous catheters. Nevertheless, even here a risk of grave paravasation events cannot be excluded. After implantation of a catheter or port-a-cath, radiologic position control or venography are therefore advisable. If central application is not possible, and administration must be performed via a peripheral vein, a «strong" vein at an anatomically advantageous location should be chosen. Preferably, this out to be the midst of the forearm. Critical locations such as the back of the hand, wrist or elbow flexure are NOT to be chosen. Steel needles and multiple punctures, in particular distal in the access area, must be avoided. Before application, correct position of the (peripheral or central!) access system must be controlled at any rate by aspiration of blood and rinsing (with carrier solution) without resistance. During application, the limb should be safely fixated, and the application site freely visible. Information enables the patient to report abnormalities early. Ongoing infusions must be monitored regularly.

The current consensus on prevention of [extravasation of] cytostatics can be learned from fig. 1.

Consensus: Paravasation Prevention

1. Information and instruction of the patients

- patient information form sheet
- immobilization of the limb during application
- immediate reporting of symptoms such as pain, burning, stinging, swelling or reddening

2. Access system

- implant newly if possible
- preferred location for application: thick veins in the middle of the forearm
- location to be avoided for application: back of hand, wrist, elbow flexure
- avoid multiple punctures, in particular punctures distal of a previously punctured vessel
- use the thinnest venflons possible **(no steel needled)**
- consider early the option of a port-a-cath system
- safely fixate the limb; the application site must remain visible

3. Control of position

- aspiration of blood
- rinsing must be possible without resistance
- central venous access system: in doubt control position by radiology, venogram

4. Application

- only by qualified staff, **avoid hurrying!**
- for continuous application via infusions pumps implant port-a-cath system
- do not inject against resistance
- close monitoring

5. Rinsing

- only with the carrier solution of the most recently administered cytostatic

fig.1: Consensus on the prevention of paravasation

General therapeutic measures

A paravasate will usually become conspicuous by pain, reddening or vesication in the vicinity of the application site. If paravasation is suspected, the infusion must be stopped at once. Infusion line or syringe, respectively, must be replaced with a 5 ml syringe, and as much of the paravasate as possible must be aspirated. Next, the venous access system must be removed under condition of aspiration. If significant amounts of liquid should have leaked into the tissue, or if liquid bubbles are present, these must be punctured by star-shaped puncture from several sides using small syringes (1 ml) and thin, sterile needles. To this end, a new needle must by used for each puncture. After this, the limb must be placed in an elevated position and immobilized. Depending on the substance, dry cooling or application of dry warmth may be indicated (see «Measures specific for individual substances»). If the substances are vesicants, the paravasation site must be presented to a (plastic) surgeon within 72 hours. At any rate, the measures taken as well as the follow-up must be documented for further evaluation of the recommendations.

These measures likewise apply to paravasates in case of central venous access systems.

Measures specific for individual substances

Supplementary therapy guidelines are based on the individual paravasated substance. This means supportive measures such as application of dry cooling or warmth as well as the use of antidotes such as dimethyl sulphoxide (DMSO), hyaluronidase or dexrazoxane. The recommendations are essentially based on few existing data and clinical experience.

Use of dry cooling

Application of dry cooling prevents further spreading of paravasated substance and harmful metabolites into the surrounding tissue by reducing local perfusion. In the case of anthracyclines in particular it must be expected that further spreading of toxic radicals released by dying cells may lead to large-scale ulcerations.

The location of the paravasation should be cooled several times a days for approx. 15 minutes. This measure is recommended for anthracyclines, amsacrin, cisplatin, dactinomycin, liposomal doxorubicin and liposomal daunorubicin, mitomycin C, and for mitoxantrone. No cooling must be applied if dexrazoxane is used as an antidote for anthracyclines. With oxaliplatin, likewise no cooling may be used.

Use of dry warmth

This is to stimulate perfusion of the tissue affected by paravasation to achieve better removal of the paravasated substance. The treatment should take place up to four times a day for about twenty minutes up to three days after paravasation. Use of dry warmth is recommended after paravasation of vinca alkaloids. It must be avoided explicitly after paravasation of taxanes.

Hyaluronidase

Star-shaped injection of hyaluronidase into the environment of the paravasation size aims at dissolving the structure of the adjacent connecting and supporting tissue in order to achieve faster removal of the substance from the tissue to reduce contact time. Hence also combination with dry warmth in the case of vinca alkaloids. Depending on the size of the paravasate, into the vicinity of the affected location up to 1500 I.U. should be injected s.c., and per application site some 250-300 I.U. should be injected. Moreover, previously approx. 300 I.U. may be injected directly into the paravasate via the still positioned access system. Hyaluronidase should be used within one hour after paravasation [16]. These measures may be very painful to the patient.

Thus, in this case supportive analgesic therapy must be contemplated.

Dimethyl sulphoxide

Dimethyl sulphoxide (DMSO) is claimed to have anti-inflammatory, radical inactivating and vasodilative effects in the treatment of paravasates. Prior to approval of dexrazoxane as Orphan Drug, DMSO was considered the only antidote supported by clinical data for paravasations of anthracyclines. In addition, it is used for other substances such as amsacrin, dactinomycin, mi-

toxantrone, mitomycin, and high-concentration cisplatin (> 0.4 mg/ml). Use as antidote is based on several trials in small numbers of patients and various observations from use. Some of the results differ markedly. Two prospective open trials on the topic use of 99% DMSO in paravasation of various substances have been presented [8, 9]. In the first trial, 16 patients were monitored for 3 months after immediate treatment (within no more than 20 minutes). No patient required surgical intervention. In the second trial, in addition to immediate application of DMSO (within no more than 10 min) dry cooling was applied every 8 hours for 3 days. All in all, 53 patients treated with DMSO and cooling after paravasation of anthracyclines were evaluated. In 38 patients, treatment resulted in complete remission of complaints, while in 14 patients the treatment period had to be extended to up to 6 weeks. In one patients, there was complete remission of the symptoms within one week but a month later a recall reaction resulting in a small ulceration at the initial paravasation site. DMSO treatment was well tolerated in both trials. In some cases, slight, local burning after application, slight erythema formation at the site of application and a significant garlic-like reek in the air exhaled by the patients were noted. The results show that use of DMSO after paravasation of anthracyclines and other defined cytostatics may be sensible. However, the reported results must be examined critically.

Unequivocal proof of paravasation and indication of the paravasated volumes are still missing. Bertelli et al. justly point out that not all paravasations occured result in ulceration, but only a fraction of them does.

DMSO is applied topically to the paravasate area as a 99% solution four to six times a day for at least 7 – 14 days. It is mandatory to perform application without pressure, «soaking" of the tissue must be avoided. Sufficiently long periods of treatment are particularly important.

Dexrazoxane (Savene®)

Since 2006, Savene® has been approved by the EMEA as an Orphan Drug, representing a novel and at the same time the currently only approved option for the treatment of anthracycline paravasates.

It is not fully understood how dexrazoxane prevents necroses, even though two modes of action of the substance are already known. Primarily, the open-ring metabolites produced by intracellular hydrolysis bind iron, thereby reducing iron-dependent oxidative stress by free radicals. In addition, the drug has antineoplastic effects by inhibition of the enzyme topoisomerase II. However, it is not known to which degree these mechanisms contribute to protection of the tissue [15].

The approval is based upon two multicentric, prospective studies without comparative branch (clinical data of previously conducted measures with DMSO were not used for comparison) with a total of 54 patients from both trials included into evaluation [10]. The primary endpoint was the rate of surgical interventions, amounting to 1.8% (one out of 54 patients). The studies for approval were exclusively based on preclinical studies in mice plus several case reports [11-13]. With regard to data quality, the authors invoke in particular verification of the paravasates by fluorescence microscopy tissue biopsy, which has not taken place in other trials, e. g. with DMSO. With regard to the paravasated volumes in the cases verified as anthracycline paravasates, no data are provided.

Moreover, the data relating to the rate of surgical interventions after anthracycline paravasation obtained by the authors from literature (25 – 50%) must be viewed with caution (possible effective treatment with DMSO remains unconsidered) so that it remains unclear in how many cases without treatment surgical intervention would really have been required.

Dexrazoxane should be applied as quickly as possible and no later than 6 hours after paravasation of anthracyclines, for three days once a day. Administration must be performed intravenously at the contralateral arm, the duration of the infusion is 1 – 2 hours. On each of days 1 and 2, 1000 mg/m², on day 3, 500 mg/m² must be administered, the absolute dose per individual administration amounting to 2000 mg. As the effect of additional measures such as application

of cold and concomitantly of DMSO has not been determined yet, no such measures should be undertaken. In animal models, concomitant application of DMSO was associated with a rather high percentage of small wounds, so that once treatment with DMSO has begun, addition dexrazoxane treatment is rather discouraged. Side effects observed when using dexrazoxane were nausea, vomiting, diarrhoea, mucositis, myelosuppression and increase of transaminase levels. Influence of previously administered chemotherapy cannot be excluded here. In the context of impaired renal function, an increase in myelosuppression was described. In addition, dexrazoxane shows mutagenic potential in vivo (murine bone marrow cells) [14]. There are also suggestions of possible but unproven carcinogenicity [14].

Savene® has a high potassium content, hence plasma levels in patients inclined to hyperkaliaemia should be monitored closely during administration. The high sodium content may likewise be important in patients under sodium restriction.

As the existing data do not allow reliable statements regarding the risk of ulcerations to be treated surgically depending on the paravasated volume of anthracycline, efforts to establish scientifically recognized criteria relating to the use of dexrazoxane appear desirable from clinical and economic perspectives.

Cytostatic	Antidote
doxorubicin daunorubicin epirubicin idarubicin	Apply dimethyl sulphoxide (DMSO) 99% four to six times a day for at least 7 – 14 days with a sterile cotton pad to the whole paravasation area without exerting pressure, and let air-dry well[1]. The area treated should be twice as large as the paravasate area. Dry local cooling several times a day for 15 minutes **OR** dexrazoxane (Savene®) as quickly as possible, no later than 6 hours after paravasation. 1000 mg/m² i.v. on each of days 1 and 2, and 500 mg/m² on day 3. Surgeon's opinion within 3 days.
dactinomycin mitomycin c mitoxantrone amsacrin cisplatin	Apply dimethyl sulphoxide (DMSO) 99% four to six times a day for at least 7 – 14 days with a sterile cotton pad to the whole paravasation area without exerting pressure, and let it air-dry well[2]. The area treated should be twice as large as the paravasate area. Dry local cooling several times a day for 15 minutes. Surgeon's opinion within 3 days.
vincristine vinblastine vindesine vinorelbine	Let hyaluronidase up to 1500 I.E. infiltrate into the paravasate area. Gentle, dry warmth therapy first for 60 minutes, then four times a day for 20 minutes. Surgeon's opinion within 3 days.
paclitaxel	Let hyaluronidase up to 1500 I.E. infiltrate into the paravasate area.

Fig. 2: Measures specific for individual substances

[1] Do not «soak» the affected area in DMSO but only brush it with the cotton dabber. Too much DMSO increases skin permeability and thus absorption of the cytostatic.

[2] Do not «soak» the affected area in DMSO but only brush it with the cotton dabber. Too much DMSO increases skin permeability and thus absorption of the cytostatic.

Contents of the paravasate emergency kit

Introduction of a paravasate emergency kit enables the attending physicians and nurses to react quickly, and contributes to prevention of severe consequences.

Contents of the paravasate emergency kit:

• DMSO puriss. 99%	2 × 100 ml
• hyaluronidase 150 I.E. (Hylase Dessau®)	10 vials
• physiologic saline 0.9% 5 ml	10 vials
• single-use syringes 1 ml, sterile	3
• single-use syringe 2 ml, sterile	3
• single-use syringe 5 ml, sterile	3
• gloves, sterile, medium size	1 pair
• cold/hot pack	2 each
• single-use cannulae 26 G, sterile	10 each
• compresses, sterile	6
• strip role, tissue-friendly (e.g. Leukosilk®)	1
• cotton wool applicator	5
• combination closure	2
• marker for labelling the affected area	
• recommendations for general and specific measures	
• documentation form sheet	

Fig. 3: Contents of a paravasate emergency kit

Compilation of a «Paravasate Guideline»

In the context of clinical quality management, a «Paravasate Guideline» should be compiled with the cooperation of the pharmacy.

Workshop «Paravasates»

For physicians and nurses, workshops on prevention and treatment of paravasates should be held regularly. The necessity for documenting the course of a paravasate and its treatment should always be emphasized. Only correct collection of all data makes it possible to optimize paravasate treatment.

In-house publication of the recommended guidelines on treatment of paravasates

Information can be spread in many ways: By publication in the internal news, on an information page on the hospital's intra-net, by adding to the in-house list or by introduction of a poster on essential measures in case of paravasation. Using the poster, emergency information is always present on the ward, and therapy delays due to tedious searching for information or even the kit can be prevented.

If guidelines have been established in the hospital, they must be found in the quality management manual and shall be binding for everyone.

Documentation and reporting of cases

Both on the national and on the international level, there are efforts being made to document paravasations and successes in their treatment. This way it may be possible to develop statistically secured therapy measures. Therefore, the kit should comprise a documentation form sheet for describing the paravasation event including patient data, symptoms, treatment and therapeutic success.

One copy of the documentation sheet should be sent from the ward to the pharmacy. The documentation may be anonymous. It is not compulsory and its purpose is to continue to develop the existing recommendations and to base these on a wide collection of data.

Currently, a network for the evaluation of the form sheets and further development of standards is being created. For anonymised capture and evaluation, the completed documentation sheets can be sent to the following address:

Ms. Mag. pharm. Patrizia Fürst-Weger, c/o Sozialmedizinisches Zentrum Floridsdorf, Krankenhaus und Geriatriezentrum, Apotheke, Hinaysgasse 1, A-1210 Wien, Tel.: 0043/1/27522-5501, Fax: 0043/1/27522-5509, email: office@paravasate.net

References:

1. Mader R et al. Paravasation von Zytostatika – Ein Kompendium für Prävention und Therapie, 2.Auflage Springer-Verlag Wien, , 2007

2. Dorr RT. Managing extravasations of vesicant chemotherapy drugs. In: Lipp HP (ed). Anticancer drug toxicity. New York: Marcel Decker, 1999: 278-318

3. Du BoisA. Clinical course and managment of paclitaxel extravasation, Oncology Reports 1996; 3:973-974

4. van Gemmern R. Gewebstoxizität und Paravasatbehandlung neuer Zytostatika, Krankenhauspharmazie 1996; 10:471-473

5. Krämer I. Zytostatika Paravasate-Set, Krankenhauspharmazie 1992; 4:154-160

6. Schneider SM Distelhorst C. Chemotherapy-Induced Emergencies, Sem Oncol 1989; 16:72-578

7. Kraft A et al. Anthrazyklin-Extravasate, Behandlungsrichtlinien und Literaturübersicht, Onkologe 2000 6:674-686

8. Olver IN et al. A prospective Study of Topical Dimethyl Sulfoxide for Treating Anthracycline Extravasation. J Clin Oncol 1988; 6:1732-35

9. Bertelli G et al. Topical Dimethylsulfoxide for the Prevention of Soft Tissue Injury After Extravasation of Vesicant Cytotoxic Drugs: A Prospective Clinical Study. J Clin Oncol 1995; 13:2851-55

10. Mouridsen HT, Langer SW et al. Treatment of anthracycline with savene (dexrazoxane): results from two prospective clinical multicentre studies. Ann Oncol 2007; 18:546-50

11. Langer SW et al. Dexrazoxane in anthracycline extravasation. J Clin Oncol 2000; 18:3064

12. Langer SW et al.. Dexrazoxane is a potent and specific inhibitor of anthracycline induced subcutaneous lesions in mice. Ann Oncol 2001; 12:405-410

13. El Saghir N et al:.Dexrazoxane for anthracycline extravasation and GM-CSF for skin ulceration and wound healing. Lancet 2004; 5:320-21

14. EMEA. Savene® Scientific Discussion http://www.emea.europa.eu/humandocs/PDFs/EPAR/savene/068206en6.pdf (February 2008)

15. Becker C, Gensthaler BM. Neu auf dem Markt – Deferasirox, Dexrazoxan und eine Vakzine gegen HIV. In:Pharmazeutische Zeitung online. http://www.pharmazeutische-zeitung.de/index. php?id=2164&no_cache=1&sword_list[0]=savene (February 2008)

16. The European Oncology Nursing Society Leitlinien zur Behandlung von Paravasaten 2007. http://www. cancerworld.org/CancerWorld/getStaticModFile. aspx?id=2339 (July 2008)

4.4. Chrono-Oncology

Chrono-oncology is a method of treatment relating the natural biological rhythms of the patient with the time of cytostatics application, therapeutically aiming at improving bioavailability or efficacy of cytostatics while at the same time reducing side effects. Insofar as clinical data are available, experience gathered in the field of chrono-oncology isused to the patient's benefit by optimizing the relationships between dosage – effectiveness – side effects.

Claus Roland, Flensburg

Chrono-oncology is the circadian scheduling (administration at specific times of the day) of cytostatics aiming at increasing the medical effects and/or decreasing the side effects of cytostatics, thereby integrating circadian rhythms. Efficacy and extent of side effects depend also on the time of application. This phenomenon is based on differences in sensitivity rhythms of normal and tumorous tissue.

Many bodily functions are subject to rhythmic changes. Here a circadian (24-h rhythm, e.g. in corticosteroids or growth factors), an ultradian (spanning less than 21 h), a circaseptian (lasting more than 1 week), circamensual (monthly, e.g. menstruation cycle) and a circaannuary (lasting more than 1 year) rhythm can be discriminated. These rhythms are controlled by «biological clocks», so-called oscillators, which may in turn be influenced by environmental factors (timers). Parameters such as urine pH, electrolyte, glucose, hormone (cortisol) and enzyme concentrations vary with the time of the day. Circadian rhythms have also been demonstrated for body temperature, heart rate, blood pressure, organ perfusion and renal and hepatic function. Likewise, circadian dependence of cytosynthetic activity has been shown for certain tissue systems such as intestinal mucosa cells and the cells of the haematopoietic system.

Adverse effects arising in these very tissues frequently hinder optimisation of cytostatics therapy.

Chronotherapy with cytostatics – chrono-oncology – aims at exploiting the phenomena of time-dependent [differences in] cell division activity between tumour and healthy tissue, integrating time-dependent cell division activity of certain cell systems into cytostatics therapy and dependence of both the efficacy and the kinetic properties of cytostatics into a therapeutic concept with the option of increasing effects and/or decreasing side effects of the drugs. This improved procedure (application at defined times) results in an increase in the therapeutic index, i.e., at the same rate of side effects an increase in effects by increasing the cytostatics dosage is possible. This in turn increases the likelihood of improved tumour response rate.

The essential mechanisms of chrono-oncology leading to increased efficacy of therapy are:

1. Chronopharmacodynamics

The effect of cytostatics depends on the time of administration. In-phase application of drugs improves the therapeutic index of cytostatics. Reasons for changes in pharmacological processes include:

- circadian variations of the number, density and affinity of receptors
- changes in membrane permeability
- differing expression of cellular defence mechanisms, e.g. glutathione level
- circadian changes in both intracellular and extracellular pH
- fluctuations of the intracellular and extracellular concentration of administered cytostatics depending on the blood supply to the tumour tissue
- interactions of cytostatics with hormones produced by the body (corticosteroids, interferons, interleukins, TNF) depending on their circadian concentrations. Interactions of this type may result both in increase and decrease of the effect.(1)

2. Chronopharmacokinetics

Kinetic processes such as adsorption, plasma concentration, distribution volume, metabolism and excretion are subject to circadian fluctuations. Influence of time on kinetic processes is caused by the following:

- Enzymatic activity of many metabolic enzyme systems (phase I reactions), including the cytochrome P-450 enzyme system, depends on the time of the day which in turn influences toxicity of cytostatics either positively or negatively. The same holds true, correspondingly, for activating enzymes and for phase II metabolic processes such as glucuronidation and sulphation reactions. The enzyme dehydropyrimidine hydrogenase (DHPD), responsible for degradation of 5-fluorouracil, has an enzymatic activity which varies depending on the time of the day. Sinusoidal dosage adaptation to the enzymatic activity of DHPD (lower doses during periods of lower enzymatic activity, and vice versa) allows to influence the therapeutic index of 5-FU.
- Circadian differences in renal and hepatic function, which in turn influence adsorption, metabolism, excretion and distribution volume.
- Circadian changes in plasma protein levels cause fluctuations of bioavailability, e.g. for cisplatin.

3. Chronocytokinetics

Determination of cell synthesis activity both of healthy and of tumour tissues depending on the time of the day.

Only few types of tumours differ from healthy tissues in respect of their synthesis activity. Ovarial carcinomas (2) and malign lymphomas, however, have developed their own biorhythm. In non-Hodgkin lymphoma, the acrophase of DNA synthesis activity is nocturnal, whereas in healthy subjects it is diurnal. However, clinic experience is currently very limited, since for practical and ethical reasons – due to [the need for] serial biopsy taking – clinical benefits for the patient are currently limited. It has also been found that slow-growing tumour entities have circadian rhythm similar to that of healthy tissue, whereas fast-growing tumours have largely lost their circadian order. Loss of this circadian order is often an indicator of progression. Moreover, temperature fluctuations

are found on the skin surface of breast cancer patients with a maximum approx. 6 hours earlier than in the healthy breast (4).

4. Chronotoxicity and chrono-efficacy

Reduction of toxicity and increase of effectiveness of cytostatics result from consistent exploitation of chronopharmacological, chronocytokinetic and chronophramacokinetic mechanisms. Animal models can be used to determine the optimal time for application of the therapeutics. Here animals are kept under standardized light/dark conditions (HALO = hours after light onset). Data are acquired based on lethality studies. Here defined doses of cytostatics are applied at different times of the day (generally in a 4-h rhythm). The time point when the percentage of surviving animals was at a maximum reflects the optimal time of application. Using a suitable correction factor, the basic data thus obtained can be extrapolated to humans. By now, effects of chronotoxicity or chronoefficacy have been demonstrated for more than 30 cytostatic agents.

Thus, in a non-randomized study in children with ALL it was found that at for equal dosages and use of the same substances (6-mercaptopurine and methotrexate) 5-year survival was 80% for vespertine but only 40% for matutinal application (5).

Most studies were performed on 5-FU/Ca-folinate and oxaliplatin, in particular in metastasised colon carcinoma, performed by the group of Lévi, Paris. Here oxaliplatin is administered at 25 mg/m² on days 1-4/5 from 10.00 – 22.00 h with the peak at 16.00 h, and 5-FU at 600-1100 mg/m² and Ca folinate 300mg/m² on days 1-4/5 in the time from 22.00 – 10.00 h with a peak at 4.00 h (8, 9, 10).

The most important results of a randomised multicentric study comparing conventional therapy with chrono-modulated therapy in 186 patients with metastasised colon carcinoma are presented below (7):

For circadian application, cytostatics with the following effect profile are particularly suitable: substances

Table:

Substance	Tumour model	Optimal time (HALO)	Parameters for efficacy	Effect of application time
cyclophosphamide	mammary carcinoma	8	tumour regression	considerable
cyclophosphamide	T9, T10 sarcoma	2	healing rate	13 – 14%
cyclophosphamide	L1210 leukaemia	12	healing rate	27%
ARA C + cyclophosphamide	L1210 leukaemia	10	healing rate	20 – 50%
ARA C	L1210 leukaemia	8	healing rate	18%
melphalan + doxorubicin*	13782 mammary carcinoma	10	rate of complete remission	38%
cisplatin + doxorubicin*	plasmocytoma	18	survival	30%

All studies were performed in mice or rats, respectively.

* For these cytostatic combinations the substance named second was given at the optimal time and the first-named at different times selected at random.

- with broad activity against a large number of tumour types
- with a strong dependence between tumour response and dosage
- with a low therapeutic range and
- with excellent [anti]tumour activity at high or very high dosages, while at the same time afflicted with a high rate of side effects.

Effect	Conventional	Chronomodulated	P
Hospitalized for toxicity	31*	10	0.001
Mucositis Functional impairment (peripheral neuropathy)	76	14	0.0001
Tumour response ›50%	29	51	0.003

* percentage of patients in Prozent

from Lévi F, Zidani R, Misset JL for the international Organisation for Cancer Chronotherapy.. Randomized multicenter trial of chronotherapy with oxaliplatin, fluorouracil, folinic acid in metastatic colorectal cancer. Lancet 1997;350:681-686

Improvement of the therapeutic index by chronomodulation of cytostatics and associated improvements in quality of life should be seen as a therapeutic option or alternative, in particular in case of intolerable side effects during chemotherapy. In this context, Focan has conducted a pharmaco-economic trial for the substances Ca-folinate/5-FU (high dosage) which has shown that in spite of the higher application costs in the chronomodulated branch, overall costs were lower in the chronomodulated branch because of lower expenses for treatment of therapy-induced side effects (6).

Conclusion:

Improvement of the therapeutic index of cytostatics generates the following benefits of chrono-oncology:

- reduction of cytostatics-induced side effects and/or increased quality of life
- specific combinations of cytostatics can result in improved tumour response rates
- economically reasonable in view of lower costs of side effects necessitating treatment
- creation of new therapy options, since the opportunity arises to combine substances which otherwise cannot be combined readily because of their side effect spectra.

References:

1. Abrahamsen JF, Smaaland, R, Sandberg S et al. (1993) Circadian Variation of serum cortisol and circulating neutrophils are markers for circadian variation of bone marrow proliferation in cancer patients. Eup J Hematol 50:206-212

2. Klevecz R, Shymko R, Braly P.; circadian gating of S phase in human ovarian cancer; Cancer Res 1987 ;47:6267-6271

3. Smaaland R, Lote K, Sothern RB, et al; DNA- synthesis and ploidy in non- Hodgkin's lymphomas demonstrate variation depending on circadian stage of cell sampling; Cancer Res 199; 53:3129- 3138

4. Mansfield CM, CarabasiRA, Wells W, et al.: Circadian rhythm in the skin temperature of normal and cancerous breast. Int J Chronobiol 1973;1:235-243

5. Rivard G, Infante- Rivard C, Hoyoux C, et al. Maintenance chemotherapy for childhood acute lymphoblastic leukemia: better in the evening. Lancet 1985;ii,1264-1266

6. Focan C.: Chronobiol Int.2002 Jan;19(1):21-41.

7. Lévi F,Zidani R Misset JL for the international Organisation for cancer chronotherapy. Randomized multicenter trial of chronotherapy with oxaliplatin, fluorouracil, folinic acid in metastic colorectal cancer. Lancet 1997;350:681-686

8. Lévi F,Misset JL, Brienza S, et al. A chronopharmacologic phase II clinical trial with 5- fluorouracil, folinic acid and oxaliplatin using in ambulatory multichannel programmable pump. High antitumor effectiveness against metastatic colorectal cancer. Cancer 1992;69:893- 900

9. Lévi F, Zidani R, Brienza S et al. A multicenter evaluation of intensified ambulatory chronomodulated chemotherapy with oxaliplatin, 5- fluorouracil and leucovorin as initial treatment of patients with metastatic colorectal carcinoma. Cancer 1999;85;2532- 2540

10. Lévi F, Zidani R, Vannetzel JM, et al. Chronomodulated versus fixed infusion rate delivery of ambulatori chemotherapy with oxaliplatin, 5- fluorouracil and folinic acid in patients with colorectal cancer metastases. A randomized multiinstitutional trial. J Nat Cancer Inst 1994;86:1608-1617

11. The chemotherapy source book, Michael C. Perry, M.D., F.A.C.P.

4.5 Handling Cytostatics on the Ward

On the ward, handling of cytostatics-containing drugs is mostly entrusted to nurses and physicians. This applies to receiving and storing the drugs, making them ready for application and administration of the pharmaceutical products as well as the management of excreta, which may also concern family members of the patients, and of inadvertent spills.

The oncology pharmacist supports the wards and units of the hospital by compiling handling instructions for the respective procedures in order to facilitate safe work and proper use of the protective equipment.

Hannelore Kreckel, Gießen

On the ward, nurses and physicians are handling cytostatics. The nursing staff is concerned with receipt of the application-ready cytostatics, delivery and subsequent storage of the products, preparation for application, treatment and care of the patient and disposal of materials no longer needed as well as of inadvertent spills.

Physicians do handling on the ward mostly during application of the pharmaceutical formulations for parenterally administered formulations.

Furthermore, family members assisting in patient care may be affected by coming into contact with the patient's excreta.

Cleaning and maintenance staff may also be entrusted with work in case of inadvertent spills.

The relevance of the hazard to physiotherapists is questionable, since they come into contact only with the amounts of substance excreted through the skin of the patient, if at all.

With regard to safe working procedures and correct handling of the protective equipment, for all of these groups of persons operating instructions are needed for handling during their respective activities. The instructions must be compiled with the focus on hygienic handling and personal protection and should also comprise, in addition to safe handling of cytostatics, handling spills and waste disposal.

Additionally, working rules must be drawn up for handling of cytostatics on the ward, and instruction appropriate to the particular workplace must be given annually (see 1.3: Working rules and instructions). The working rules may be supplemented with standard operating procedures. On the basis of his/her specialised professional knowledge, which is expressly referred to in TRHS 525, the pharmacist may assist in compiling the working rules and giving instructions. Of course, responsibility with the line superior.

Delivery of cytostatics (see also 3.7: Delivery of the products to the oncological ward) and storage on the ward

The application-ready cytostatics are delivered shrink-wrapped into plastic film, in separately labelled containers which are breakage-proof, liquid-tight and sealable. These boxes arrive at the ward where they are accepted by competent staff. The tasks of this staff comprise checking the delivery for completeness and transferring the products to the correct storage location according to the name on the label. The storage location should be separate from all other drugs and products. In case of storage in the refrigerator, a separate shelf or compartment should be reserved, preferably the lowermost one, to prevent contamination of other products in case of leakage of liquids.

Since it is known that the cytostatics containers may be tainted with external contamination and in spite of careful work in the pharmacy cross-contamination of the application-ready preparations cannot be reliably ruled out, gloves should be worn during unpackaging from the outer packaging.

Making ready for application

Cytostatics are used in various pharmaceutical forms.

During everyday routine on the ward, most of them are administered parenterally as infusions or injections. These formulations as well as intraoperatively used rinsing solutions and solutions for instillation are provided by the dispensary ready for application. The same applies to ophthalmics, since they are sterile formulations and preparation in the pharmacy is performed under aseptic conditions.

By contrast, in most hospitals orally administered drugs are made ready on the ward. Capsules, tablets and liquid oral formulations such as drops or syrups must be made ready for application. In most cases, dermatics such as creams, ointments or solutions are provided by the pharmaceutical manufacturer ready for application.

If preparative steps remain to be be performed on the ward, these should be done in a quiet place so to avoid disturbances of the person doing the work. The workplace surface should be made of a material that can be cleaned easily. The person doing the work must wear suitable protective clothing.

Orals – solid formulations

TRHS 525 stipulates the use of forceps or a spoon for dispensing solid oral formulations.

Coated formulations such as coated tablets, capsules or dragées should be used preferentially, since their coating minimizes the risk of contamination.

Capsules should not be opened, tablets should not be split or broken to avoid scattering of the contents. If dosage reasons make splitting indispensable, the appropriate dosage in a suitable form should be ordered from the dispensary.

If splitting is indispensable and must be done on the ward, this should be done using a special tablet splitter or cutter serving only this purpose. To this end, it can be placed in a clip-closure bag, and the splitting can be done in the closed bag.

In rare and exceptional cases it may be necessary to prepare CMR pharmaceuticals for tube application. A number of different techniques are available. The least laborious technique, which is, however, not suitable for coated tablets and

film-coated tablets with water-soluble films, comprises placing the the tablet into a syringe which is then filled with liquid so that the tablet is suspended with the help of the liquid.

Crushing solid formulations into a homogeneous powder should be performed only in a self-contained unit. Tablet splitters offered by several vendors, which can be placed into a clip-closure bag of appropriate size, are suitable for this. The powder is taken up with liquid into a syringe from the lower sections of the device. This step requires some skill to be performed within the closed clip-on bag. If none of the above possibilities are realisable, and tablets must nevertheless be split, a dust protection mask must be worn. The same applies to opening capsules for the application of the contents. Producing a ready-to-administer preparation in the dispensary is a sensible thing to do.

Orals – liquid formulations

In the treatment of adults, liquid oral formulations are rarely used for cytostatics. However, treating children with solid oral formulations can be challenging, in particular if the number or size of the tablets is large. Thus liquid forms such as syrups are required.

If such liquid forms are not offered by any pharmaceutical manufacturer, manufacture should be performed in the pharmacy. They are filled into containers allowing easy and precise withdrawal without contaminating the container. For multi-dosage containers, withdrawal aids should be considered, though single-dosage containers must be preferred.

Parenterals

In most cases preparation of cytostatics for parenteral application is now entrusted to specialised pharmacy staff.

Making ready of parenterals for administration by the staff of the ward comprises, in addition to providing the necessary materials, filling infusion systems with a carrier solution free of active ingredients, unless this has already been done in the pharmacy.

If the nursing staff are responsible for filling the infusions systems, this work should be performed at a quiet workplace on a liquid-tight mat. All materials are

placed at hand before starting work. After the injection system has been filled, it must be connected to the syringe or infusion container. For safety reasons, bottles must be pierced while they are standing and bags while they are lying on the work surface; a swab must be placed around the luer lock connection.

To allow for low-contamination connecting and disconnecting, applications systems are preferably used which are either tightly welded to the bags (e. g. Maco Pharma International GmbH) or allow simple and safe change of the solutions while avoiding incompatibilities and allowing low-contamination connecting and disconnecting (e. g. by Braun Melsungen AG, Division Medical, CODAN Medizinische Geräte GmbH & Co KG, Baxter GmbH).

Use of the systems must be coordinated with the ward, and all persons involved must be familiar with their correct use.

The TRHS 525 lists virustatics among CMR drugs, and the same regulations apply. Thus, in a few hospitals preparation of certain CMR drugs remains to be done in the ward area and must be performed under appropriate safety precautions. If this situation exists and cannot be changed, the pharmacist may assist to ensure safe handling based on the TRHS 525. For preparation, the minimum standard with mat, pressure release systems for avoidance of aerosol formation and overpressure must be complied with. Self-contained systems (see 3.3.1. Implements for cytostatics manufacture) must be preferred. A conclusive discussion as to what must be considered as a self-contained system in the sense of TRHS 525 and the bulletins by the professional associations still has to take place. However, the safety standard will have to be higher when working without suitable additional safety implements such as a safety hood according to DIN.

Monoclonal antibodies of ATC code L01XC (e.g. bevacizumab, cetuximab, panithumab, trastuzumab, alemtuzumab, rituximab, gemtuzumab) were evaluated by the Professional Association for the Health and Welfare Services (BGW Forschung: Bewertung monokonaler Antikörper zum Schutz Beschäftigter, October 30th, 2008), giving instructions for the use of personal protective clothing.

Administration of cytostatics

Parenterals

In the majority of cases, administration of the application-ready cytostatics for parenteral use is entrusted to the physician. To this end, he/she needs trousers, closed shoes and a coat as protective clothing, and shall wear gloves. The luer lock adaptor is connected to the patient's access system.

When the system does not permit contamination-free disconnection from the patient, disconnection is done on a mat, the connection point enclosed in a swab. Slightly contaminated materials such as swabs are collected in a container, e. g. a waste bag, which is then sealed and disposed of as domestic waste (see 4.1. Waste disposal).

In case of paravasation, storage location and use of the paravasation kit must be familiar (see 4.3. Paravasation).

Orals – solid forms

All solid oral formulations may be presented to the patients in a plastic beaker. The patient should be instructed to wash his/her hands after taking the medicine, i. e. after touching the pharmaceutical product.

Orals – liquid forms

If liquid forms are delivered to the ward, measuring is the only task that should be left to the nursing staff. This should be done on an absorbent mat with a liquid-tight underside, measuring should be done, if possible, using a syringe which is brought closed to the patient. The syringes to be used should preferably be unsuitable for parenteral application in order to prevent mistakes. Alternatively, a liquid may be filled into a beaker having a lid and thus be presented to the patient. The patient is instructed to fill the beaker, after taking the medicine, with a beverage of his/her choice and drink the contents to ensure that he/she has taken the entire dose of the drug. If the pharmacy provides single-dose units, the residues therein may be taken by rinsing with a liquid acceptable to the patient, thus guaranteeing complete emptying. If the patients are children, the beakers should be refilled by the nursing staff.

Topics – dermatics, ophthalmics

Pharmaceutical products for topic application present a high risk of contaminating the surroundings of the area to be treated. In applying liquid and semi-liquid formulations, use of protective gloves is mandatory. In the case of industrially manufactured products, gloves are provided together with the product, and the package insert comprises a note on the glove material. If products manufactured in the pharmacy must be administered, it should me made sure that suitable gloves are used.

When administering eye drops, substance flushed out of the eye by tear fluid should be absorbed using swabs, and the surroundings should be covered as carefully as possible. Covering the surroundings with fatty ointments or film as it is routinely done, e. g., in the treatment of ulcerations, is generally not recommended, since hydrophobic properties of the substance may promote permeation into this phase. Use of topically applicable pharmaceutical products always comprises providing the patient with sufficient information on how to self-administer the drug.

Handling excreta

In day-to-day ward routine, handling the patients' excreta is one of the tasks of the nursing staff and will only rarely be performed by family members of a patient. In the latter case, the family members should be informed about proper handling. (See also 4.9: Handling excreta).

Management of inadvertent spills

Actions to be taken in case of inadvertent spills primarily focus on decontamination of people and areas, avoidance of spreading cytostatics and cleaning of contaminated surfaces. The place where the decontamination kit is stored should be known to all the ward staff. It is recommended to keep store the paravasation and decontamination kits in the same place.

As a rule, decontamination of persons has precedence over decontamination of areas. The focus is on immediate changing of contaminated (protective) clothing, thorough cleaning of the skin and rinsing of the eyes if necessary.

Area decontamination after spills comprises measures aiming at primary absorption of the spilled substances and is complemented by subsequent cleaning. In this case, cleaning may be performed only by instructed staff wearing personal protective equipment according to the hazard situation, comprising at least, however, protective coat and protective gloves. Both decontamination and cleaning are performed according to a corresponding plan whose implementation is among the subjects of instruction (see also 4.2: Decontamination after inadvertent spills).

Disposal

The principle that avoidance of waste has precedence over disposal of waste also applies to day-to-day ward routine. Partially, this can be realized by returning unused preparations. Depending on type, amount and shelflives, further use by the pharmacy for another patient may be possible. Return transport from the ward to the pharmacy should be subject to the same guidelines as delivery and be performed in accordance with defined rules. Even if products that were not used in patients cannot be reused in the preparation unit of the pharmacy, they should still be returned, since disposal containers for larger quantities of substances are generally available in the pharmacy but not on the ward.

For reasons of economy, a disposal device for shrink-wrapping (see 4.1. Disposal of wastes) of used materials on the ward is acceptable only on wards producing large amounts of waste. The contents of waste bins containing only slightly contaminated waste may be fed into domestic waste processing. Waste bins for separate collection of slightly contaminated wastes are recommendable since they instil greater awareness for waste processing. Infusion sets should be discarded in connected state, i. e. together with the emptied container. For this work, TRHS 525 does not require wearing gloves, but non-sterile gloves should be worn whenever contamination cannot reliably be ruled out.

4.6. Handling Cytostatics in the Physician's Practice

Drugs prepared in the pharmacy may be accepted only by appropriately instructed, qualified staff of the physician's practice.

Shipments must be controlled for completeness, intactness, plausibility and date of expiry.

Preparations for parenteral application should be shipped as a unit with an infusion system connected and filled with carrier solution. The supplying pharmacist has to work towards performing application only via suitable access systems.

So-called «replugging» of infusion systems should be avoided.

The preparations are administered by the attending physician in cooperation with the nursing staff.

Application is done under under continuous vital monitoring.

Personal protection equipment to be worn by the staff is subject to the applicable regulations and should comprise at least coats, gloves and an absorbent mat.

After completion of the application, all contaminated materials are sealed and disposed of according to their legal waste classification.

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Delivery to the physician's practice

In the practice, the consignment must be handed over to qualified staff who have received appropriate instructions (by the pharmacy) which have to ensure that the delivered cytostatics preparations are inspected without delay.

In the practice, a sufficiently large area must be available to store the preparations in organised fashion. Here the application-ready products delivered are compared to the requirements for the patients to be treated in order to identify missing preparations as soon as possible. Any missing preparations can then still be requisitioned at once. This should minimize the hurry resulting from so called «cito» (last-minute) preparations.

Prior to application, the products are visually controlled for integrity, turbidity or precipitations.

Preparations not to be applied promptly must be intermediately stored in suitable fashion, since the date of expiry given is valid only under the stated conditions of storage. Therefore a refrigerator for products to be stored in a cool place must be present. Cooled preparations must be warmed to suitable application temperature before use.

Therapy form sheet

It is expedient to deliver supportive medication prescribed (primarily anti-emetics, drugs for forced diuresis, etc.) together with the preparation. The included medication schedule shows the temporal order of all drugs to be applied while at the same time serving for documentation of the performed application by paraphe. Suitable overview plans can be generated by most cytostatics programs and are a service for the applying staff.

Plausibility check

Before being administered, the preparation must be examined for plausibility (5-C rule: correct patient, correct drugs, correct dosage, correct application and correct application time). This is especially important for the stated stability of the infusion solution, where the maximum duration of the infusion must be taken into account!

Infusion system

With regard to the requested cytostatics infusions for parenteral application, delivery with connected infusion systems should be requested. «Attaching» an infusion generally cannot be done without leakage of infusion medium. The danger of contamination of the applying staff can be reduced significantly by using a pre-connected infusion system flooded with carrier solution. Preferably, systems with luer lock connection and additional access routes allowing flooding before and rinsing of the line after application should be used. Using these systems, safe and simple changing of the solutions, avoiding incompatibilities, and low-contamination connecting and disconnecting is possible. Such systems are offered by various vendors (e.g. B. Braun Melsungen AG, Division Medical, CODAN Medizinische Geräte GmbH & Co KG, Baxter GmbH, Maco Pharma International GmbH). When disconnecting the infusion, use a liquid-tight, absorbent mat if contamination-free disconnecting is not possible.

Personal protection of the administering staff

The personal protective equipment worn by the administering staff should consist of coats which may also be practice coats to be washed separately (but no private clothing) and suitable protective gloves. This personal protective equipment is also to be worn when handling ointments and tablets containing cytostatics and contaminated materials. According to TRHS 525, for the handling of CMR drugs, including application of injections or infusions, hazard assessment and appropriate protective measures are required. Specifically for physicians' practices, the BGW has published a guidebook «Detecting and assessing hazards GP 5.1 – physicians' practices». When wearing protective clothing, here gloves in particular, focus is on personal protection. The applying staff has to observe the Technical Rule for Biologic Materials (TRBM 250) for wearing latex gloves in analogy to blood sampling. In terms of hazardous wet work, the Technical Rule for hazardous Substances [and] Sensitising Substances (TRHS 540) is relevant.

With regard to the wearing of gloves, it must be kept in mind that in many practices employees do not wish to «scare» their patients by wearing gloves. In this situation the attending pharmacist should strive to inform the staff and patients in agreement with the physician. The necessity is easily communicated

by pointing out that gloves (even non-sterile ones) additionally serve to protect the immunosuppressed patient from nosocomial infections by staff and hence the protection of the patient.

Splitting, dissolving or levigating of cytostatics tablets or dragées in the practice results in contamination of the workplace and is therefore not acceptable. Here the competent pharmacist must discuss the issue and provide portioned formulations if required (Chapter 4.5 Handling cytostatics on the ward).

Access for application

For handling the patient's access system, in an interdisciplinary discussion operating instructions should be generated. Important points are:

- no access systems e. g. at the back of the hand
- use veins at the extensor side of the forearm only
- in case of mastectomy (lymph draining disturbance), use arm contralateral to the dialysis shunt only
- administer cytostatics with strong local toxicity only via a central access system as an infusion (CVC; port-a-cath with Huber needle)
- cytostatics with local toxicity may be administered only as a bolus via a peripheral access system and only by an experienced physician (no delegation to medical support staff)
- steel cannulae (butterfly) must not remain inside the vein, danger of perfusion
- check position of access system before administration of the drug, relocate in case of doubt

These measures simultaneously serve to prevent paravasation (see chapter 4.3 Paravasates). General hygiene guidelines conform to those of blood sampling (see there).

Monitoring vital parameters

Administration of the drugs to the patient is done under permanent monitoring of vital parameters. The following parameters are controlled:

- responsiveness (cave: some patients sleep!)
- blood pressure (RR) and heart rate
- excretion (diuresis), if necessary 24-h urine; weight control as a possibility for out-house use, balance, patient diary
- respiration (dyspnoea)
- position of access system

Disposal

For disposal of the application system, a cytostatics waste bin should be placed in the therapy room to avoid spilling during transport. (See chapter 4.1 Waste disposal)

Cleaning

Drip stands, electric pumps, couches, chairs or beds must be cleaned regularly. Here protective gloves must be worn. Bed-clothing does not require any special treatment, however there is the question of contamination with excreta (urine etc.). This issue is discussed in chapter 4.9 Handling excreta.

Patient information

The patient must be informed that he is receiving a very potent (but beneficial) drug which is intended only for him in his condition but may harm others, who therefore require protection. Patients must be freed from the idea of «being poisoned». The pharmaceutical staff can further support a planned therapy, e.g. by explaining supportive medication to counteract the notion of «I am already taking so much, do I need this stuff too?»

(Hygienic) handling in the domestic environment can likewise be addressed when counseling the patient (see chapter 4.7. Handling cytostatics at home).

Close and «courageous» cooperation of the pharmacist with the physician's practice which he caters is desirable. This activity represents an important facet

of the activities of the pharmacist in oncology, offering the pharmacist manifold chances to get involved with patient care. If suitable pharmaceutical services are offered, many questions can be discussed and answered locally. Thus contributed competence of the pharmacists strengthens the profile of the profession. The presence of the pharmacist will not remain unnoticed by the patients either, and they will perceive it as a positive addition to the care team.

References:

Heese, B., Mühlen, A. zur : Umgang mit Zytostatika, Bayrisches Staatsministerium für Gesundheit. 2002

Petrahn, A. et al: Untersuchung einer möglichen Gesundheitsgefährdung durch beruflich bedingte Exposition gegenüber Zytostatika, Munich 1999

TRGS 525, 3.5 (5), Persönliche Schutzausrüstung Ausgabe 1998, BarbBl. Nr. 5/1998

http://www.baua.de/nn_16770/de/Themen-von-AZ/Gefahrstoffe/TRGS/pdf/TRGS-525.pdf

Sichere Handhabung von Zytostatika, Merkblatt M620, as of 2008

http://www.bgw-online.de/internet/generator/Inhalt/OnlineInhalt/Medientypen/BG-Informationen/M620__Sichere_20Handhabung_20von_20Zytostatika,property= pdfDownload.pdf

König, H.J., Leitfaden für den onkologisch tätigen Arzt, Perimed, Erlangen 1991

Krämer, I.: Onkologische Pharmazie. In: Jaehde et. al: Klinische Pharmazie Stuttgart 1998

Margulies et al: Onkologische Krankenpflege 3rd ed., Springer Verlag 2005

http://www.baua.de/nn_15116/de/Themen-von-A-Z/Biologische-Arbeitsstoffe/TRBA/pdf/TRBA-250.pdf

4.7. Handling Cytostatics at Home

An increasing number of cytostatic therapy regimens require continuous application of a drug over a period of 24 h up to several days, increasingly performed in outpatient care.

Patients, family members and the outpatient nursing staff must be trained for domestic handling of cytostatics. The training should consider the following points in particular:

- **Special aspects of handling cytostatics**
- **Handling devices for administration**
- **Measures in case of incidents and spills**
- **Procedure in case of paravasation**
- **Handling the patient's excreta**
- **Waste disposal**

An individual care plan should be prepared in cooperation with the pharmacist (see chapter 5.1).

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For implementation in the domestic environment, cytostatic therapy regimens with continuous infusion of a drug for a period of 24 h up to several days should be considered. The goal is to achieve effective plasma levels and consequently better response rates; moreover, simultaneous radio- and chemotherapy is made possible.

In order to spare the patients hospitalization, for several years various pumps systems have been used for application, allowing continuous infusion at home. In the physician's practice or health care centre, respectively, these pumps are

connected to the appropriate catheter systems and disconnected at the end of the infusion period. In the meantime, the patient is be at home and can pursue his normal daily activities as far as his health permits.

In order to guarantee safe outpatient care, pharmaceutical services are required to go beyond mere filling of the administration system. In addition to patient counseling, the practice staff and the responsible nursing services are instructed. For ensuring drug safety, written information about special aspects in the use of the respective system is recommended. It is advisable to compile separate information material for patients in order to inform them specifically about handling and what action to take in the event of an incident.

Issues specific to the handling of cytostatics are essentially covered by 1.3 Hazard assessment, working rules and instruction and 3.7 Delivery of the manufactured products to the oncological therapeutic institution. For further details on infusion pumps see also 3.3.1.1. The training should cover in particular the following points: Concerning action to be taken in the case of an incident, the physician's practice and the patient should be provided with defined, intelligible operating instructions by the pharmacy according to 4.2 Decontamination after inadvertent release. The pharmacy's services include providing a phone number for emergencies. The physician and if necessary the pharmacy will exolain to the patient how to identify paravasation in the rare situation that there is no central access system. In case of paravasation, consult 4.3 Paravasation. For handling the patient's excreta, in analogy to 4.9 Handling excreta efforts are being made to have the physician's practice and the pharmacy provide standardised information. Waste disposal is regulated in a binding way by the pharmacy in accordance with 4.1 Waste disposal and in agreement with the oncological therapy unit and, if required, the nursing service and/or family doctor's practice.

To summarize, training and organisation of care in the domestic sector should comprise the following aspects; written operating instructions for patients, family members and nursing services must also be provided:

1. Principles of the cytostatics therapy prescribed and the regimen implemented

2. Basic information about the type of the patient's parenteral access system, such as
   - PORT system
   - Hickman or Broviac Catheter
   - central venous catheter
3. Type and duration of the administration of the pharmacotherapy
4. Brief introduction to the mobile electronic pump systems or elastomeric pumps used
5. Hygiene standards for handling of drugs for parenteral application
6. Hygiene standards for handling of the catheter system.
7. Special effects / side effects / interactions of the cytostatics therapy
8. Action in case of defects and / or leakage of the cytostatics solution, use of the spill kit
9. Action in case of problems during cytostatics therapy, emergency numbers.
10. Handing over emergency phone numbers

The training performed is documented appropriately.

Administration systems for continuous infusion (see also 3.3.1.1 Infusion pumps for the administration of cytostatics)

A basic distinction is made between electronic and mechanical pump systems, which will be described here only in outline.

a) Elastomeric pumps

These pump systems comprise, in a rigid or flexible sheath, a tube made of an elastomeric membrane which is filled with the drug solution like a balloon. Its intrinsic elasticity creates a pressure resulting in forced discharge of the contents, via the infusion line, into the patient's catheter system. Here the flow rate is regulated by flow restrictors such as glass capillaries. In general, particle filters with air separators are integrated into the infusion line.

Advantages: Very light pump systems; simple filling; visual monitoring of the infusion by diminishing balloon volume.

Disadvantages: Single-use system causing high costs; no alarm function in the event of an incident; depending on the pump system inaccuracies since the glass capillaries regulate flow rate depending on temperature; flow rate fluctuations; with flexible sheath: danger of puncture and thus leakage of the drug solution.

Exemplary products: (Baxter) Folfuser, Infusor, Intermate; (Medac) Surefuser; (Braun) Easypump

b) Mechanical pumps

Infusion bags, generally made of ethinyl vinyl acetate, are filled aseptically and laid into plastic boxes. Spring systems build up the necessary pressure for emptying the bag. Flow restrictors are integrated into the infusion line.

Advantages: Low costs, since the infusion bag is the only single-use article.

Disadvantages: No alarm function; imprecisions in running time; flow rate fluctuations; higher weight; inadequate visual control of the residual volume, in some systems damage to the infusions bag may result in leakage of the drug solution.

Exemplary products: (Onkowork) Onkoworker, (Fresenius) Ultraflow

c) Electronic pumps

Electronic pumps control flow rate by means of peristaltic or rotary drives. All therapy-relevant data such as flow rate and duration and often the infusion profile as well can be programmed. In addition to circadian rhythms, a multichannel system even allows to infuse a plurality of drugs. Most pumps can also be used for other infusions regimens such as PCA, TPE, antibiotics etc. The pump heads are connected to the filled single-use bags via suitable transfer systems. When they are equipped with high-performance batteries, the patients enjoy just as much flexibility as with the other systems. Infusion pressures are sufficient even for intra-arterial infusion.

Advantages: High therapeutic flexibility; high precision; alarm functions (pressure, air, etc. alarm); thus high therapeutic safety/reliability; cost-effective in long-term use

Disadvantages: Often very heavy; high acquisition costs; depending on the model: possibility of false alarm, often inadequate protection against leakage of the infusion bags

Exemplary products: (Braun) Multifuse, (Logomed) Pegasus series, (Smith Medical) CADD series and Graseby series

The pump system is selected according to the following criteria:

- sufficient accuracy of flow rate
- therapeutic regimen (circadian rhythms necessary?)
- flexibility of the patient
- adequate protection from leakage
- safety from false alarms in electronic pumps
- costs

Catheter systems

fig. 1: central venous port-a-cath system

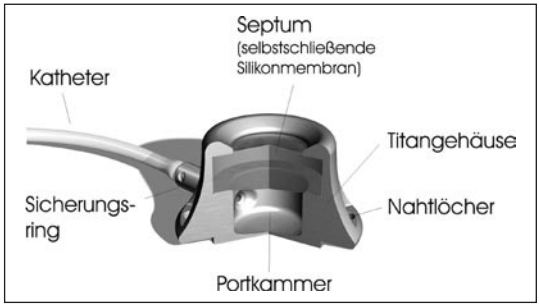

fig. 2: structure of a fully implantable port-a-cath system

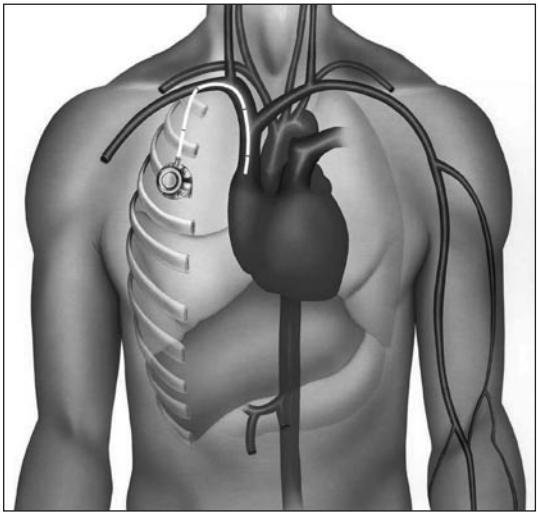

fig. 3:
typical implantation site of a central venous port-a-cath system

Implantation of a venous or possibly arterial port-a-cath system is standard. Central venous catheters and Hickman-Broviac catheters need constant attention and generate a high rate of complications. These systems should not be used for outpatient chemotherapy. Because of the danger of paravasation, indwelling needles must not be used without supervision by a physician.

Here pharmaceutical service also extends to the required medical products:

a) Port needles

For port-a-cath systems, only single-use Huber needles may be used. Different types of needles allow to optimally pierce the port. Depending on the thickness of the subcutaneous adipose tissue layer, needles with lengths from 15 mm to 25 mm are generally used. Various inner diameters allow gravity-assisted infusion in practice, smaller diameters increase wearing comfort and reduce the danger of infections. However, these needles have higher flow resistance and necessitate pump systems. Various closing plates increase waring comfort, some come with adhesive rings integrated to fixate the needle after piercing. In most systems, closure clamps are attached to the line system.

Attention must be paid to the following points:

- selection of correct needle length
- selection of appropriate internal diameter according to the type of the infusions
- selection of the flattest closing plate possible, if the needle shall remain in place for several days
- presence of a clamp
- visual control of the puncture site in case of longer indwelling time, not possible with integrated adhesive rings

Exemplary products: (Smiths Medical) Gripper, (B. Braun) Cytocan, (Fresenius) Intrastick

In vitro puncture of a port-a-cath system (Images for training by Logomed)

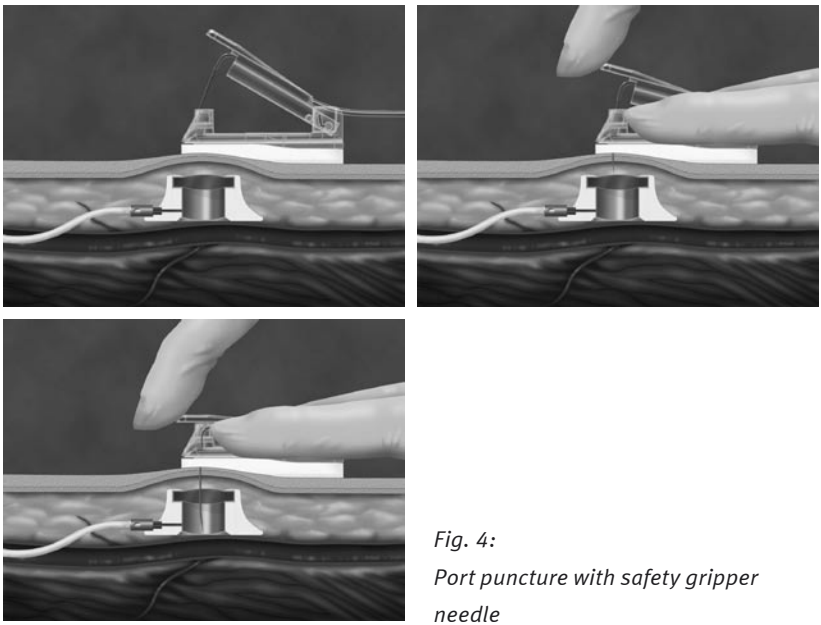

Fig. 4:
Port puncture with safety gripper needle

b) Dressing system

For dressing the port needles, use sterile slit compresses, adhesive bandages and sterile polymer films. Here selection depends on needle type and, above all, on indwelling time.

Attention must be paid to the following points:

- with unpadded closing plates, always bolster underneath with sterile slit compresses
- in case of longer indwelling time, provide outer dressing with sterile polymer films, do not leave for more than 7 days (e.g. Tegaderm, Suprasorb)
- for puncture sites that are not directly visible, change of dressings at least every 3 days; in case of pain at the puncture site, change immediately, medical examination
- acceptable skin tolerance, change of dressing material in case of allergic reactions
- mild disinfectants, e.g. Softasept (B. Braun)
- port needle tubes must always be secured against being pulled (e.g. Fixomull® stretch, 2 stripes, 1 cm wide)

c) Closing systems, extension systems, inline filters

If infusion systems are frequently changed at the tube of the port needle, use of safety locks which are screwed upon the port needle tube in lieu of conventional closure cones is recommended. For connecting a new infusion system, only the luer lock adapter of the valve must be disinfected, [the need for] screwing off with the danger of germs entering the open catheter tube is reduced (e.g. BD Posiflo 2-way i.v. adapter).

When using extension lines, additional non-return valves (e.g. R-Lock, Impromediform) should be incorporated to avoid reverse flow in the event of unnoticed disconnection. Since so-called Heidelberg extensions are not pressure-resistant and at night the patient may lie on them and compress them, pressure-resistant

lines must be used instead. For mobile patients, pressure-resistant spiral lines are the material of choice, since they combine maximum flexibility with simultaneous strain relief of the central venous catheter systems. (Spiral line, e.g. Impromediform)

For infusions over several days, the use of positively charged, self-venting 0.22 mm inline filters near the patient increases microbial safety, since these have useful life of up to 96 h (e.g. 0,22 µm + antibacterial filter, Impromediform). However, the manufacturer of the filter must be consulted regarding compatibility of the filter material with the drugs.

Attention must be paid to the following points:

- for daily connections, use safety valves
- non-return valves if required
- pressure-resistant connector lines
- for mobile patients, use pressure-stable spiral lines
- for infusions lasting several days without system change, additional 0.22 µm inline filter after verification of compatibility

On-call service

If an incident occurs, the patient must be able to obtain help immediately. A pump defect may always result in displacement of the port-a-cath system. In serious cases, this may necessitate removal and re-implantation of the port. The Ordinance on the Operation of Medical Devices (Medizingeräte-Betreiberverordnung) demands implementation of an on-call service at the pump vendor's. In the case of electronic pumps in particular, the operator must reactivate or exchange the pump on-site in case of failure.

Paravasation can be virtually excluded if the port needle is positioned correctly and the dressing optimally applied, including relief of the tensile load. Nevertheless, for domestic use only cytostatics with a low risk of paravasation should be used. Thus, use of anthracyclines is virtually excluded. Common outpatient infusion therapies with durations from 24h to several days include

continuous infusion of 5-fluorouracil, either after administration of of calcium folinate or with simultaneous infusion of sodium folinate. In focus practices with sufficient experience, however, even several-day infusions of ifosfamide with MESNA are performed domestically.

In any case, the patient must have a plan relating to procedures in case of paravasation at home, depending on the degree of danger, listing the required drugs and implements.

Since a bag system defect would lead to contamination of the domestic environment, the pharmacy should be familiar with potential sources of malfunction when using the various application systems. In order to meet this requirement and avoid trouble, the pharmacist should have an overview of the market, have individual systems demonstrated and, if required, test them to apply the system best suited to the individual use. Apart from cost-benefit aspects, consideration of safety issues should be natural for a patient-oriented service pharmacy. The important task of selecting an appropriate application system and training patients in time to avoid hazardous situations is rationally delegated to the pharmacy.

If problems should arise nevertheless, the patient must be enabled to obtain help as quickly as possible.

Responsibilities of the pharmacy:

- establishing an on-call service, via pharmacy and / or physician's practice or outpatient department
- teaching patients to handle the administration system
- providing a spill kit if the physician should insist on an administration system liable to leak.

References:

Schulungsmaterial Baxter Deutschland GmbH, Edisonstraße 3 – 4, 85716 Unterschleißheim

Schulungsmaterial Logomed, Klarenplatz 11, D-53578 Windhagen

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4.8. Management of Clinical Trials in Oncology

By participating in clinical trials in oncology, the clinical pharmacist contributes to quality assurance in this field.

His particular attention focuses on the drug to be studied, whose proper shipment, storage, preparation and/or making ready, documentation, distribution and destruction he shall manage on the basis of all applicable legal regulations.

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1. Clinical trials in oncology

Nowadays clinical trials of drugs in oncology are regarded as interdisciplinary tasks, where – in addition to physicians – pharmacists also make their particular contributions, in cooperation with various experts, to quality assurance. Patient protection and gathering of valid data on the trial drugs by means of standardised procedures enjoy top priority during the performance of clinical trials.

Over the most recent years, European law has been implemented more and more in national pharmaceutical law.

In the amendments 12 and 14 of the German Pharmaceuticals Act, the legal foundations of clinical trials in Germany have been redefined.

A clinical trial in humans is defined by § 4 XXIII of the German Pharmaceuticals Act as any study performed in humans which is intended to

- study or demonstrate clinical and pharmacological effects of drugs or
- detect side effects
- or study resorption, distribution, metabolism or excretion with the goal of verifying safety and efficacy of the drugs.

As a consequence of the definition of «clinical trial», all interventional, prospective clinical trials, including so-called Investigator-Initiated Trials (IIT), therapy optimization trials, Phase IV trials are subject to the requirements of the German Pharmaceutical Act and the Ordinance on GCP. Good manufacturing practice (GMP) applies to the manufacture of the trial preparations.

The BfArM as the supreme competent office is responsible for the approval of the individual clinical trial. The Ethics Committee «in charge», where in accordance with the law of the land there are pharmacist represented as well, in addition to physicians, priests and patients' representatives, assesses compliance with ethical standards. Their vote of acceptance must be presented prior to inception of a clinical trial.

In oncology, clinical trials for drugs are usually highly complex projects, due to the difficulty of the conditions to be treated, the diversity of the individual approaches in form of the drugs to be tested, and the various trial designs. Tab. 1 summarizes some special characteristics of clinical trials in oncology which the pharmacist is confronted with.

Tab. 1: Special characteristics of clinical trials in oncology

Type of clinical trial	Phase I – IV For cytostatics: clinical trial phase II – IV Trials conducted by commercial sponsors, trials conducted by physicians and groups groups of physicians as Investigator-Initiated Trials (IIT), usually so-called «therapy optimization trials», where use of approved drugs with non-approved indications, dosages or therapies aims at improving medical standards or care
Trial drugs	Conventional cytostatics, monoclonal antibodies, VEGF inhibitors, vaccines, gene-therapy drugs, antibiotics, anti-emetics, virustatics, haematopoietic growth factors
Study design	open, blinded, double-blinded, crossover, against standard regimen

2. When is a request for a manufacturing permit for clinical trial drugs required?

For pharmacies, from the amendments of the German Pharmaceutical Law there result clear definitions for the type and scope of their activities. For the pharmacist, it is important to know whether the pharmacy requires a manufacturing permit for certain activities, or when such a permit may be waived.

For clinical trials, there is no manufacturing permit required for the area catered by a dispensary, as long as the manufacture of trial preparations consists in refilling, repackaging or relabelling of drugs approved in the EU (§ 13 IIa German Pharmaceutical Law).

Reconstitution is likewise not included into the definition of manufacture and consequently does not require a manufacturing permit according to § 13 German Pharmaceutical Law either. This was confirmed by a verdict of the Administrative Court of Oldenburg on December 19th, 2007. Thus, e. g., dissolving a trial substance, e.g. a cytostatic or an antibody provided by the industry to a study centre in the context of a multicentric trial, is unproblematic, since dissolution does not constitute manufacture sensu stricto.

A manufacturing permit is not required in the context of IIT either, when approved drugs are being used and the sponsor does not perform any manufacturing operations with the exception of labelling (Ordinance on GCP § 4 II).

Moreover, the trial preparations may be manufactured outside a manufacturing plant in a commissioned pharmacy, when the conditions of § 14 IV 1 German Pharmaceutical Law are met. According to these conditions, manufacture in the pharmacy is done at the responsibility of a manufacturer who in turn must possess a manufacturing permit according to § 13.

So here manufacture of trial preparations may be performed outside the manufacturing company by a commissioned pharmacy. Suitable rooms and qualified staff must be available. The pharmacy must be named in the permit document.

The expiry date of clinical trial drugs may be modified («re-labelled») in a testing centre by an assignee of the manufacturer. This applies to trial prepa-

rations of the institution only (§ 14 IV 2, German Pharmaceutical Law). The centre concerned must be listed in the manufacturing permit by an Advice of Amendment.

A pharmacy may act as manufacturer with sole responsibility only if in possession of a manufacturing permit according to § 13 German Pharmaceutical Law.

If the pharmacy is in possession of such a manufacturing permit, a copy thereof must be annexed to the request for permission. In this case it is permissible to name in the request the pharmacy as the responsible entity for approval of the trial drugs.

For all activities exceeding those described above, e.g. manufacture of trial drugs for multicentric, non-commercial trials without a commercial GCP sponsor that is a pharmaceutical entrepreneur as defined by the German Pharmaceutical Law, a manufacturing permit is required for the manufacture of trial drugs according to German Pharmaceutical Law – both for intravenous, oral and other preparations, including the placebos.

Over the last years, a number of pharmacies – often dispensaries of university hospitals and connected with so-called coordination centres for clinical trials (CCTs) – have acquired manufacturing permits for the manufacture of trial drugs according to German Pharmaceutical Law. Thus they may manufacture trial drugs not only unicentrically, for the own area of supply, but also for others, multicentrically.

The advantages of requesting the manufacturing permit comprise the clear extension of competences, enabling of trials not initiated by commercial sponsors, e.g. physicians, manufacture of small and very small batches which can hardly be produced in industry scale.

Thus, networking is made possible.

3. Tasks of the clinical pharmacist in the context of clinical trials

Below, we will focus on the role of the pharmacist in performing clinical trials.

No matter which type of trial, whether a special manufacturing permit is required or not, within the framework provided by the German Pharmaceutical Law the pharmacist is responsible for dispatching the tasks entrusted to him/her in accordance with GCP and GMP.

In preparation for participation in clinical trials, the pharmacy gets ready for the assigned tasks. Whether by the operating procedures generated in their quality management system, whether by the SOPs produced during the approval process in the context of the special manufacturing permit, performance of the tasks will always be based on standardized, validated procedures.

The regulations for the staff to be employed, their continued training and appropriate assignment, qualification of the operating areas, hygiene measures, storage and transport of starting materials, intermediates and final products, manufacturing processes, approval, retained samples, policy in case of complaints, recalls, storage of trial drugs, their destruction and the comprehensive documentation of all processes must be complied with.

It is beyond the scope of the present paper to present all measures required for acquiring a trial drug manufacturing permit.

What is presented below is intended to serve only as a stimulus for the issues which the clinical pharmacist has to face when assuming tasks in the field of clinical trials. However, it essentially describes the situation in the simplest and probably most frequent case, namely whenever a commercial sponsor delegates certain tasks not requiring a manufacturing permit to pharmacies.

Some of the partners in performing clinical trials and their responsibilities are listed in Tab. 2:

Tab. 2: Partners in performing clinical trials (Selection)	Responsibilities within clinical trials
Sponsor	has overall responsibility for the clinical trial; natural person or legal entity assuming responsibility for initiation, organization and financing of a clinical trial in humans, mandatory according to the German Pharmaceutical Law
Monitor	oversees correct performance of the clinical trial on behalf of the sponsor, especially documentation, employed by the sponsor or the originating institute (CRO)
Investigator	usually physician, dentist Principal investigator: if several investigators are working at one site, at least 2 years of experience in clinical trials with drugs Head of clinical investigation: in multicentric investigations
Study nurse	Specially trained employees – mostly nursing staff – specially trained in the care of trial patients and in the execution of clinical trials and correspondingly support the investigator in practical execution.
Clinical pharmacist	As employee of a pharmacy, responsible for coordination of clinical trials in the pharmacy and in cooperation with sponsors, monitors and investigators.

The clinical pharmacist provides a number of services in the context of his participation. These include the tasks listed in Tab. 3:

Tab. 3: Services of the clinical pharmacist in the execution of clinical trials
Acceptance of the trial drugs
Correct storage of the trial drugs
Control of stored stock
Labelling of the trial drugs
Randomisation
Blinding of administration-ready preparations of the trial drugs
Distribution: Handing over the trial drugs to the investigators
Documentation of used trial drugs
Acceptance, storage and disposal of unused trial drugs
Documentation of all procedures named
Participation in generating the trial protocol, especially in IITs
Studies on stability and compatibility of the trial drugs, especially in IITs

This results in special advantages for everybody involved in the clinical trial:

Tab. 4: Advantages of participation of the clinical pharmacist or of pharmacies in the clinical trial

- The sponsor will permanently have a central contact person for the local trial drug
- The investigator can focus on the patients and studying the effects of the trial drug
- The sponsor, investigator and patient receive a trial drug manufactured or prepared in accordance with GMP
- The process chain from receipt of the trial drug down to handing over to the investigator is validated and under special supervision of the competent drug specialist

The services to be provided by the pharmacist, as well as his rights and duties towards the sponsor, investigators, monitor and hospital management must be defined precisely in the contracts concluded between the individual hospital management and the sponsor or investigator, respectively. Since clinical trials are mostly financed by third-party funds, the general sponsoring guidelines must be complied with, with special focus on transparency and separation regulations. It is also important to clarify whether participation of the pharmacists/pharmacy in the context of the clinical trial constitutes official business. This is required for actuarial reasons.

The responsibilities of the pharmacy manager and his employees with regard to the required services must likewise be defined precisely. Depending on the number and scale of the clinical trials, a trial manager / trial coordinator (in case a manufacturing permit is requested, these are the production manager and the control manager) of the pharmacy may have to be named and registered in advance. Employees of a pharmacy participating in a clinical trial must be named and recorded beforehand. Usually, submission of a CV and naming as employees in the clinical trial by signature will be required. Once these basic requirements are met, prior to an individual study further points must be clarified. These result from the study protocol and are listed in Tab. 5.

Tab. 5: Workflow planning
Temporal workflow planning
Procedures between pharmacy and sponsor, ordering institute, monitor
Procedures in the pharmacy
Procedures between pharmacy and investigator, trial central, ward
Providing and preparing all necessary materials • information, e.g. investigators' brochure, study protocol, instructions for the pharmaceutical field • trial drug • implements (medical products: special syringes, infusions bags, lines and applicators) • labels • materials for documentation, e.g. inventory form sheets (Drug Accountability form)
Spatial prerequisites/design • storage areas, lockers • preparation areas: sterile or aseptic or non-sterile preparation • area layout
Training of employees • dissemination of all information required for the requested service

After completion of all approval procedures and [implementation of] the necessary organisational regulations the clinical trial can begin. The clinical investigation proper begins with the so-called «initiation visit».

For correct workflow within the pharmacy, the following points must be observed (Tables 6 – 12):

Tab. 6: Arrival of the trial drugs
• defining the persons authorized to receive deliveries • processing only by authorized persons previously named and recorded • inspection for completeness and intactness, compliance with transport conditions • documentation of goods received – confirmation of acceptance • copy of confirmation of acceptance to be returned to sponsor • documentation of current stocks and goods added in the drug accountability list (stock list)

The trial drugs must also be stored in accordance with specified criteria:

Tab. 7: Storage; authorisation to add and withdraw trial drugs
• separate from other drugs • locked cabinet or room, refrigerator, freezer • regulation of authorisation to add and withdraw, only by authorized persons (as few as possible) • monitoring of storage conditions (humidity, temperature) • immediate documentation in the drug accountability list after every withdrawal

In the context of clinical trials, the sponsor may entrust the pharmacy with randomisation work.

Tab. 8: Randomisation support
• In the case of comparison of different regimens for the same indication • Comparison active drug/placebo • Comparison test drug against standard drug
Exemplary, simplest procedure: • A randomisation list is prepared by an institute for medical data processing using a mathematical procedure • Corresponding randomisation envelopes are provided to the responsible clinical pharmacists • The investigating doctor communicates a corresponding randomisation • The patient receives a randomisation envelope in accordance with this randomisation number • In this randomisation envelope it is stated which therapeutic regimen the study patient will receive. • For emergencies, an unblinding procedure must be defined

In clinical trials of oncological drugs, making ready in the pharmacy is often mandatory.

Tab. 9: Making ready

- defining authorized persons
- general conditions and safety standards for preparation of drugs apply
- preparation according to the sponsor's binding instructions
- deviations are allowable only after consultation
- for each patient, always use an exactly defined number of vials
- no further use of previously opened vials for other patients (complicates keeping of the inventory list)
- label the administration-ready trial drugs with the label provided by the sponsor
- at any rate, identify with a label «For clinical trial»
- documentation of the making ready in the study folder – e. g. with a second label supplied by the sponsor, in addition: person performing the preparation, date and time of day
- destruction of the vials used, empty containers (e.g. in tablets) or blisters, if required: documentation of destruction by protocol and with the signature of a witness (because of the Hazardous Substances Act, used vials and empty containers should not be kept)

An exact procedure must be followed when handing over the study medicines to the investigating doctor:

Tab. 10: Handing over the trial drugs

- procedure exactly as defined in the study protocol
- coordination with the respective investigator, the nursing staff of the ward or with the study nurse, especially in the case of drugs which must be administered quickly for reasons of stability
- coordination with the transport service
- compliance with transport requirements, e.g. cooled storage, protection from light, transport duration
- documentation of the handing over: person, date, time

With regard to reconsignment of trial material to the pharmacy, the items listen in table 11 should be pointed out:

Tab. 11: Reconsignment to the pharmacy

- In the case of trial drugs made ready on the ward: Return of empty containers to the pharmacy: vials, blister, etc. – acceptance, identification and documentation
- In the case of unused test drugs: acceptance, identification, documentation, storage, on not account to be re-used for any other trial patient
- After consultation with the monitor if required: Return to manufacturer for destruction, documentation of the reconsignment
- After consultation with the monitor if required: counting, destruction, documentation of destruction

The activities of all partners involved into a clinical investigation are regularly controlled by the monitor. Each of his visits should be carefully prepared by the competent pharmacist. In general, the following visits are scheduled (Tab.12):

Tab. 12: Audits – Sequence and subjects

Before the trial begins: Start-up visit

- inspection of the storage areas and storage facilities
- inspection of the areas for making ready
- inspection of the existing procedures
- information about the clinical trial
- discussion of the requested procedure

Intermediate visits, by appointment (approx. every 6 weeks)

- check for proper storage, making ready, handing over, return of containers, documentation

Final audit

- checks as above
- defining the procedure for returning or destroying unused trial drugs
- decision on keeping or return of trial drugs
- archiving the trial documents according to the Ordinance on GCP

The above conditions apply whenever the functions of the individual partners are clearly assigned and the legal requirements undoubtedly fulfilled.

In case of doubt it is sensible to contact the local authorities so that the planned trial can be conducted in unison with the authorities and without flaw regarding legal regulations pertaining to drugs and pharmacies.

References:

1. Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 , BGBl. I S. 394, zuletzt geändert durch Artikel 9 Abs. 1 des Gesetzes vom 23. November 2007, BGBL I S. 2631

2. Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (GCP-Verordnung - GCP V) vom 9. August 2004, BGBl Jahrgang 2004 Teil I Nr. 42 S. 2081-91

3. Verordnung über die Anwendung der Guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft – AMVH (Arzneimittel und Wirkstoffherstellungsverordnung –AMWHV) vom 3. November 2006, BGBl. Jahrgang 2006 Teil 1 Nr. 51, S. 2523 vom 11. November 2006

4. Richtlinie 2001/20/EG des Europäischen Parlaments und des Rates vom 4. April 2001 zur Angleichung der Rechts- und Verwaltungsvorschriften der Mitgliedsstaaten über die Anwendung der Guten klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Humanarzneimitteln (ABl. EG Nr. L 121 S.34)

5. Richtlinie 2003/94EG der Kommission vom 8.Oktober 2003 zur Festlegung der Grundsätze und Leitlinien der Guten Herstellungspraxis für Humanarzneimittel und für zur Anwendung beim Menschen bestimmte Prüfpräparate (ABl. EU Nr. L 262 S. 22)

6. Van Gemmern R, QuapoS 3, Qualitätsstandards für den pharmazeutisch-onkologischen Service , Institute for Applied Healthcare Sciences (IFAHS e.V.), 2003. S. 262-71

7. ADKA-Leitlinie: Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia, Krankenhauspharmazie, 24 (6), S. 195-2001 (2003)

8. Mende, A., Antragsstellung auf Genehmigung einer Klinischen Prüfung, Vortrag, Bonn, 06.02. 2006

9. Wagmann, A., GMP-Anforderungen an Prüfpräparate, Vortrag, 07.2006

10. 7 B 3409/07, VG Oldenburg, Beschluss vom 19.12.2007 - Die Rekonstitution (Verflüssigung) eines Arzneimittels im Rahmen einer klinischen Prüfung www.dbovg.niedersachsen.de

11. Chase, D. Kennzeichnung von Prüfpräparaten, Vortrag, Bonn 17.05.2005

12. Seibert-Grafe, M., Relevanz der Änderungen für IITS und deren Auswirkungen auf die KKS – Auswirkungen der 12. AMG-Novelle auf die klinische Forschung in Deutschland – Bilanz nach einem Jahr, Workshop der Paul-Martini-Stiftung, Vortag, 29.09.2005

13. Moldenhauer, I., 12. Novelle des Arzneimittelgesetzes: Was ist neu?, Vortrag, Halle, 09.02.2005 14.

14. Grundsätze der Verantwortlichkeiten bei der Durchführung klinischer Studien, Deutsche Forschungsgemeinschaft und Bundesministerium für Bildung und Forschung, 12.07.2005

15. Huber, S. Grundregeln für die GCP-konforme Durchführung von klinischen Prüfungen, Teil III, Darmstadt 30.11.2005

4.9. Handling Excreta

Excreta of patients treated with cytostatics may contain significant amounts of cytotoxic substances.

Handling of excreta is done with the focus on protecting the health of all persons involved, as well as on the applicable legal regulations for disposal (see 4.1 «Disposal»).

Thanke Mehrtens, Hannover

Investigations into the pharmacokinetics of anti-neoplastic substances have shown that the danger to physicians and nursing staff they pose does not end with the administration of the cytostatics: Excreta of patients treated with cytostatics may still contain significant amounts of cytotoxically effective substances, which may be either the cytostatic or its active metabolites. In studies, exposed persons suffered slightly, but significantly more frequently than control persons, from gastrointestinal symptoms such as diarrhoea or from neurological symptoms (headache). Skin contact with cytotoxic substances was identified as the cause [1, 2, 3]. In the course of transferring cytostatics therapy from the inpatient to the outpatient sector, family members of tumour patients have become more affected by this issue.

Legal basis

According to TRHS 525 [10], chapter 5.2.4, body fluids or excreta of patients under CMR therapy are not to be classified as hazardous substances. This statement refers the Ordinance on Hazardous Substances (Gefahrstoffverordnung) which classifies, according to guideline 1999/45/EC, cancerogenic and mutagenic substances as hazardous if the substance contained therein reaches or exceeds a relative mass of 0.1 %.

Due to the dilution of the cytostatics ingested by the patient in the patient's blood (approx. 5 - 7 l) and the other body compartments, the Professional Association

for the Health and Welfare Services (Berufsgenossenschaft BGW) assumes that the relative mass in body fluids of patients will be below 0.1 % [11].

Excreta after high-dosage therapies or vomited gastric contents after oral administration of cytostatics constitute an exception since here the relative mass of cancerogenic cytostatics may exceed 0.1 %.

Excretion pathways and duration of the excretion of cytostatic substances

A number of publications [4, 5, 6, 7, 8, 9, 20] describe the duration of the excretion of relevant amounts as well as excretion routes and recommended duration of protective measures. A summary of the recommendations on the duration of protective measures published there is found in table 1.

Excretion after instillation into body cavities

a) Intra-peritoneal application

There are studies on the cytostatics contents of body fluids for intra-peritoneal application of various cytostatics. Normally, after intra-peritoneal administration only small amounts of the substance enter systemic circulation. Of this, the major portion enters the bloodstream, a minor portion is carried off in the lymph. Thus, high intra-peritoneal substance concentrations contrast with relatively low plasma levels. However, there are large inter-individual fluctuations.

Cisplatin:

Conti et al. state that after hyperthermic intra-peritoneal administration of cisplatin (50 – 90 mg/m²) approx. 20 % of the administered amount enter systemic circulation, as the substance is mostly adsorbed by tissue. Only approx. 20 % of the administered substance were excreted into urine [14].

Protective measures are recommended for 48 h after surgery [15].

Mitomycine:

A study by van Ruth concludes from pharmacokinetic calculations that approx. 50 % of the intra-peritoneally administered dose of 35 mg/m² enter systemic circulation. In approx. ⅓ of patients, after therapy there was leukopenia of

degree ¾. In blood samples taken 18 h after therapy begin, no more mitomycin could be detected [16]. 7 – 8 % of the administered dose were excreted into urine within 2 h [17]. In another study, 24 h after administration of cytostatics no mitomycin could be detected in the urine any more [15].

Mitoxantrone:

Immediately after intra-peritoneal application of 20 – 50 mg/m², the average concentration in peritoneal fluid amounted to 8700 ng/ml, and to 490 ng/ml after 168 h. Systemic absorption of mitoxantrone from peritoneal fluid into blood occurred only to a very low degree, plasma levels were 34 ng/ml one hour after infusion and only 1 ng/ml after 168 h. In the study mentioned above, the peritoneal liquid was drained after 4 h. From 7 to 30 % of the administered dose were recovered in the drained liquid [12].

b) Intra-pleural application

A study on intra-pleural mitoxantrone therapy of malign pleura effusions [13] revealed, at a dosage of 30 mg, concentrations of up to 10 mg of mitoxantrone per ml of pleural fluid during the first 20 h after instillation, with very strong inter-individual variation of the values. Approx. 15 % of the dose administered intra-pleurally entered systemic circulation. Here, too, strong inter-individual variation of the values was seen so that in individual mitoxantrone cases plasma levels were as high as after i.v. application.

c) Intravesical instillation

After instillation of mitomycine into the bladder, likewise only a small fraction of the cytostatic is resorbed. Thus it must be assumed that the dose applied is almost quantitatively excreted into the urine (intense blue colouration). Since for intra-vesical instillations a dosage of 20 – 40 mg mitomycine in 20 – 40 ml of liquid is recommended, i.e. the concentration already amounts to 0.1 %, the urine does contain quantitatively high amounts of a cytostatic, but its concentrations will generally be slightly below the permissible limit of 0.1 %. In doubt, contact the competent authorities for proper disposal.

Handling excreta of patients receiving cytostatics therapy as inpatients

1. Information

Information should be written intelligibly, and recommendations should be easy to implement.

In the course of annual instructions, nurses and physicians are informed about excretion routes and times of the substances playing a role in their field of work. This can be done using suitable lists; however, the simpler rule to consequently observe protective measures for 48 hours after therapy will be sufficient for most of the substances and easier for the staff to memorize [18, 19]. Other authors recommend to generally observe protective measures for 7 days [21].

In patients treated with cytostatics, urine collection should be avoided for the first two days. If body fluids are drained via drainages, closed collection systems are expedient. For incontinent patients, consequent skin protection is recommended [19].

Very detailed recommendations also comprise establishing appropriately separated toilets for the patients [21]. Men should sit down for micturition [21].

Information of family members is important, especially in the field of paediatric oncology (changing diapers, using single-use diapers).

2. Protective clothing

When disposing of excreta containing cytostatics, wearing protective gloves is mandatory, if required protective coat, goggles and overshoes as well [19]. Suitable protective gloves are made of latex, neoprene or nitrile rubber. In case of major contaminations, protective clothing as recommended by the BGW must be worn (see chapter 4.2. Decontamination after inadvertent release and chapter 3.2. Personal protective equipment).

3. Disposal of body fluids

Excreta where the contents of cytotoxic substances may be assumed to amount to less than 0.1 % are disposed of into the sewerage. Vomited gastric contents

after oral administration as well as excreta of patients receiving high-dosage therapy must be disposed of as toxic waste.

If at least two hours have elapsed between ingestion of the cytostatic and vomiting, the relative mass of of the cytostatic may be expected to be below 0.1 %, allowing for simpler disposal into the sewerage. Some recommendations discuss whether to flush the toilet at least twice in this case [19].

4. Disposal of contaminated materials

Generally, single-use materials to be destroyed after use must be preferred to reusable items [21]. When using reusable items, afterwards they must be cleaned thoroughly, if possible twice [21].

Clothing contaminated with excreta, sweat or blood should be packaged liquid-tight and sent to the laundry labelled as done with infection clothing [18, 21]. Some recommendations even suggest to perform two rounds of washing [19, 21]. If danger to the transport staff or the laundry employees cannot be ruled out, it is recommended to destroy the clothing in accordance with the legal recommendations for waste.

5. Cleaning contaminated surfaces

Successful cleaning is possible by wiping the contaminated surfaces first with diluted sodium lye and then with isopropanol [22] (see chapter 4.2 Decontamination after inadvertent release).

Handling excreta of patients receiving cytostatics therapy as outpatients

1. Information

During the consultation session, the patient or family members should be provided with information in an adequate form, oral and if possible in writing as well. All operating instructions require explanation.

It is recommended to address the following points:

• It is mandatory to avoid contamination of the environment.

- Vomiting within two hours after ingestion of oral cytostatics may contaminate surfaces.
- Men should sit down for micturition.
- What kind of protective clothing may be required?
- How to dispose of contaminated objects?
- What cleaning agents are available?

2. Protective clothing

Single-use gloves made of latex, neoprene or nitrile rubber can be used for disposing of contaminated excreta, but immediately after use they must be taken off, turning the inside out, and disposed of. Next, the hands must be cleansed thoroughly. At home, protective clothing may be waived if during the consultation session it has emphasized that potentially contaminated clothing must be changed immediately and cleaned.

Keeping a kind of «spill kit» in readiness may be a service in the sense of pharmaceutical tumour patient care. The kit should comprise a sufficient number of protective gloves, one or several liquid-repellent aprons, possibly also protective goggles and overshoes and a surface decontamination agent. It is recommended to design this kit for the therapy with substances which are excreted quickly and primarily renally (e.g. carboplatin). For substances excreted over a longer period with lower daily amounts, at least information on minimal protective clothing must be added.

3. Disposal

In outpatient treatment, high-dosage therapies generally do not play any role. Thus, excreta of patients under cytostatics therapy may be disposed of into the sewerage since it may be assumed that the relative amount of CMR substances will be below 0.1 %. If a patient vomits within two hours after oral administration of a cytostatic, the vomit may be disposed of into the toilet (flush several times, then clean contaminated surfaces several times). Alternatively, the vomit may be disposed of, carefully packaged, in rubbish bags into the waste.

4. Disposal of contaminated materials

During the advisory meeting it must be emphasized that it is mandatory to avoid contamination of cushions and carpets, pillows, blankets or mattresses (recommend slip-covers of mattresses). Contaminated clothing, bedclothes or towels should be changed immediately and then washed in the washing machine (if possible with additional rinse cycle / intensive washing)

5. Cleaning contaminated surfaces

The surfaces must be wiped several times using an agent suitable for decontamination of the respective substance. In the consultation session, a suitable agent, e. g. combined use of diluted sodium lye / isopropanol, must be recommended (see chapter 4.2 Decontamination after unintentional release).

References:

1) Valanis BG, Vollmer WM, Labuhn KT and Glass AG: Association of antineoplastic drug handling with acute adverse effects in pharmacy personnel; Am J Hosp Pharm, Vol 50, Mar 1993, Pages 455-462

2) Valanis BG, Labuhn K, Valanis B, Schoeny R, Loveday K, Vollmer WM. Nurses' and pharmacists' exposure to antineoplastic drugs: findings from industrial hygiene scans and urine mutagenicity tests. Cancer Nurs. 1998 Apr;21(2):79-89.

3) Valanis BG, Vollmer WM, Labuhn KT, Glass AG. Acute symptoms associated with antineoplastic drug handling among nurses. Cancer Nurs. 1993 Aug;16(4):288-95.

4) Harris J, Dodds LJ: Handling waste from patients receiving cytotoxic drugs; The Pharmaceutical Journal, September 7, 1985, Pages 289-291

5) Cass Y, Musgrave CF: Guidelines for the safe handling of excreta contaminated by cytotoxic agents, Am J Hops Pharm, Vol 49, Aug 1992, Pages 1957-1958

6) Dimtscheva O, Mehrtens T, Carstens G: Vorsichtsmaßnahmen beim Umgang mit kontaminierten Ausscheidungen nach Zytostatikatherapie, Krankenhauspharmazie, 19. Jahrgang, Nr. 7, 1998, Seite 330

7) Mehrtens T: Umgang mit Ausscheidungen nach Zytostatikatherapie, Krankenhauspharmazie, 21. Jahrgang, Nr. 4, 2000, Seite 148

8) Allwood M, Stanley A, Wright P: The Cytotoxics Handbook, 3rd Edition 1997, Radcliffe Medical Press Oxford / New York: Handling of waste from patients receiving cytotoxic drugs

9) Eitel A, Scherrer M, Metz L, Kümmerer K: Umgang mit Zytostatika, Bristol-Myers-Squibb 1999

10) Technische Regeln für Gefahrstoffe TRGS 525 "Umgang mit Gefahrstoffen in Einrichtungen zur humanmedizinischen Versorgung", Bundesarbeitsblatt 5 / 1998

11) Heinemann A, Zytostatika im Gesundheitsdienst – Informationen zur sicheren Handhabung von Zytostatika, Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtpflege, Hamburg, April 2008 (Bestellnummer M620)

12) Nagel JD et al.: Clinical pharmacokinetics of mitoxantrone after peritoneal administration, Cancer Chemother Pharmacol (1992), 29, 480-484

13) Musch E et al.: Intrapleurale Mitoxanthron-Therapie zur Behandlung maligner Pleuraergüsse, Aktuelle Onkologie, Bd. 66, 1992, S. 1-17

14) Conti M et al.: Clinical Pharmacology of Intraperitoneal Cisplatin-based Chemotherapy; Journal of Chemotherapy, Vol. 16, Suppl. N. 5 (23-25), 2004

15) Jähne J et al: Intraoperative (hypertherme) intraperitoneale Chemotherapie- Überlegungen und Aspekte zum sicheren intra- und postoperativen Umgang mit Zytostatika , Langenbecks Arch Chir (1997), 382, 8-14

16) Van Ruth S et al.: Population Pharmacokinetics and Pharmacodynamics of Mitomycin during Interoperative Hyperthermic Intraperitoneal Chemotherapy, Clin Pharmacokinet 2004, 43 (2), 131-143

17) Van Ruth S et al.: Pharmacokinetics of intraperitoneal mitomycin C, Surg Oncol Clin N Am 12 (2003), 771780

18) ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs Am J Hosp Pharm. 1990; 47:1033-49

19) Polovich M, Blecher CS, Glynn-Tucker EM, McDiarmid M, Newton SA. Safe handling of hazardous drugs. Pittsburgh (PA): Oncology Nursing Society (ONS); 2003.

20) Crash-Karte Zytostatika, zu beziehen über Teva Deutschland / GRY-Pharma GmbH

21) ISOPP Standards of Practice: J Oncol Pharm Pract 2007; 13 Suppl

22) Kiffmeyer T et al: Außenkontaminationen von Medikamentenverpackungen – Vorschläge zum Reinigungsverfahren, Krankenhauspharmazie 2001; 5: 207-212

Active substance	Recommended time for wearing protective clothing	
	Urine	**Faeces**
amsacrin	3 days	2 days
bendamustine	6 hours [6] 6 days [9]	
bleomycin	3 days	
busulfan	1 day	
carboplatin	1 – 2 days	
carmustine	4 days	
chlorambucil	2 days	
cisplatin	7 days	
cyclophosphamide	3 days	5 days (after oral administration)
cytarabine	1 day	
dacarbazine	1 day	
dactinomycin	5 day	7 days
daunorubicin	2 days [5,6,7,8] 7 days [9] possibly reddish discolouration of urine	7 days
docetaxel	1 day	2 days
doxorubicin	6 days	7 days
epirubicin	7 days	5 days [4,5,6,7,8]

Active substance	Recommended time for wearing protective clothing	
	Urine	Faeces
etoposide	4 days [4,5,6,8] 5 days [9]	6 days [9]
fludarabine	3 days	
fluorouracil	2 days	5 days (after oral administrat.) [4] 5 – 7 days [9]
gemcitabine	1 day	
hydroxyurea	2 days	
idarubicin	3 days	7 days
ifosfamide	2 days	
lomustine	4 days [6] 2 days [9]	7 days
melphalan	2 days	7 days (after oral administration)
mercaptopurine	2 – 3 days	5 days
methotrexate	3 days	7 days
mitomycin	1 day	
mitoxantrone	6 days possibly blueish-green discol-ouration of urine	
nimustine	4 days	
oxaliplatin	3 days	
paclitaxel	1 day	2 – 5 days
procarbazine	2 days	
tioguanine	1 days	
thioTEPA	3 days	
topotecan	2 days	
treosulfan	1 days	
trofosfamide	1 days	
vinblastine	4 days	7 days
vincristine	4 days	7 days
vindesine	4 days	7 days
vinorelbine	4 days	7 days

5. Pharmaceutical Counseling

Requirements for providing the service:

The pharmacy continually strives to implement pharmaceutical counseling and advice as a part of the oncological service. Direct contact with the patients to be provided with drugs and infusion solutions must be sought. Service is provided taking into consideration the peculiarities of ward and outpatient treatment. Information may be communicated directly via contact with patients or indirectly by producing and distributing information material for the patients. In addition, the pharmacy is a reliable partner of the attending physicians and nurses where it comes to advice relating to the drugs used. These activities also belong to the service in the context of implementing patient-oriented pharmaceutics for tumour patients.

For implementation of counseling and advice, a structured approach by the employees in the cytostatics department is required. Communication of therapy-relevant data by the physician is required for counseling and advice accompanying the therapy (see 3.4.1. Request form sheet). Direct counseling and advice are provided when personal contacts with patients are possible.

Michael Höckel, Eisenach

Order of structured counseling:

a. First contact with the patient

First contact should be used for consultation about current chemotherapy and supportive medication, ideally before or at the beginning of the therapy session. Important issues relating to the prescribed cytostatics include:

- type of infusion solution and brief description of the quality-assured preparation
- storage recommendations when using pumps
- information on taking/usage
- type and place of effect
- adverse effects which may occur (explain sense and purpose of prophylactic and needs-adjusted use of supportive medication and mention auxiliaries such as having a wig made)
- point out interactions with other drugs being used, foodstuffs and unconventional agents («CAM»), as far as known to the counseling pharmacy
- provide memo or information brochure about the prescribed chemotherapy
- explain possibilities and use of continuous counseling (e.g. patient card, telephonic callbacks)
- documentation of the issues covered by the first talk

b. First subsequent talk at the begin of the next therapy cycle

If after the first session the patients expresses a desire for concurrent counseling by the pharmacy, having another talk at the begin of the next therapy cycle is expedient.

Issues which may be covered by subsequent talks:

- briefly resume the first talk
- discuss questions not answered in the first talk
- ask about well-being
- advise about new drugs if any change has been made
- inform about other drugs from the non-oncological field of prescription
- provide memo, if required

• further memo for the pharmacy

Accompanying talks

If the patient has opted for a patient card or is in treatment for a longer time in an oncological centre or hospital, continuous pharmaceutical counseling is advisable. Talks and contacting occur on the following occasions:

a. Upon change of the prescription
Counseling focuses on the drug, its relation to the previous therapy etc.

b. When revisiting the centre / hospital
Brief routine contacts

In the context of pharmaceutical counseling brief talks are held on the phone or in the pharmacy.

Continuous counseling aims at:

• improvement of the quality of life of the counseled patient

• promotion of compliance (observance of adherence)

• avoidance of side effects

• identification of drug-related problems

• motivating the patients to comply with his/her therapy plan by informing about drug effects and avoidance or reduction of side effects

Indirect pharmaceutical counseling

It is expedient to produce written information material for patients (contents based on the topics of the counseling mentioned above) about the drugs used and the supportive medication prescribed in cooperation with physicians and nurses, and also to regularly participate in visits in the hospital. In the majority of cases, oncology patients are not presented with the patient information of the drugs used in the context of oncological therapy. Oral information is provided by the physician, and the patient signs a consent form on chemotherapy describing the general problems which may occur in the context of cytostatics treatment. The pharmacy should supplement this information with written

patient-relevant information on the individually used drugs, which is then handed to the patient concomitantly to administration of the drugs. At the same time, it is expedient to indicate the possibility of personally addressing the contact person in the supplying pharmacy. In the context of drug safety, this kind of drug information should be implemented as a minimum offer; it is also prescribed by the Ordinance on the Operation of Pharmacies for reasons of drug safety.

Indirect pharmaceutical counseling aims at:

- drug safety by safe application of the drugs
- supporting medical therapy and nursing activities
- avoiding side effects and complications

Documentation

In outpatient treatment, documentation begins with the patient's decision for pharmaceutical counseling. The patient's written consent to storage of data related to him/her in the pharmacy for counseling follows with the decision in favour of counseling.

If possible, the patient should be informed in the first talk about the possibility of intense counseling using a patient file. The documentation of the patient file should be presented as a tool for guaranteeing intense pharmaceutical service accompanying the therapy.

In stationary pharmacotherapy, information density is high due to patient files being kept. Here the oncology pharmacist may likewise, in agreement with the medical and nursing employees, document his own notes. Filing a copy of information material handed to the patient for documentation and information of the physicians and nurses is recommended.

Comprehensive pharmaceutical counseling aims at:

- maintaining or improving quality of life
- promoting compliance or supporting adherence relating to the therapy

• reducing fears by informing

• avoiding medication errors.

The pharmacist works in a team with physicians, nurses and members of other professions participating in the counselling of tumour patients and their family members. Potential medication errors may be avoided most sustainably, for the protection of the patients, by patient-oriented work of the pharmacy working in oncology jointly with other care providers. An error reporting systems complements this kind of interdisciplinary cooperation and guarantees establishment of a learning system suitable for everyday use.

References:

Apotheker, N. N.: Krebs erlebt, DAZ(25)1998, S.2344-2347

Cipolle, Robert J., Strand, Linda M., Morley, Peter C.: Pharmaceutical Care Practice, New York 1998.

Höckel M., Heckl U., Nagel G.A: Der Krebs-Patient in der Apotheke, Deutscher Apotheker Verlag, Stuttgart 2003

Jaehde, Radziwill, Mühlebach, Schunack: Klinische Pharmazie, Deutscher Apotheker Verlag, Stuttgart 2003

Parker P.E., Finkbiner K.L.: The Expanding Role of the Oncology Pharmacist. Oncology Issues 2002; 17(6): 34 – 36

Schaefer, M.: Grundlagen und Bedingungen von Informationsvermittlung und Patientenberatung. In: Framm, Schaefer, Derendorf: Patientenberatung in der Apotheke, Stuttgart 1996, S.25-40.

Schneider E.: Muß Hilfe professionell sein? Beratung und Begleitung von Krebsbetroffenen aus psychoonkologischer Sicht, Forum DKG(12)1997, S.381-384.

Wertheimer, Albert I, Smith, Mickey C.: Pharmacy Practice. Baltimore 1989.

Westfeld, M., u.a. (2006): Maligne Erkrankungen. Manuale zur pharmazeutischen Betreuung Band 8. Govi-Verlag, Eschborn

5.1. Preparing a Counseling Plan

The counseling plan is an integral part of pharmaceutical counseling. It serves to perform pharmaceutical counseling of a patient, thereby focussing on issues and results. In the plan, all counseling interventions are documented. The result of these interventions is assessed in defined intervals using previously determined control parameters.

The counseling plan is the result of systematic analysis of all drug-related problems of a patient according to the so-called SOAP (Subjective, Objective, Assessment and Plan) design:

Subjective	**complaints and problems of the patient are ascertained and documented.**
Objective	**here measurable, objective parameter are determined and documented.**
Assessment	**the aforesaid objective and subjective problems are analysed systematically, and various approaches with their advantages and disadvantages are discussed.**
Plan	**the counseling plan is established based on the preceding analysis. In this plan, therapy goals are defined, and the measures for reaching these goals are precisely documented. After a suitable period, control parameters are used to verify achievement of the goals, and the results are recorded in writing.**

Barbara Eirmbter, Viersen

Advantages of SOAP analysis

High-quality pharmaceutical counseling of oncological patients is a very complex and time-consuming task. In order to fulfil this task as efficiently as possible, creation of a SOAP-based counseling plan is recommended. The following points argue in favour of this:

- Work according to the SOAP design necessitates very precise wording of drug-related problems and helps to discriminate between medical problems (which the physician should solve) from pharmaceutical ones.
- In the counseling plan, definite measures for solving these problems are documented, and their success is controlled regularly so that ineffective measures can be identified and modified quickly.
- A counseling plan actively involves the patient into coping with his problems and complaints by offering trainings, keeping protocols and the assessing interventions successes. Thus, his self-responsibility is strengthened, and he gets the feeling that he is able to do something for himself to combat his disease. Investigations by the hospital for tumour biology in Freiburg have shown that patients with with a greater sense of responsibility for themselves and a will to «take their fate into their own hands» do have a higher life expectancy.
- The counseling plan may at the same time be used for documenting the counseling service.
- A written plan designed according to the SOAP concept facilitates getting into the case for stand-in colleagues, thereby enabling them to continuously continue the counseling of a patient.

Performing the SOAP analysis:

Obtaining data

SOAP analysis begins with obtaining subjective and objective data. If counseling session is held in a public pharmacy, most information can be obtained from the discussion with the patient. Medications profile and data from the chemotherapy protocols furnish further important information. Attempts to talk to the attending oncologist or family doctor should always be made.

In the hospital or in nursing institutions most of the required information is available in the form of the patient file and the nursing report. A discussion with the patient is nevertheless indispensable.

To accelerate data collection and enable quick access to documentation, it is advisable to use a standardised form sheet. This can be self-developed or derived from software for pharmaceutical counseling. Such a form sheet also helps to remember important questions such as those about allergies of the patient.

The form sheet should be structured as follows:

1. General patient data such as name, address, date of birth
2. Social background such as marital status, children, living and dwelling situation, nutritional habits, alcohol and tobacco consumption
3. Short medical anamnesis with questions on organ function and metabolism disturbances, size and weight
4. Drug anamnesis with up-to-date medication profile including over-the-counter preparations, homoeopathic preparations, «natural medication» and «folk medicine» or «household remedies»
5. Space for notes on the patient's subjective complaints
6. Objective data such as weight, partial blood count, creatinine value and liver values are comprehended best in tables and/or presented graphically in order to detect trends quickly.

Analysis

The subsequent analysis aims at investigating the individual problems in order of their importance (for the patient!) from as many perspectives as possible. Here all factors causing or influencing the problem should be considered.

It is important not to accept any preconceptions with regard to cause or course of a disease or to jump to conclusions from complexes of symptoms. All conclusions should be verified (e. g. by quotations from literature).

The analysis is documented in writing.

Establishing the plan

Next, in the discussion with the patient, his/her family members and other persons providing care and/or the attending physician, based on the analysis therapy goals are defined and included into the counseling plan. Here the goals should be worded clearly and in a way understandable for the patient. The steps required for reaching this goal are discussed with all involved persons and likewise documented in writing. These goals should be understood and accepted by all to guarantee compliance. It may be expedient (e. g. for handling certain implements) to create an information leaflet for the patient and his family members. If behavioural changes are desired (such as increasing the amount of liquid food additives drunk per day or week), it may be helpful to have the patient keep a diary or log.

Evaluation

Success or failure of any measure initiated must be measurable (e. g. weight gain) or observable (reduction of the pain attacks recorded by the patient in his pain log – see 5.2.2 Management of analgesic therapy) within a time frame fixed in the plan.

After the control period, each measure is evaluated. If any measure should not have had the desired success, it is important to explain the possible reasons to the patient in order to motivate him/her for further measures and to maintain his/her compliance.

Non-compliance is not the patient's fault but indicates that the measures were not appropriate for this particular patient.

References:

Taxis, K, Arzneimittelanamnese, Therapiebeurteilung und Pharmazeutische Betreuung. In Schneemann, H. (Hrsg.), Young, L., Koda-Kimble, M.: Angewandte Arzneimitteltherapie, Klinisch-Pharmazeutische Betreuung in Fallbeispielen, Berlin 2001

Lennecke, K, Pharmazeutische Betreuung. In: Jaehde, U., Radziwill, R., Mühlebach, S., Schunack, W (Hrsg.), Lehrbuch der Klinischen Pharmazie, Stuttgart 2003, 179-200

Gräfe, KA, Dem Denkstil des Patienten Respekt zollen, Pharm Ztg. 2003, 148:1927-1929

Schneider, J, In Schritten zum Erfolg. Pharm. Ztg. 2002, 147:3969-3964

Gensthaler, M, Orientierung schafft Vertrauen. Pharm Ztg. 2002, 47:2096-20970

Heyn, G, Betreute Patienten haben weniger Nebenwirkungen. Pharm. Ztg. 2003, 148:2822-2833

Riess, B, Die Lebensqualität stärken: Pharm. Ztg. 2003, 148:650-651

Dersch, D Patient assessment tool for pharmacists, Am J Health-Syst Pharm 2008, 65:702-703

Zierler-Brown S, Brown TR, Chen D, Blackburn RW Clinical Documentation for patient care: Models, concepts, and liability consederations for pharmacists Am J Health-Syst Pharm 2007 64: 1851-1858

5.2.1. Anti-Emetic Support Therapy

Nausea and vomiting are described by patients as feared and particularly unpleasant side effects of anti-neoplastic therapy. When particularly pronounced, these side effects may lead to premature termination of the therapy.

For these reasons, efficient anti-emetic support therapy ought to be guaranteed.

In selecting a suitable therapy, the following should be taken into consideration:

- **emetogenic potential of the therapy**
- **different phases of nausea and vomiting**
- **therapy guidelines by recognized professional societies based on the rules of evidence-based medicine (EBM)**
- **individual risk factors**
- **drug interactions**
- **pharmaco-economic aspects**

Implementation of the selected therapy should be supported by

- **cooperation of patient, physician, pharmacist and other affected persons,**
- **measures to promote concordance,**
- **suggestions for additional prophylactic measures.**

Dr. Andrea Liekweg, Hamburg, and **Dr. Martina Westfeld**, Münster

During anti-neoplastic therapy, the cancer patient is confronted with a selection of systemic treatment concepts such as cytostatic chemotherapy, immunotherapy and hormone therapy. These various approaches are complemented by support therapy attempting to maintain or improve, respectively, quality of life and to be able to perform anti-neoplastic therapy unhindered.

Even after introduction of 5-HT_3 antagonists, nausea and vomiting are still particularly feared and considered unpleasant by the patients (1). More recent studies find that this point is not that important any more and e. g. fatigue has gained importance. Sometimes these side effects may, if strongly pronounced and difficult to treat, lead to premature termination of therapy. Therefore efficient prophylactic anti-emetic support therapy should be guaranteed.

1. Emetogenic potential of therapy

The selection of a suitable anti-emetic support therapy depends mostly on the emetogenic potential of the substances administered. Here not only the substances as such but also their dosages play an important role (2). Table 1 shows a part of the classification based on the current guidelines by MASCC and ASCO. In contrast to previous guidelines, the drugs are now classified into four rather than five emetogenic classes. Classes 3 and 4 of the obsolete guideline are joined to form the class of moderately emetogenic drugs in the new guideline.

Often, however, chemotherapy is not performed as a monotherapy, but various substances are combined. For such combination therapies, estimating the emetogenic potential is more difficult. The only combination therapy mentioned by the current guideline is the therapy with cyclophosphamide and an anthracycline which is mostly used in adjuvant therapy for mammary carcinoma; it is classified as having high emetogenic potential (3).

For all other combinations there is the recommendation to administer anti-emetic prophylaxis according to the classification of the individual drug with the highest emetogenic potential.

Tab. 1: Emetogenic potential of selected intravenously applied cytostatics (from: Kris et al. 2006)

Emetogenicity	Frequency of vomiting [%]	Substance
High	›90	carmustine cisplatin cyclophosphamide › 1500 mg/m² dacarbazine
Moderate	30 – 90	carboplatin oxaliplatin cyclophosphamide ≤ 1500 mg/m² cytarabine › 1 g/m² doxorubicin › 60 mg/m² epirubicin daunorubicin ifosfamide irinotecan
Low	10 – 30	paclitaxel docetaxel mitoxantrone topotecan etoposide methotrexate fluorouracil gemcitabine bortezomib cetuximab trastuzumab
Minimal	‹10	bevacizumab bleomycin busulfan fludarabine rituximab vinblastine vinorelbine vincristine

2. Individual phases of nausea and vomiting

In anti-emetic support therapy is is important to consider the individual phases of chemotherapy-induced nausea and vomiting since they are based on different pathophysiological mechanisms. These individual mechanisms must be taken into consideration during therapy and have a particular impact on the selection of the drug (see below). Nausea and vomiting are classified as acute, delayed or anticipatory.

Acute vomiting begins per definitionem during the first 24 hours of treatment. Here chemotherapy and radiotherapy release mostly serotonin from the enterochromaffinic cells of the small intestine, which activates the vomiting process via specific receptors (5-HT_3 receptors) which are found e. g. at the nervus vagus endings. Further serotonin receptors are found in the chemoreceptor trigger zone in the area postrema, which in turn relays information to the vomiting centre in the formatio reticularis. In addition to serotonin, dopamine (via D2 receptors) and neurokinin-1 (via NK1 receptors) are involved in the induction of nausea and vomiting, albeit to a lower degree.

Delayed vomiting begins on day 1 to 5 after [initiation of] therapy. The reasons for delayed vomiting have not been fully elucidated yet. In contrast to acute vomiting, however, this form is mediated less by serotonin. Here rather the neurotransmitters neurokinin-1 (Substance P) and dopamine play an important role.

Anticipatory vomiting occurs already before initiation of the therapy and is psychically motivated. It is conditioned by previous experiences of nausea and vomiting and may be induced, for example, by the sight of the infusion solution or by entering the hospital. Therapy of this form of vomiting is usually very difficult.

3. Therapy guidelines by recognized professional societies based on the rules of evidence-based medicine (EBM)

Therapy guidelines for optimal anti-emetic therapy are published by various professional societies. They are compiled and updated based on the rules of evidence-based medicine (EBM). A selection of such therapy guidelines is shown in table 2.

Table 2: Overview of the various guidelines for the treatment of nausea and vomiting

Society	Year	Title
ASCO	2006	American Society of Clinical Oncology guideline for anti-emetics in oncology: update 2006 (1)
MASCC	2008	Prevention of chemotherapy- and radiotherapy-induced emesis: results of the Perugia Consensus Conference (2)
ESMO	2005	ESMO Minimum Clinical Recommendations for prophylaxis of chemotherapy-induced nausea and vomiting (NV) (3)
ASHP	1999	ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery (4)

The MASCC and ASCO recommendations for anti-emetic prophylaxis are summarized in table 3. In comparison to preceding guidelines, in particular the use of neurokinin-1 receptor antagonists such as aprepitant in highly emetogenic chemotherapies is an innovation to be named. From the recommendations in table 3 it can be seen that the 5-HT_3 antagonist group play an important role in prophylaxis of acute vomiting but are not the drugs of choice in the delayed phase (4). Here mostly dexamethasone and aprepitant are used (5).

In anticipatory vomiting, because of the psychogenic cause the benzodiazepine group is indicated, in particular lorazepam. The exact dosages can be learned from the guidelines listed in table 3.

Whereas the 5-HT_3 antagonists previously approved in Germany (odansetron, granisetron, dolasetron and tropisetron) were equivalently applicable, palonosetron, approved in 2005, is a substance which markedly differs from the

Table 3: anti-emetic therapy of different degrees of emetogenicity (from MASCC Guidelines 2005 and ASCO 2006)

Emetogenicity	Acute vomiting		Delayed vomiting	
	Substances	Degree of evidence	Substances	Degree of evidence
High	5-HT_3 antagonist + dexamethasone + aprepitant (or fosaprepitant)	I A	dexamethasone + aprepitant (or fosaprepitant)	II A
Moderate	5-HT_3 antagonist + dexamethasone	I A	dexamethasone if required, additional 5-HT_3 antagonist	II A II B
Low	single drug, e. g. low-dosage dexamethasone	III D	none	n.a.
Minimal	no anti-emetic therapy	V D	none	n.a.

n.a. = no data available

others, especially with regard to its pharmacokinetic properties. With a terminal half-life of approximately 40 hours, palonosetron may be applied once intravenously prior to the begin of chemotherapy and is still effective during the delayed phase.

4. Individual risk factors

Apart from the emetogenic potential of cytostatics, individual risk factor for the patient may be defined (see table 4) (6). These have indeed been documented in clinical trials, but remain mostly unconsidered in therapeutic practice.

However, they may serve to complete the description of the patient and to provide orientation with respect to better or worse tolerance to chemotherapy.

Table 4: Individual risk factors

Factors for high individual risk
• Poor control in preceding therapy cycles
• Female gender
• Low alcohol consumption
• Low age

5. Drug interactions

Drug interactions attract more and more attention of attending physicians and clinical pharmacists. Literature provides extensive information on theoretically possible or previously described pharmacokinetic, pharmacodynamic and pharmaceutical interactions. With clinical evidence missing, assessment of clinical relevance is usually left to the physician deciding on the therapy. In oncology, not only the highly potent anti-neoplastically active substances are responsible for drug interactions. The supportive drugs must be considered as well (7, 8), not only with regard to the selected anti-neoplastic therapy but also to the drug used for the therapy of other primary disorders. Riechelmann &al. who have studied this very group of patients detected potential drug interaction in approximately one-third of patients. About two-thirds of interactions were classified as of at least intermediate severity (7).

Exhaustive presentation of this issue is not possible here. However, table 5 summarizes the basic characteristics of the substance classes used in prophylaxis and therapy of nausea and vomiting.

Table 5: drug interactions of widely used anti-emetics

	Mechanism of drug interaction	Frequently used substances which interact
5-HT_3 antagonists	Substrates of the cytochrome P450 enzyme system (mostly CYP 2D6) **no** enzyme inhibition or induction	carbamazepine, phenytoin (inductors)
	sodium channel blockage after high dosages	QT interval prolongation
	unclear	suspected: cyclophosphamide and cisplatin relative to odansetron (5)
NK1 receptor antagonists	CYP 3A4	phenytoin, carbamazepine (inductors), benzodiazepines
	moderate inhibitor and	dexamethasone (reduce dosage by 50%)
	inductor	hormonal contraceptives
Glucocorticoids		live vaccine, antidiabetics, aprepitant (see above)
	CYP 3A4 inductor	few data on clinical relevance, possibly because duration of glucocorticoid therapy is too low

6. Pharmaco-economic aspects

Because of the pressure to cut costs in healthcare, therapy guidelines are compiled not only based on clinical studies but also taking into account pharmaco-economic studies. Here the use of 5-HT3 antagonists in particular is eyed critically. With the expiry of patent protection for odansetron and granisetron, however, there are now generics available whose price is some 35% below that of the original (as of May 2008). Nevertheless, administration of 5-HT_3 antagonists should be restricted to prophylaxis of acute vomiting and emergency treatment of delayed vomiting.

7. Interdisciplinary cooperation

In addition to compiling the guidelines, implementing them in practice is of crucial importance. Implementation requires close cooperation of physician, nursing staff, pharmacist and patient in order to guarantee the best therapy possible. Pharmacists, for example, may provide assistance by delivering to the ward anti-emetic support therapy for the individual patient jointly with the chemotherapy and controlling compliance with the guidelines by documentation of drug use. Establishing a «communication network» including all those involved may contribute to enhancing information flow and thus guarantee optimal therapy for patients.

Apart from the aspects mentioned so far, which will usually affect cooperation between physician, pharmacist and nursing staff, counseling and information of the patient is likewise of great importance. It serves mostly to improve compliance or concordance, respectively.

8. Concordance

Whereas «compliance» is a rather unidirectional term («the expert prescribes, the patient complies»), the term «concordance» includes the patient's needs and wishes as well. The term is defined as agreement among the patient and the «expert» with regard to the pharmacotherapy respecting the patient's needs and wishes. Measures for promoting concordance are shown in table 6 (9).

9. Prophylactic measures

Patient self-management is likewise of high importance in the context of support therapy and can be supported by the pharmacist. Measures for the promotion of

Table 6: Measures to promote concordance (from Reymond and Lennecke, 2003, modified)

Measures to promote concordance
• Information and motivation of the patients about:
a) benefits and necessity of the therapy
b) begin of the therapy
c) dosage, administration interval
d) time of taking
e) interactions with foodstuffs
f) duration of treatment
g) frequency of undesirable drug effects
• Providing dosage cards and application plans

Table 7: Prophylactic materials in case of nausea and vomiting

Advice on prophylaxis of nausea and vomiting
• avoid large meals
• have 5 - 6 smaller meals per day
• cold foods are frequently tolerated better than warm ones, same with cooled drinks
• stimulate appetite using by sour comfits, foods or drinks
• sufficient fresh air
• bridge difficult phases with sleep, relaxing music or walking in the open
• do not eat sweet, very fatty, strongly spiced or fried foods
• avoid strong smells

self-management mostly comprise suggestions of further prophylactic measures. In the context of a therapy for nausea and vomiting, these are mostly nutritional advices (see chapter 5.2.6 Nutritional therapy). An overview of prophylactic measures is shown in table 7.

The goal of support therapy is to assuage therapy-induced undesirable drug effects and thus to maintain the patient's quality of life during therapy. In the field of anti-emesis, this can be achieved by complying with the points listed above.

References:

1. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer. 1997;76(8):1055-61.

2. Grunberg SM, Osoba D, Hesketh PJ, Gralla RJ, Borjeson S, Rapoport BL, et al. Evaluation of new anti-emetic agents and definition of antineoplastic agent emetogenicity--an update. Support Care Cancer. 2005 Feb;13(2):80-4.

3. Gralla RJR, F.; Tonato, M. PERUGIA INTERNATIONAL CANCER CONFERENCE VII, MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER-anti-emetic GUIDELINES BASED ON: THE CONSENSUS CONFERENCE ON anti-emetic THERAPY. 2008.

4. Nemec K. [Nausea and vomiting in oncologic therapy. Guidelines for use of setrone]. Pharm Unserer Zeit. 2007;36(5):362-7.

5. Nieber K, Schoppmeyer K. [Prevention of nausea and vomiting. Aprepitant, the first therapeutic acting NK-1 receptor antagonist]. Pharm Unserer Zeit. 2007;36(5):373-80.

6. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, et al. Recommendations for the use of anti-emetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. J Clin Oncol. 1999 Sep;17(9):2971-94.

7. Riechelmann RP, Zimmermann C, Chin SN, Wang L, O'Carroll A, Zarinehbaf S, et al. Potential drug interactions in cancer patients receiving supportive care exclusively. J Pain Symptom Manage. 2008 May;35(5):535-43.

8. Georgy A, Neceskas J, Goodin S. Antiemetic care for patients with breast cancer: focus on drug interactions and safety concerns. Am J Health Syst Pharm. 2007 Nov 1;64(21):2227-36.

9. Reymond JPL, K. Compliance. In: Jaehde UR, R.; Mühlebach, S.; Schunack, W., editor. Lehrbuch der Klinischen Pharmazie Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH; 2003. p. 241-53.

5.2.2. Management of Analgesic Therapy

In the course of their disease, most tumour patients suffer from pain. Cause, type and intensity of pain may differ. Pain must be diagnosed early and treated consequently and appropriately by all available means. In the design of a therapy regimen, this must be considered; its pharmacotherapeutic approaches may be combined with other possibilities of treatment.

Thanke Mehrtens, Hannover

Classification of tumour pain

Tumour-associated pain occurs in 60 – 90% of the patients, as the tumour growing without control will infiltrate soft tissues, metastasise into bones and compress and infiltrate nerves, veins and lymph vessels. In addition, in 5 – 20% of patients pain is caused by secondary disorders or complications (e. g. zoster neuralgias, decubitus, venous thromboses and fungal infections). [1]

10 – 25% of patients suffer from therapy-induced pain. This pain may be a complication of surgery (due to nerve lesions and scarring), radiation therapy (due to neuropathy and mucositides) or chemotherapy.

Of course, pre-existing pain syndromes, so-called tumour-independent pain such as migraine or arthritis, will continue to require therapy.

Types of pain

Nociceptorial pain is caused by tissue damage. Stimulation of nociceptors in skin, connective tissue, muscles and/or bones causes pain which is usually well-localized, described as dull, terebrant, dragging or stabbing and is increased by movements (somatic pain). If visceral nociceptors are activated by compression, infiltration, relocation or inflammation, the resulting visceral pain is often difficult to localize and is described as deep and spasmodic.

Neuropathic pain is caused by nerve damage or irritation (compression, infiltration). They are accompanied by sensory (e. g. paraesthesia and dysaesthesia) and motorial (paresis) disturbances. Nerve damage is experienced by patients as burning or tingling persistent pain.

Paroxysmal pain is pain occurring from a stable level of pain at rest. This may happen either without observable trigger or under stress (moving, coughing).

Documenting pain

A structured pain anamnesis will comprise the following questions:

• where?	location? emanation?
• how?	quality? intensity?
• when?	temporal course? development?
• by what?	triggering, enhancing, reducing factors?
• why?	causal connections?
• concomitant complaints?	nausea?

Duration of the condition, size and location of the tumour, neurological disturbances, skin alterations and previously performed measures are likewise documented. Moreover, the living conditions of the patient, his/her psychical situation and his/her resources must be considered in the development of a therapeutic strategy.

Standardized rating scales should be used for anamnesis, [monitoring of] therapy progress and evaluation thereof. In assessing pain intensity, one-dimensional scales (VRS = verbal rating scale, VAS = visual analogue scale or NRS = numeric rating scale) facilitate documentation. The patient marks on the scale how strongly he feels his pain.

Below, the scales are briefly described:

Verbal rating scales (VRSs) generally have a four- to five-step grading:

• no pain

• slight pain

• intermediate pain

• strong pain

The VRS design is easy to understand and may thus be used with the majority of patients. Its disadvantage is that it is very coarsely graded and will detect minor changes only poorly.

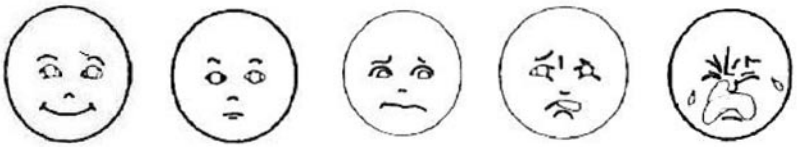
The NRS (numeric rating scale) requires the patient to have higher capacities for abstraction, but in contrast to a VRS it offers the possibility of documenting minute alterations in the perception of pain. Here, the number «0» describes absence of pain and «10» the strongest pain imaginable.

0 1 2 3 4 5 6 7 8 9 10

The visual analogue scale also requires some capacities for abstraction and thus cannot be used with all patients. However, it allows exact assessment of pain and documentation of changes.

no pain strongest pain imaginable

Children at between four and ten years of age may estimate pain intensity using a «smiley scale». Here pain intensities are visualized by means of smileys with appropriate facial expressions.



0 - 1 - 2 3 - 4 5 - 6 7 - 8 9 - 10

Older children (10 years and above) may also work with a visual analogue scale. For children under four years of age, only external assessment remains, e. g. using the KUSS scale (KUSS = Kindliches Unbehagen- and Schmerzskala, Infantile Discomfort and Pain Scale). Both scales grade pain with 0 – 10 points.

Score	0	1	2
Weeping	no weeping	crying, whining	screaming
Facial expression	smiling	calm, quiet	grimacing
Verbal	positive expressions	no or other complaints	complains about pain
Posture	neutral	tense, upright, rocking	rearing up, convulsed
Legs	neutral	kicking, struggling	drawn to the body

The assessments should be performed several times a day and documented in the form of a pain diary to obtain a more differentiated representation. For further assessment of pain, multidimensional instruments as described in detail in the guidelines listed in the annex are suitable. The BPI (Brief Pain Inventory), for example, also logs pain-related impairment of activities of daily living, relations with other persons, well-being and mood.

During the initial phase, the patient will have to present at the physician's frequently for control and adaptation of the therapy; later longer intervals may be interspersed.

Changes in the perception of pain

Pain being a subjective perception, it is influenced by psychical factors. Sorrows and fear, sadness and depressions may increase the perception of pain and therefore require consideration and concomitant treatment.

Therapy

In the beginning there is the attempt to eliminate the cause for pain by surgical, radiotherapeutic and chemotherapeutic measures if possible (causal therapy). At the same time, individual symptomatic analgesic therapy is initiated, with

the focus on oral medication. Medication is structured in accordance with the WHO pain ladder and administered according to a fixed schedule based on the patient's needs. Associated symptoms and side effects also need treatment. Acute pain is treated with fast-acting oral formulations; intravenous or subcutaneous injections may also be required. Chronic pain is treated with long-acting or depot formulations which are administered according to an individually fixed schedule. Transdermal therapeutic systems (TTSs) should be used only in cases of stable need for opioids. For the treatment of fits of pain, fast-release formulations are additionally prescribed to the patient. Regular control of analgesic medication is necessary to adapt it to the present needs. If required, co-analgesics are administered to supplement analgesic therapy. In addition, non-pharmaceutical therapy comprising psychosocial and physiotherapeutic measures is established as an integral part of therapy.

WHO pain ladder

Rung 1: Non-opioids* and/or co-analgesics

Non-opioid analgesics inhibit prostaglandin synthesis, thereby exerting analgesic and antiphlogistic effects. Combinations of different NSAIDs should be avoided, since the effects are not additive, but the toxicities are. Upon longer administration, gastrointestinal and cardiovascular risks must be kept in mind. At rung 1, diclofenac, ibuprofen or naproxen are frequently prescribed. The effects of metamizole on tumour pain is less well established, paracetamol has poor effect on bone or soft tissue pain.

The term «co-analgesics» is used to denote drugs which affect the perception of pain without having directly analgesic effects. Usually, they are psychotropics. For paroxysmal pain, drops or fast-release tablets are suitable. As an alternative to morphine, oral oxycodone, hydromorphone or sublingual buprenorphine may be used. Transdermal therapeutic systems (TTS) or parenterally administered opioids (PCA pumps = patient-controlled analgesia pumps) are used in particular in patients with dysphagia or severe vomiting. Pethidine is not recommended since the drug is effective only for a short time any may lead to increased excitability of the CNS with tremor and/or convulsions.

Rung 2: Weak opioids* and/or non-opioids and/or co-analgesics

If the non-opioids are insufficient to control the pain, or if contraindications preclude their use, weak opioids are prescribed. The two substance groups may be rationally combined (additive effect). Among this group, in particular dihydrocodeine, tilidine/naloxone or tramadol are used.

Rung 3: Strong opioids* and/or non-opioids and/or co-analgesics

If the drugs of rung 2 are insufficient to control the pain, strong opioids, often sustained-release morphium, are prescribed. They may be rationally combined with non-opioid analgesics and psychotropics. For paroxysmal pain, drops or fast-release tablets are suitable. Transdermal therapeutic systems (TTSs) or parenterally administered opioids (PCA pumps = patient-controlled analgesia pumps) are used in particular in patients with dysphagia or severe vomiting. Pethidine is not recommended since the drug is effective only for a short time any may lead to increased excitability of the CNS with tremor and/or convulsions.

Parenteral analgesic therapy

Analgesic pharmacotherapy should preferably be oral, but if as a consequence of the tumour disorder oral administration of medicaments is no longer possible (e. g. in the case of oesophagus carcinoma) or if there is severe vomiting, therapy must be switched to parenteral. Further indications comprise malabsorption, ileus or the need for administering very high dosages of a drug. Portable PCA pumps facilitate outpatient therapy. Continuous infusion of analgesics will not only establish stable blood levels but also facilitate titration of the pain situation by giving the patient the possibility to trigger a bolus application at the PCA pump in case of paroxysmal pain. Opioids and non-opioids may be combined (pay attention to the compatibility of the drugs!). Morphine, metamizole, tramadol or piritramide may be used. Subcutaneous therapy is considered as the application method of choice since it is less invasive and less susceptible to interference but equally effective as intravenous application and therefore particularly well suited for outpatients. The opioid is continuously applied by a portable pump via a subcutaneous injection needle to a location which is subclavicular, in the anterior thorax wall or abdominal. In case of pain,

flushing, swelling or leakage at the injection site, the location is changed. If an intravenous access system has been implanted (Hickmann catheter, port-a-cath system), this access may be used for intravenous therapy.

Some of the pumps described in chapter 3.3.1.1. «Infusion pumps for the application of cytostatics» may be used for analgesics therapy as well. Literature relating to use, filling and compatibility of mixed infusions is provided by the individual vendors of the pumps. When selecting a PCA pump, the possibility of bolus administration must be contemplated.

Therapy adaptation

Difficult-to-manage side effects (sedation, cognitive impairments, nausea, constipation) frequently necessitate changing the route of application or the drug. This holds true not only for the analgesic but also for the concomitantly administered co-therapeutics, if applicable. For opioid dosages, conversion tables are available. The dosage equivalents stated therein must be taken as orientation guides only, necessitating close monitoring of the therapy. In switching over, begin with half of the calculated necessary daily dosage of the new drug and add fast-acting acute medication, then increase basis medication gradually and adjust acute medication.

Therapy of undesirable side-effects of analgesic medication*

Below, therapy of some important side effects of analgesic medication is discussed.

Nausea/vomiting

In is recommended to administer an anti-emetic for the first 14 days of opioid therapy. If nausea should spontaneously reoccur during therapy, the cause must be investigated. The following drugs are available for therapy: alizapride, metoclopramide, dimenhydrinate, domperidone and haloperidol. In case of insufficient effect, 5-HT_3 antagonists and/or glucocorticoids are used.

Constipation

In tumour patients, conservative measures for the prevention of constipation such as roughage-rich diet, increased hydration and physical activity are fre-

quently no longer possible. Hence laxatives should be prescribed according to the individual needs. Drugs such as bisacodyl or sodium picosulphate, lactulose and osmotically active substances are available.

Further side effects

Under opioid therapy, the following undesirable effects frequently occur, likewise necessitating treatment:

Possible side effect	Therapeutic approach
sedation, confusion	adjust dosage or change drug
perspiration	anticholinergics, sage preparations, change of opioid
pruritus	antihistaminics, skin care, change of opioid
urine retention	reduce co-analgesics (especially tricyclic antidepressants) and anticholinergics, administer parasympathomimetics, adjust opioid dosage or change drug
xerostomia	mouth care, lozenges

Special pain syndromes*

Treatment of neuropathic pain

Neuropathic pain forms such as burning spontaneous pain, paroxysmal pain attacks and evoked pain respond to therapy with tricyclic antidepressants (e. g. amitryptiline). Anticonvulsants (carbamazepine, gabapentin, pregabalin) have good efficacy in paroxysmal pain attacks. Baclofen is indicated for the treatment of pain with spastic components, dexamethasone in case of nerve compression and increased intra-cranial pressure.

Treatment of bone and soft tissue pain

In many cases, bone pain is stress-dependent, i.e. the pain at rest is easily managed, but therapy does not cover stress intervals. Bone pain responds well to

NSAIDs and opioids, in case of spasticity baclofen may be used. In these cases, bisphosphonates (pamidronic acid, ibandronic acid, zoledronic acid) are often used successfully. In many cases of bone pain, radiation therapy is indicated.

Treatment of visceral pain

In addition to the pain, accompanying vegetative symptoms (nausea, perspiration, tachycardia, constipation) must be treated. In certain cases, due to strong vomiting or dysphagia the drugs cannot be administered orally, and other routes of application must be selected. In these cases, spasmolytics such as N-butyl-scopolamine or NSAIDs with a spasmolytic component and glucocorticoids are used.

* Pharmacokinetics, dosages, side effects and interferences of the drugs listed can be learned from the textbooks listed in the annex, the guidelines referred to and the summary of product characteristics accompanying the preparations, hence they are not discussed in more detail here.

5.2.3. Alopecia – Comment

Hair cells are highly replication-active and are damaged by administration of cytostatics, with the following consequences::

- **After moderate injury, a portion of the hair follicles terminate their growth earlier, enter the resting phase after a brief transition phase and expire simultaneously after two to four months.**
- **After very strong injury, hair is formed poorly so it breaks off prematurely. Alopecia begins as early as two weeks after application of chemotherapy, and all hair is lost within a few weeks, excepting those in the resting phase.**

Michael Höckel, Eisenach

Not only the hair of the scalp but also of the eyelashes, eyebrows, beard and of the rest of the body is affected. Not all cytostatics result in equally strong alopecia. There are also substances which barely affect hair growth; details can be learned from the respective summary of product characteristics. After polychemotherapy, however, alopecia of differing degree is very frequent.

Drugs resulting in alopecia comprise: cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fluorouracil, hydroxyurea, idarubicin, ifosfamide, interferon alpha, irinotecan, methotrexate, mitomycin, paclitaxel, thioTEPA, topotecan, vinblastine, vincristine, vindesine.

Drugs with low risk for alopecia: carboplatin, cisplatin, gemcitabine, vinorelbine, mitoxantrone.

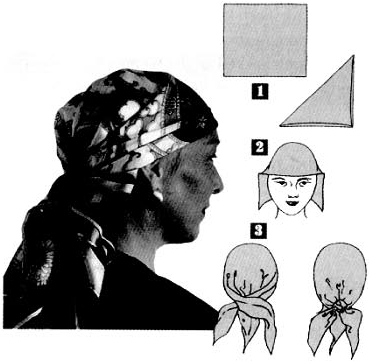
Cool-caps are occasionally used at the patient's request. There is little scientific evidence, however, for the effectiveness and safeness of this measure. The reduced circulation of blood to the scalp results in a reduced local concentration of the cytostatic administered, but this may protect any metastases present in

the scalp. Moreover, reducing the blood supply to the scalp only seems logical for substances with a short half-life and for administration as a bolus or short infusion.

After explaining the situation to the patient, the possibility of wearing a wig and the use of scarves should be discussed. A wig can be prescribed by the doctor. Providing information about the actual probability of hair loss during the use of the respective cytostatic agent is a central task of the pharmacy giving advice. It is important to stress the high regeneration capability of the hair follicles; new hairs are already visible one to two months after completion of the chemotherapy and hair begins to grow on the head at the same time. It should also be pointed out that the new hair may be different from the old; hair that was formerly straight may become wavy, and vice versa. There is no scientific evidence that hair growth after chemotherapy can be promoted by medication.

The pharmacist should provide information about the possibilities for covering the head and about the need to protect a scalp that is sensitive to sunlight. The patient should be told where wigs can be bought locally and should be given patient leaflets and an explanation of what they contain. If patients prefer to wear a scarf, brochures about tying techniques can be kept in readiness. If the patient wishes to wear neither a wig nor a scarf, advice must be given about the importance of protection from the sun since the exposed scalp is very sensitive to sunlight. In view of the loss of eyelashes and eyebrows, advice about make-up is helpful for women and should be offered in public pharmacies.

Headscarf binding techniques

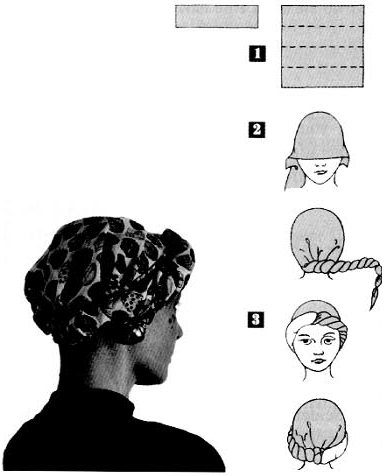


"Caroline"

1. Fold up the square cloth to form a triangle
2. Place the scarf deep down into the face, with the point towards the neck, and lay back the front ends laterally.
3. Fasten the ends with a knot over the third point at the neck.

Variants:

- You may roll up the fringe.
- You may pull the top over the knot or hide away the ends.
- You may somewhat loosen the scarf at the back of the head to gain volume.



"Fatima"

1. Scarf (50 cm × 160 cm) or large square cloth folded up into a scarf.
2. Pull the scarf deep down over the forehead and into the face, form the ends into a «coil» at the neck and lay the roll laterally forwards. Depending on the length of the scarf, the «coil» will encircle the head once to twice.
3. Roll the fringe of the scarf from the end (neck) to the forehead over the «coil», then push the rest of the fringe upwards under the «coil».

Variants:

- You may attach the «coil» to the scarf using a brooch.
- You may form a little spiral at the end.
- You may leave the «coil» fully visible.

References:

Höckel M., Heckl U., Nagel G.A: Der Krebs-Patient in der Apotheke, Deutscher Apotheker Verlag, Stuttgart 2003

Schmoll et al. (2006): Kompendium Internistische Onkologie. Springer, Berlin

Westfeld, M., u.a. (2006): Maligne Erkrankungen. Manuale zur pharmazeutischen Betreuung Band 8. Govi-Verlag, Eschborn

5.2.4. Management of Mucositis

Depending on the localization, mucositis is termed stomatitis, oesophagitis, cystitis, etc. It is a side effect frequently occurring during chemotherapy and radiotherapy in the context of the treatment of tumour patients. Mucosal lesions may be extremely painful and strongly affect the quality of life of tumour patients.

The pharmacist presents suggestions for the prophylaxis and therapy of mucositis for individual patients and gives recommendations for prophylaxis and therapy in cooperation with the oncological team and in the context of quality assurance.

Dr. Annette Freidank, Fulda

The term mucositis describes an inflammation of the mucous membranes. It may affect any mucous membrane and becomes manifest, inter alia, as conjunctivitis, stomatitis, gingivitis, parodontitis, glossitis, pharyngitis, oesophagitis, gastritis, enteritis, colitis, or vaginitis.

Most frequently described is, and most recommendations exist for, inflammation of the oral mucosa, so that this form will be discussed in more detail below. In the interest of simplicity, the term will be used only for inflammation of the oral mucosa.

Symptoms of mucositis include reddening, increased temperature, pain, oedema formation, ulcerations, bleeding and atrophy. These may be extremely stressful for the patient. Trials have described postponement of the next cycle (35%), dosage reduction (60%), termination of the regimen (30%), necessity for feeding tube (70%), fever (60%), hospitalization (62%), dosage reduction (23%), pain (63%), and weight loss (61%) [1].

Xerostomia may result in difficulty in swallowing (65%), loss of taste (63%) and problems in speaking (60%) or eating (54%) [2]. Thus mucositis may massively affect success of the therapy or strongly reduce quality of life [3]. These complications may increase therapy costs to 2-3fold [1, 4].

Genesis and risk factors

Genesis of mucositis is multifactorial. The traditional explanation of mucositis by direct cytotoxic effects of radiation and chemotherapy describes only a subset of the process. By now, a 5-phase model is accepted in the description of the pathogenesis of mucositis [5-7]:

- initiation – Radio- or chemotherapy causes DNA damage in basal epithelial cells and thus leads to formation of reactive oxygen species which damage further submucosal cells
- up-regulation and generation of messenger signals – radio-, chemotherapy or reactive oxygen species induce apoptosis and up-regulate pro-inflammatory cytokines
- signal transfer and amplification – pro-inflammatory cytokines such as tumour necrosis factor lead to further tissue damage and initiate the inflammatory cascade
- ulceration and inflammation – loss of mucosal integrity results in painful lesions, infections are possible
- healing – formation of a new epithelial layer, of cells and tissue

Mucositis often occurs between the 4th and the 14th day of therapy [8]. Apart from the cytostatics used, irradiation, surgery, the current state of the oral cavity (dental status, status of the mucosal membrane) and the patient's general condition are responsible for manifestation of a mucositis.

Improved understanding of pathogenesis may lead to development of more effective substances [9].

Risk of III° or IV° mucositis

Depending on therapy

docetaxel + radiotherapy	98 %
paclitaxel + 5-fluorouracil + radiotherapy	75 %
anthracyclines + docetaxel + 5-fluorouracil	66 %
platinum + taxanes + radiotherapy	64 %
docetaxel	13 %

Depending on the tumour type (determining therapy)

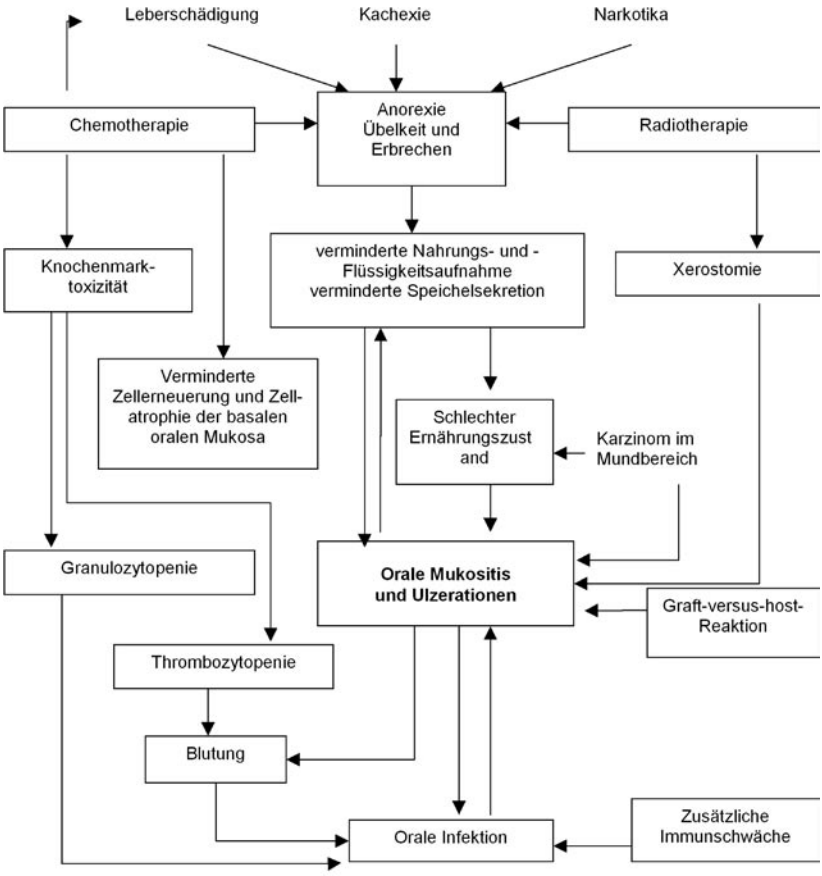
bone marrow transplantation + full body irradiation	64 %
gastrointestinal tumours	53 %
oesophagus carcinoma	46 %
tumours of the head and neck	42 %
ALL	34 %

From: [10]

In irradiation, apart from individual and accumulated dosage, the site of irradiation is decisive. Thus patients after irradiation of the saliva glands are in particular danger of xerostomia due to the damage to the glands which may be reversible or irreversible [11]. Focused, fractionated application of radiotherapy increases efficacy while at the same time reducing side effects.

Further risk factors for manifestation of a mucositis include abuse of nicotine and alcohol, poor oral hygiene, pre-existing lesions, neutropenia and immunosuppression [12]. Mucositis in children, gender-specific differences and and genetic factors have received little attention so far; in women, the risk for mucositis induced by 5-fluorouracil is five times higher [13, 14].

The relationships are visually presented in the following diagram


Leberschädigung
Kachexie
Narkotika
Chemotherapie
Anorexie
Übelkeit und
Erbrechen
Radiotherapie
Knochenmark-
toxizität
verminderte Nahrungs- und -
Flüssigkeitsaufnahme
verminderte Speichelsekretion
Xerostomie
Verminderte
Zellerneuerung und Zell-
atrophie der basalen
oralen Mukosa
Schlechter
Ernährungszust
and
Karzinom im
Mundbereich
Granulozytopenie
Orale Mukositis
und Ulzerationen
Graft-versus-host-
Reaktion
Thrombozytopenie
Blutung
Orale Infektion
Zusätzliche
Immunschwäche

from: [15]

Classification

There are various classifications, grading mucositis by objective and subjective criteria into 3 to 4 categories. The goals differ among these classifications (trials, care planning, side effect profile), so that still no unified, validated and generally applicable system exists [16].

Various assessment instruments [16-18]

Abbrev.	Name	Categories
CTC	Common Toxicity Criteria (NCI – National Cancer Institute)	0-4
OAG	Oral Assessment Guide	1-3
OMAS	Oral Mucositis Assessment Scale (NCI)	0-3
OMI	Oral Mucositis Index	0-3
WHO	World Health Organisation	0-4

For assessment of the full side effect profile of a therapy, the WHO and NCI classifications are frequently used. Assessment of mucositis combines some objective characteristics with the patient's ability to eat and drink.

	I°	II°	III°	IV°
WHO	oral pain, erythema	oral erythema, ulcerations, solid food possible	deep ulceration, liquid food required	possible
CTC	soreness, erythemas, painless ulcerations	moderately painful erythemas, oedemata or erosion, solid food	highly painful erythemas, oedemata or erosion, liquid food, analgesics	no oral feeding

For trials or care planning focussing on mucositis, the OMAS and OAG scores limited to assessment of oral mucositis are better suited, since here the state of the oral cavity is described in much more detail [17].

OAG category	1	2	3
voice	Normal	Deep or hoarse	Difficulties in speaking/ Speaking painful
Swallowing	Normal	somewhat painful	Cannot swallow
Lips	Smooth, pink, moist	dry and fissured	Ulcerated or bleeding
Tongue	Pink, moist, with papillae	coated or without papillae, shining with or without reddening	blistered or fissured
Saliva	watery	inspissated or viscous	absent
Mucosa	Pink and moist	reddened or coated (increasingly whitish) without ulcerations	ulcerations with or without bleeding
Gingiva	Pink and tight	Oedematous with or without reddening	spontaneous bleeding, possibly accompanied by pressure, e. g. in masticating
Teeth/ dental prostheses	Clean, no deposits	calculus or deposits locally	calculus or deposits generalized in the area between teeth and gingiva
All points are added: up to 8 points no mucositis 9 – 16 points moderate mucositis 17 – 24 points severe mucositis			

For patients in danger, regular documentation of the status of the oral cavity in the patient file has been found expedient. Localisation, area and severity of mucositis and, if applicable, the corresponding measures should be documented regularly by imaging.

Developing recommendations for the prophylaxis and therapy of mucositis

There is a very large number of trials relating to prophylaxis and therapy of mucositis. Evaluation of these trials and comprehension into generally applicable recommendations is exceedingly difficult because of the following points:

- trial quality (blinding, randomisation, number of patients, inclusion of patients) is often insufficient
- the risk for developing mucositis depends on many different factors
- there is no generally applicable classification for assessment of mucositis
- mucositis arises, depending on the therapy regimens, after days, weeks or several cycles
- prophylaxis and therapy of mucositis must be done over extended periods of time, making control and documentation of the measures difficult
- patient compliance is indispensable for therapeutic success
- severity of mucositis depending on various factors (xerostomia, neutropenia, etc.), the substances or measures must be used individually and deliberately.

Cochrane Reviews

In 2008 two Cochrane reviews on prophylaxis and therapy of mucositis were published. Evaluation mostly focuses on formal aspects, the summary of the substances receiving positive assessment must be seen thoroughly critically from a pharmaceutical-clinical perspective.

Prophylaxis

Of 270 trials on mucositis prophylaxis, 188 were excluded, and in den remaining 89 trials 33 different interventions were studied in a total of 7523 patients. 12 interventions showed – usually weak – evidence for a benefit, only for 4 interventions (amifostine, Chinese medicine, hydrolytic enzymes, cryotherapy) there was more than one study with positive results [19].

Therapy

Of 84 trials on mucositis therapy, 26 trials with a total of 1353 patients were included. In 15 trials mucositis-related efficacy was assessed, in 12 trials pain reduction was evaluated. For mucositis therapy, four substances (allopurinol, growth factors, immunoglobulin, human placenta extract) were judged as favourable [20].

Implementation in clinical routine

From a clinical-pharmaceutical perspective, some trials must be commented on critically: A trial where administration of folic acid is expected to have a positive effect under 5-FU therapy should be excluded beforehand because of the mechanism of action. Routine use of Chinese medicine, honey, calcium phosphate or zinc sulphate for prophylaxis or subcutaneous administration of human placenta extract or immunoglobulins is also to be viewed rather critically (danger of allergic reactions, quality assurance). The overall evaluation of growth factors as solutions for rinsing the mouth and subcutaneously does not appear expedient either. Nevertheless, these Cochrane reviews should be taken into account when developing recommendations, since the most recent trials on mucositis are listed and assessed.

MASCC Guidelines

In 2004, the first guideline on treatment of mucositis was published by the «Mucositis study group» of the MASCC (Multinational Association of Supportive Care in Cancer), and in 2005 it was updated [21] [22] [23].

For prophylaxis, the following recommendations are given [24]:

- Evaluation of a cooperative oral care plan by an interdisciplinary team – involvement of a «dental professional» – use of a soft toothbrush, use of validated assessment tools for grading pain and assessing the status of the oral cavity
- radiotherapy – benzydamine in patients with tumours of the head and neck and moderately high radiation dosage
- chemotherapy – cryotherapy in case of 5-fluorouracil bolus and high-dosage melphalan
- high-dosage therapy of haematologic tumours – palifermin

For therapy, the following recommendations are given:

- cryotherapy for high-dosage melphalan

The following measures are assessed critically:

- radiation therapy – sucralfate is not recommended
- chemotherapy – chlorohexidine, pentoxyfylline, GM-CSF mouth washs are not recommended
- laser only in specialized centres

Implementation in clinical routine

If the MASCC guidelines are adhered to, protective substances may be used only in a small subset of tumour patients. For the recommended oral care programs, it is likewise not stated which solutions to use for rinsing.

The MASCC are well aware of these deficiencies and initiate various trials or give recommendations for performing further studies [25].

Further reviews and meta-analyses assess substances and measures from various perspectives, however essentially without new insights, even though in individual cases they may deviate from assessment [27-29].

Summary of expedient substances and measures

In addition to specific measures, analgesic therapy, nutrition and anti-infectious therapy should be treated and documented [30].

List of the measures and substances studied

Measures, substances	Cochrane prophylaxis [19]			Cochrane therapy [20]			MASCC guideline [10, 24, 26]	
Assessment	0 – not better than placebo or no therapy + – weak evidence (bias, number) – – negative assessment						P – prophylaxis T – therapy	
	S	P	B	S	P	B		
aciclovir	1	57	0	∅	∅	∅	P	Do not use
allopurinol	2	35 – 92	0	1	44	+	∅	
aloe vera	1	58	0	∅	∅	∅	∅	
amifostine	11	845	+	∅	∅	∅	∅	
antibiotics, topic	5	1004	0	∅	∅	∅	P	Do not use
benzydamine	1	36	+	2	71	0	P	Pat. with tumours of the head and neck and radiotherapy
beta-carotene	1	10	0	∅	∅	∅	∅	
calcium phosphate	1	94	+	∅	∅	∅	∅	
chamomile	1	135	0	∅	∅	∅	∅	
Chinese medicine	2	›147	+	∅	∅	∅	∅	
chlorohexidine gluconate	7	470	0	∅	∅	∅	P	Do not use

Measures, substances	Cochrane prophylaxis [19]			Cochrane therapy [20]			MASCC guideline [10, 24, 26]	
Assessment	0 – not better than placebo or no therapy + – weak evidence (bias, number) – – negative assessment						P – prophylaxis T – therapy	
	S	P	B	S	P	B		
clarithromycine, systemically	1	70	0	∅	∅	∅	∅	
combinations	∅	∅	∅	1	142	0	∅	
cryotherapy	4	384	++	∅	∅	∅	P	
folic acid	1	125	--	∅	∅	∅	∅	
glutamine	6	258	0	∅	∅	∅	∅	
growth factors, syst.	5	241	0	1	61	+	∅	
growth factors, top.	4	211	0	3	106	+	∅	
histamine gel	1	39	0	∅	∅	∅	∅	
honey	1	40	+	∅	∅	∅	∅	
human placenta extract	∅	∅	∅	1	120	+	∅	
hydrolytic enzymes	2	149	+	∅	∅	∅	∅	
immunoglobulins	∅	∅	∅	1	81	+	∅	
iseganane	3	1234	+	∅	∅	∅	∅	
keratinocyte growth factor /palifermin, &c.)	3	335	0	∅	∅	∅	T	High-dosage therapy

Measures, substances	Cochrane prophylaxis [19]			Cochrane therapy [20]			MASCC guideline [10, 24, 26]	
Assessment	0 – not better than placebo or no therapy + – weak evidence (bias, number) – – negative assessment						P – prophylaxis T – therapy	
	S	P	B	S	P	B		
laser therapy	∅	∅	∅	∅	∅	∅	P	in centres
misonidazole	1	40	0	∅	∅	∅	∅	
oral care programs	3	791	+	∅	∅	∅	recommended	
pentoxyfylline	1	140	0	∅	∅	∅	∅	Do not use
pilocarpine	2	278	0	∅	∅	∅	∅	
polyvidone-iodide	2	172	0	∅	∅	∅	∅	
prednisone	1	66	0	∅	∅	∅	∅	
propantheline	1	12	0	∅	∅	∅	∅	
prostaglandin	3	93	0	∅	∅	∅	∅	
sucralfate	8	556	0	3	114	0	Do not use	
tetrachlorodeca-oxide	∅	∅	∅	1	62	0	∅	
traumeel	1	30	0	∅	∅	∅	∅	
vitamin e	∅	∅	∅	1	18	0	∅	
zinc sulphate	1	27	+	∅	∅	∅	∅	

(S – Number of trials; P – Number of patients; B – Assessment; ∅ – no data; measures assessed positively are underlined)

- Oral care programs

Prophylactic measures include assessing dental status prior to begin of therapy and tooth sanitization as far as required; if necessary, the affected teeth must be pulled. Furthermore, intensive training of the patients with regard to oral hygiene is required. The measures should be controlled and documented regularly. Apart from hygiene, regular rinsing is indispensable for prophylaxis.

- Physical measures
  - Cryotherapy after 5-FU Bolus, and limited to the use of antimetabolites with high potential for mucositis
  - Laser therapy in centres
- Chemical substances
  - amifostine
  - palifermin (possibly further keratinocyte growth factors)
  - benzydamine in radiation patients
- Symptomatic, not as a general prophylaxis, but when symptoms necessitate it
  - Systemic analgesic therapy
  - Antibiotics, antimycotics, antiviral substances if the patients are in danger,
  - immunosuppression, positive tests for germs
  - growth factors for neutropenia treatment
  - rinsing in xerostomia
- Not recommended
  - chlorhexidine
  - sucralfate
  - alcoholic solutions

- dye solutions
- «homemade» combinations

Use of any other substances is not evidence-based and should be performed only under controlled conditions. When selecting the substances, those with the least side effect profile should be preferred. Possible allergic reactions and immunomodulating effects must be heeded, costs and practicability must be paid attention to.

Costs matter insofar as the measures are frequently not paid for the insurance companies and must be conducted, in particular in prophylaxis, for extended periods of time. Therefore, acceptance by the patient is extremely important here – no measure can be effective unless performed.

In the prophylaxis and therapy of mucositis, work in a multiprofessional team (nursing staff, dentist, dental technician, pharmacist, radiologist) is of crucial importance. For evaluating substances by trials and for developing new trials, the type of assessment should be paid attention to; a generally applicable assessment tool for mucositis ought to be available. Moreover, the positive effect of any substance in a specific patient cohort with a more or less similar therapy cannot be transferred to other tumour entities, since the risk factors differ – xerostomia in irradiation, use of antimetabolites, neutropenia, age and gender of the patients.

Thus protective or therapeutic substances must be used selectively.

The pharmacist's task in the multiprofessional team

Because of the frequency and consequences of mucositis and the low efficacy of [currently used] substances, mucositis therapy is a wide field for the use of insufficiently tested substances and methods. Thus, it is an essential task of the clinical pharmacist to critically evaluate the methods applied.

Here the following points must be observed:

• Are there any validated trials for the method applied?

- What kind of patients were treated (restrictive selection of patients – which therapy, permissive selection of patients)?
- Which side effects must be expected?
- Costs and practicability of the measure?

Unified recommendations should be made in cooperation with the nursing staff and the physicians of the individual institute. Use of dye solutions, alcoholic solutions or home-made combinations must be avoided. The focus should be on intensive counseling of the patient with regard to oral hygiene and regular rinsings. The substance used is of minor important compared to consequential rinsing of the mouth, inspection of the oral cavity and documentation of the findings. Further measures such as tube feeding, systemic analgesic therapy and treatment of neutropenia are crucial to the duration and severity of an existing mucositis [31, 32].

It remains to be hoped that in future more comprehensive, evidence-based recommendations may be given.

1. Murphy, B., Clinical and Economic Consequences of Mucositis Induced by Chemotherapy and/or Radiation Therapy. The Journal of Supportive Oncology, 2007. 5: p. 13-21.

2. Dirix, P., et al., The influence of xerostomia after radiotherapy on quality of life. Support Care Cancer, 2008. 16: p. 171-179. 7.

3. Rosenthal, D., Consequences of Mucositis-Induced Treatment Breaks and Dose Reductions on Head and Neck Cancer Treatment Outcomes. The Journal of Supportive Oncology, 2007. 5: p. 23-31.

4. Silverman, S., Diagnosis and Mangement of Oral Mucositis. The Journal of Supportive Oncology, 2007. 5: p. 13-21. 5.

5. Niscola, P., et al., Mucositis in patients with hematologic malignancies: an overview. Haematologica, 2007. 92: p. 222-231.

6. Sonis, S., Pathobiology of Oral Mucosits: Novel Insights and Opportunities. The Journal of Supportive Oncology, 2007. 5: p. 3-11.

7. Bowen, J. and D. Keefe, New pathways for Alimentary Mucositis. Journal of Oncology, 2008.

8. Margulies, A., et al., Orale Mukositis bei Patienten unter Tumortherapie. Der Onkologe, 2007. 13: p. 350-355.

9. Posner, M. and R. Haddad, Novel Agents for the Treatment of Mucositis. The Journal of Supportive Oncology, 2007. 5: p. 33-39.

10. Feyer, P., M. Steingräber, and P. Ortner, Mukositis guidelines. Im Focus Onkologie, 2004. 11: p. 5760.

11. Grau, C., et al., Oral Complications of Radiotherapy in Head and Neck Cancer. American Journal of Cancer, 2004. 3: p. 291-298.

12. Robien, K., et al., Predictors of Oral Mucositis in Patinets Receiving Hematopoietic Cell transplants for Chronic Myelogenous Leukemia. Journal of Clinical Oncology, 2004. 22: p. 1268-1275.

13. Anthony, L., et al., New thoughts on the pathobiology of regimen-related mucosal injury. Support Care Cancer, 2006. 14: p. 516-518.

14. Fadda, G., G. Campus, and P. Luglie, Risk factors for oral mucositis in paediatric oncology patients receiving alkylant chemotherapy. 2006.

15. Margulies, A., et al., Onkologische Krankenpflege. 2002, Berlin: Springer-Verlag. 564.

16. Onkologiepflege, Erfassungsinstrumente - Mukositis. 2008(20.11.2008).

17. Sonis, S., et al., Validation of a New Scoring System for the Assessment of Clinical Trial Research of Oral Mucositis Induced by Radiation or Chemotherapy. Cancer, 1999. 85: p. 2103-2113.

18. WHO, Handbook for results of cancer treatment. 1979, Geneva: World Health Organization. 16-17.

19. Worthington, H., J. Clarkson, and O. Eden, Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database of Systematic Review 2007, 2007(3): p. CD000978.

20. Clarkson, J., H. Worthington, and O. Eden, Interventions for treating oral mucositis for patientes with cancer receiving treatment (Review). Cochrane Database of Systematic Review, 2008(2): p. DOI: 10.1002/14651858.CD001973.pub3.

21. Barasch, A., et al., Antimicrobials, mucosal coating agets, anesthetics, analgesics, and nutritional supplements for alimentary tract mucositis. Support Care Cancer, 2006. 14: p. 528-532.

22. Bensadoun, R., et al., Amifostine in the management of radiation-induced and chemo-induced mucositis. Support Care Cancer, 2006. 14: p. 566-572.

23. Bueltzingloewen von, I., et al., Growth factors and cytokines in the prevention and treatment of oral and gastrointestinal mucositis. Support Care Cancer, 2006. 14: p. 519-527.

24. Keefe, D., et al., Updated Clinical Practice Guidelines for the Prevention and Treatment of Mucositis. Cancer, 2007. 109: p. 820-831.

25. Keefe, D., Intestinal mucositis: mechanisms and management. Current Opinion in Oncology, 2007. 19: p. 323-327.

26. Rubenstein, E., et al., Clinical Practice Guidelines for the Prevention and Treatment of Cancer TherapyInduced Oral and Gastrointestinal Mucositis. Cancer, 2004. 100 Suppl: p. 2026-2046.

27. Koestler, W., et al., Oral Mucositis Complicating Chemotherapy and/or Radiotherapy: Options for Prevention and Treatment. 2001.

28. Stokman, M., et al., Preventive Intervention Possibilities in Radiotherapy- and Chemotherapy-induced Oral Mucositis: Results of Meta-Analyses. Journal of Dental Research, 2006. 85: p. 690-700.

29. Harris, D., et al., Putting Evidence into Practice. Clinical Journal of Oncology Nursing, 2008. 12: p. 141-152.

30. Lalla, R. and D. Peterson, Treatment of Mucositis, Including New Medications. Cancer Journal, 2006. 12: p. 348-354.

31. McGuire, D., et al., The role of basic oral care and good clinical practice principles in the management of oral mucositis. Support Care Cancer, 2006. 14: p. 541-547.

32. Keefe, D., et al., Severe mucositis: how can nutrition help? Current Opinion in Clinical Nutrition and Metabolic Care, 2007. 10: p. 627-631.

5.2.5. Diarrhoea Management

Diarrhoea is a serious complication in the treatment of tumour disorders. It may occur as a side effect of certain cytostatics therapies or of irradiation.

The pharmacist works out suggestions for prophylaxis and therapy of diarrhoea in individual patients, and in cooperation with the oncological team he/she presents recommendations in the context of quality assurance.

Hannelore Kreckel, Gießen

Mucositis induced by chemotherapy or radiotherapy is a is a serious complication in the treatment of tumour patients (see 5.2.4 Mucositis). Mucositis of the gastrointestinal tract will frequently result in diarrhoea. If the diarrhoea symptom worsen in spite of treatment, this may imply dosage-limiting toxicity of chemotherapy. Furthermore, delays in the temporal progress of treatment may result. Patient compliance is reduced, and severe cases of diarrhoea are potentially life-threatening (1). Therefore it is mandatory to immediately start treatment upon the slightest symptoms of diarrhoea.

It is estimated that approximately 10% of all people with advanced tumour disorder suffer from acute or persisting diarrhoea (2). Substances which typically induce diarrhoea comprise capecitabine, cisplatin, cytosine-arabinoside, cyclophosphamide, daunorubicin, docetaxel, 5-fluorouracil, gefitinib, interferons, irinotecan, leukovorin, methotrexate, oxaliplatin, paclitaxel, raltitrexed, sorafenib, sunitinib and topotecan (3, 4, 5). Combination therapy with fluoropyrimidines and irinotecan increases the risk for diarrhoea to 50 – 80%. High-dosage regimens likewise result more frequently in diarrhoea symptoms (2).

According to the National Cancer Institute Common Toxicity Criteria for Adverse Events, diarrhoea is graded as follows (6):

Grade 0	no diarrhoea
Grade 1	Increase to < 4 defecations per day above the baseline value or low increase of intestinal losses above the baseline value
Grade 2	Increase to 4 – 6 defecations per day above the baseline value, intravenous hydration indicated for < 24 h, moderate increase of intestinal losses above the baseline value, no impairment of activities of daily living
Grade 3	Increase to ≥ 7 defecations per day above the baseline value, intravenous hydration indicated for ≥ 24 h, hospitalization, severe increase of intestinal losses above the baseline value, activities of daily living impaired
Grade 4	Life-threatening consequences (e. g. haemodynamic collapse)
Grade 5	Death

Factors causing diarrhoea

Apart from chemotherapy, use of laxatives (including large amounts of artificial sweeteners), high-magnesium antacids, antibiotics or prokinetics and undesirable effects of cardiac glycosides, potassium salts, misoprostol, propanolol, colchicine or theophylline must be contemplated as possible causative factors of diarrhoea (7). Previous surgery, infectious disease, stress, neuroendocrine tumours, metastases in the abdominal cavity, radiation therapy and graft-versus-host reactions after bone marrow transplantations may also cause diarrhoea. Pseudomembranous enterocolitis induced by Clostridium difficile and normally associated with long-term antibiotics treatment were also observed in tumour patients treated with chemotherapy but receiving no antibiotics (8).

Prophylaxis and treatment

It is desirable to have the tumour patients informed about the possible occurrence of diarrhoea even before the initiation of treatment. They should be informed in detail about possibilities for treatment and supportive measures. Furthermore, they should receive in advance written instructions relating to measures for systemic therapy and a prescription for appropriate medication. In the context of pharmaceutical counseling and in cooperation with the physician,

the pharmacist can guarantee information and education of the patient with regard to the possibilities provided by the catalogue of measures to be taken.

Dietary measures

Patients should be instructed to make moderately spiced, easily digestible food with low, insoluble roughage content the main part of their diet, to avoid strongly spiced, fried and rich products and to compensate sodium and potassium losses by appropriate hydration. For compensation of dehydration, preparations analogous to the «WHO Rehydration Mix» (e. g. Elotrans®, Oralpädon®) may be used. In addition, low-acid juices, preferably mixed with low-carbonic acid mineral waters, are suitable. Very hot and very cold drinks, fruit juices and high-osmolarity liquid food must be eschewed. Foods rich in potassium (such as bananas, peaches, apricots, mashed potatoes) are suitable for potassium replenishment and generally tolerated well.

Dairy products are a general problem in patients with lactose intolerance. In addition, in patients under chemotherapy, damage to the intestinal villi may lead to reduction of lactase expression so that patients who previously had no problems may also be affected (9). Therefore ingestion of dairy products should be reduced or avoided in such patients. Lactose-free dairy products are an alternative. Buttermilk and yoghurt are often tolerated, thanks to the presence of active lactic acid bacteria. Cheese products are acceptable, since lactose is enzymatically degraded during production. Many industrially manufactured milk-based dietary supplements are free from lactose and can thus be used without problems (see 5.2.6. Diet).

Dietary measures alone are recommended only for 0° – I° diarrhoea (10).

Pharmacotherapy

If patients with diarrhoea problems present in the pharmacy, an infectious cause should also be contemplated. In this case, drugs reducing peristalsis are contra-productive. In this case, («empirical») antibiotics therapy is indicated. Symptoms such as fever, blood in the faeces and exsiccation necessitate immediate medical consultation.

When using antibiotics, the following situations and symptoms should be taken into consideration:

Diarrhoea, exsiccation, malabsorption, electrolyte losses, neurological symptoms, immunological problems, nutritional status and age of the patient, gastrointestinal and rectal complaints of the patient.

A selection of drugs and substances used:

Loperamide, a synthetic opioid, is among the most frequently used drugs in chemotherapy-induced diarrhoea. A maximum daily dosage of 16 mg conforms with the approval status in Germany. Symptom-oriented high-dosage therapy with 2 mg every two hours is recommended (11). In a trial, this two-hour administration was interrupted only when the patient would not defecate for 12 hours. On average, each patient received 42 mg of loperamide (10 – 144 mg). In patients with grade 3 diarrhoea or worse, loperamide seems to be less effective, independent of the dosage (13).

Opium tincture is used only rarely and then mostly in case of diarrhoea with spasms.

Some publications recommend ***diphenoxylate***, another synthetic opioid, for treatment in combination with atropine (10). Because of its addictive potential, this substance is no longer available in Germany.

Carbo medicinalis is generally used for the absorption of toxins in cases of diarrhoea. In a trial, the use of activated charcoal for prevention of late-onset diarrhoea under irinotecan therapy was tested with the goal of absorbing the SN38 metabolite and thus preventing mucosal damage. On the evening before therapy and 48 [?] later twice a day, the patients received 5 ml of an aqueous suspension (1 g of charcoal). Statistically significant insights could not be gained from the study, because the cohort size was too low. There was a trend towards reduction of the severity of irinotecan-induced diarrhoea (14). For final evaluation, further studies will be required. When using charcoal, it must be kept in mind that it may prevent absorption of other orally administered drugs.

The swelling agent ***pectin*** (e. g. in Aplona®) does increase consistency of the faeces, but it exerts no influence on their frequency and water content. There

is no reliable proof of its efficacy in [the treatment of] chemotherapy-induced diarrhoea (3).

Cholestyramine has been found effective in [the treatment of] radiation-induced diarrhoea. The substance is administered in dosages amounting to one bag with each meal and at bedtime (7). However, side effects, in particular flatulence and constipation, are frequent, and the drug interacts with numerous others.

The α_2 receptor antagonist ***clonidine*** stimulates absorption and reduces intestinal secretion. Because of its anti-hypertensive effect it must be used with care. Recommended dosages are 0.1 mg twice a day with a daily increase by 0.1 mg up to an intervall of 0.4 to 0.6 mg twice a day (8).

Octreotide, a long-acting somatostatine analogue, is approved in Germany for – in addition to other indications – the treatment of endocrinally active gastrointestinal tumours, but not for therapy of chemotherapy-induced diarrhoea. Nevertheless the drug is used in cases of severe diarrhoea and has been approved by the FDA for the treatment of severe, loperamide-resistant diarrhoea. The drug has been used for the treatment of diarrhoeas caused by cisplatin, 5-FU and irinotecan. Both a preparation which is applied subcutaneously several times a day, and a sustained release formulation to be administered once a month are commercially available. Use of the sustained release formulation must be preceded by subcutaneous testing of efficacy and tolerability in accordance with the FDA approval. In accordance with the recommendations by an expert panel, after a high-dosage loperamide treatment of I° – II° diarrhoea 100 – 150 µg of octreotide should be administered subcutaneously every eight hours (11). In severe diarrhoea, dosages of 500 – 1500 µg subcutaneously or intravenously as a bolus every eight hours are recommended as «first line» therapy (11). A trial by Meropol et al. failed to demonstrate prophylactic efficacy (15). Among the most frequently occurring side effects, each in about 15% of cases, there are burning pain at the injection site and abdominal complaints (16). When using octreotide, the advantages of treatment should be balanced against the possible side effects and «cost effectiveness» of the therapy (17).

N-butyl-scopolamine, an anticholinergic and spasmolytic, is used to assuage spasmodic complaints. If required, a dosage of 1 – 2 tablets every 4 hours is recommended. Bioavailability of the substance is low.

The parasympatholytic agent ***atropine*** has the same effects and is sometimes used for acute diarrhoea under irinotecan; however, corresponding central nervous side effects must be expected.

Racecadotril – also known as «acetophane» – is an orally applicable selective inhibitor of enkephalinase and is used for treatment of acute diarrhoea. In Germany, the substance is approved only for supplementary, symptomatic treatment of infants and children, accompanying oral hydration and electrolyte replacement. The substance is a prodrug which is metabolised to the active metabolite thiorphane preventing the degradation of endogenous enkephalines and thereby reducing secretion of water into the lumen of the intestine. In a trial, the drug was used at a dosage of 100 mg three times a day (18). In a phase II trial, prophylactic administration was found ineffective (19). Racecadotril may also be combined with loperamide. The side effect profile of the drug shows no undesirable gastrointestinal effects and was comparable to the use of placebo (20).

Budesonide as orally applicable, locally effective synthetic steroid was tested in a small study for the therapy of irinotecan- and 5-fluorouracil-induced diarrhoea after failure of loperamide treatment. The authors were able to observe reduction of complaints by at least two NCI toxicity grades (21).

In case of proctitis, the complaints may be reduced by products comprising ***steroids*** (cream, rectal foam).

In patients with pancreatic tumours developing diarrhoea during radiation therapy, substitution of ***pancreatic enzymes*** should be considered, since lack of these enzymes may result in diarrhoea.

Among the drugs undergoing clinical testing there is TJ-14, a ***baicalin-containing inhibitor of ß-glucuronidase*** which was tested successfully in irinotecan-induced diarrhoea by a Japanese group (22). Inhibition of the â-glucuronidase of the endogenous intestinal microflora prevents re-conversion of irinotecan

metabolite without anti-neoplastic activities to the active substance, thereby reducing duration and severity of diarrhoea.

Celecoxib was tested with contradictory results in irinodecan[sic]-induced diarrhoea (3). As it is a selective COX-2 inhibitor, both its inhibitory effects on prostaglandin metabolism and its anti-angiogenetic effects may be responsible for the efficacy.

Glutamine is a non-essential amino acid which is among the most important energy sources of the gastrointestinal tract and contributes to the maintenance of the intestinal microflora. An Italian group have shown oral administration of glutamine to reduce the changes in intestinal absorption and permeability induced by 5-FU, suggesting protective effects against occurrence of diarrhoea (23). In his review, Savarese concludes that oral administration of glutamine may be recommendable for the prevention of chemotherapy-induced gastrointestinal side effects (24).

For assessment of the use of ***alkalising substances*** such as sodium bicarbonate, magnesium oxide and the like as well as of ***antibiotics*** for reduction of gastrointestinal toxicity, further studies will be required (3).

5-HT$_3$ receptor antagonists, whose use is established in the treatment of chemotherapy-induced vomiting (see 5.2.1 Management of nausea and vomiting), are effective in irritable bowel syndrome and may thus be useful in the treatment of chemotherapy-induced diarrhoea (25).

Summary

Immediate and intensive treatment of diarrhoea induced by chemotherapy and radiotherapy can increase the quality of life of tumour patients and reduce overall treatment costs. It is the pharmacist's task to help prevent repercussions of diarrhoea such as weakness, electrolyte loss and exsiccation.

References:

1. Arbuckle RB, Huber SL, Zacker C, The Consequences of Diarrhea Occuring During Chemotherapy for Colorectal Cancer: A Retrospective Study; The Oncologist 2000; 5:250-259

2. Wadler, S, Benson III, AB, Engelking C, Catalano R et al., Recommended Guideline for the Treatment of Chemotherapy induced Diarrhea, J Clin Oncol 1998; 16(9):3169-3178

3. Richardson G, Dobish R, Chemotherapy induced diarrhea J Oncol Pharm Practice 2007 13:181-198

4. Motzer RJ, Rini BI, Bukowski RM et al., Sunitinib inpatients with metastatic renal cell carcinoma. JAMA. 2006; 295:2516-24

5. Strumberg D, Richly H, Hilger RA et al. Phase I clinical trial and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 inpatients with advanced refractory solid tumors, J Clin Oncol. 2005;23:065-72

6. National Cancer Institute: Common Toxicity Criteria Manual, 9.8.2006 http://ctep.cancer.goc /forms/CTCAEv3.pdf

http://www.nci.nih.gov (Dezember 2007)

7.www.cancer.gov/cancetopics/pdq/supportivecare/gastrointestinalcomplications/HealthProfessonal/page6 (Dezember 2007)

8. Ippoliti C, Antidiarrheal agents for the management of treatment-related diarrhea in cancer patients Am J Health-Syst Pharm 1998; 55:1573-1580

9. Hyams JS, Batrus CL, Grand RJ, Sallan SE, Cancer chemotherapy-induced lactose malabsorption in children; Cancer 1982; 49(4):646-650

10. Shah A, BCCA Guidelines on chemotherapy-induced diarrhea 14. Oktober 2004. In de Lemos ML ed BC Cancer Agency Drug manual. Vancouver, British Columbia: BC Cancer Agency http://www. Bccancer.bc.ca/NR/rdonlyres/4E/EF86A-EAA5-4F3C-B147-B2512799F6B3/7371 Guidelines for Management of CID.pdf (Dezember 2007)

11. Kornblau S, Benson AB, Catalano R, Champlin RE et al. Management of cancer treatment-related diarrhea. Issues and therapeutic strategies, J Pain Symptom Management 2000; 19(2):118-129

12. Abigerges D, Armand JP, Chabot GG, Da Costa L et al. Irinotecan (CPT-11) high-dose escalation using intensive high-dose loperamide to control diarrhea. J Natl Cancer Inst 1994; 86(6):446-449

13. Cascinu S, Biachiasao E, Amadori D et al High-dose loperamide in the treatment of 5-luorouracil-indued diarrhea in colorectal cancer patients. Support Care Cancer 200, 8(1):65-67

14. Michael M, Brittain M, Nagai J et al Phase II study of activted charcoal to prevent irinotecan induced diarrhea J Clin Oncol 2004; 22:44410-17

15. Meropol NJ, Blumenson LE, Creaven PJ, Octreotide does not prevent diarrhea in patients treated with weekly 5-fluorouracil plus high-dose leucovorin. Am J Clin Oncol 1998; 21(2):135-138

16. Gebbia V, Carreca I, Testa A, Valenza R et al. Subcutaneous octreotide versus oral loperamide in the treatment of diarrhea following chemotherapy, Anticancer Drugs 1993; 4(4):443-445

17. Gilbar JP., The role of octeotide in symptom management in oncology and palliative care, J Oncol Pharm Practice 2000; 6(3):81-91

18. Wang HH, Shieh MJ, Liao KF A blind, randomized comparison of racecadotril and loperamid for stopping acute diarrhea in adults. World J Gastroenterol 2005; 11(10):1540-1543

19. Ychou M, Douillard JY, Rougier P, Adenis A et al. Randomized comparison of prophylactic antidiarrheal treatment versus no prophylactic antidiarrheal treatment in patients receiving CPT-11 (irinotecan) for advanced 5-FU-resistant colorectal cancer: an open-label multicenter phase II study. Am J Clin Oncol 2000; 23(2):143-148

20. Lecomte JM, An overview of clinical studies with racecadotril in adults Int J Antimicrob Agents 2000 14 (1):81-87

21. Lenfers, BH, Loeffler, TM, Droege, MC, et al. Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment, Ann Oncol 1999; 10(10):1251-1253

22. Mori K, Kondo T, Kamiyama Y, Kano Y, Tominaga K,Preventive effect of Kampo medicine (Hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer, J Cancer Chemotherapy & Pharmacology 2003; 51: 403-406

23. Daniele B, Perrone F, Gallo C, Pignata S, et al. Oral glutamine in the prevention of fluorouracil induced intestinal toxicity: a double blind, placebo controlled, randomised trial, Gut 2001; 48: 28-33

24. Savarese D, Al-Zoubi A, Boucher J; Prevention of Chemotherapy and radiation induced toxicity with glutamine; Cancer Treat Rev 2003; 29:501-513

25. Schultz M, Schölmerich J, Kullmann F, Management chemotherapieinduzierter Diarrhöen Z Gastroenterol. 2004; 42(6):527-538

5.2.6. Nutrition Therapy

Depending on the type of the oncological disease, almost every patient suffers from more or less developed malnutrition caused by the disease itself or to the therapy. In addition to aggravation of the general condition, this cachexia leads to diminished therapy tolerance with increased occurrence of side effects.

In medical nutrition therapy, the well-being of the patient, observable in terms of appetite and pleasure in eating of the patient and not necessarily of maintaining weight, must be focussed upon.

Dietary advice should also explain changes in taste perception and food tolerance as well as increased nutritional requirements to the patient and, in cooperation with him/her, show the physician and other persons involved possible ways of adapting eating habits.

It is expedient to provide information material and instructions on what to do.

Svenja Sander, Hamburg

Tumour cachexia

In their initial stage, many tumorous diseases present very unspecific symptoms. For example, the first sign of a tumour disease is often severe weight loss which prompts seeing a physician. Patients with pulmonary tumours, pancreatic carcinomas and tumours of the upper gastrointestinal tract are primarily affected (1). Cachexia poses a problem also in advanced stage of tumour diseases. Cachexia worsens prognosis of tumour diseases, lowers responses to chemotherapy treatments increases mortality ratio is increased during surgery (2). Energy deficiency alone does not provide an explanation for the degree of tumour cachexia. Various mediators, such as e.g. tumour necrosis factor α,

interleukin-1 and interleukin-6 as well as substances secreted from tumours, are being discussed (3).

Malnutrition is frequently caused by therapy in addition to increased energy consumption by tumour activity. In combination with this, tumour patients also suffer from:

- feeling of repletion 60%
- altered perception of taste 46%
- anorexia 40%
- nausea or vomiting 27%
- dysphagia or mastication disturbances
- inflammations of the oral cavity
- depressive mood alterations

General measures

Many patients would like to take actively supporting actions to combat their tumour disease. For them, nutrition is a simple way even if there is no diet which may heal a tumour disease. Altering the nutritional habits of the patient to a healthy, wholesome diet may have a positive impact on his/her well-being. However, a radical change of nutrition is not to be recommended, since this is usually coupled with decreased food intake. So-called «cancer diets» are explicitly to be cautioned against (4).

The following tips may be helpful to motivate tumour patients to eat under the altered conditions during a therapy:

- Offer food according to the patient's desire, i.e. get the the patient involved into the selection of his diet without major changes; it is essential that patients will eat at all, keep their appetite and ingest sufficient amounts of food. Orientation to self-kept logs of the patient is good, however, in order not to provoke aversion, favourite meals should be avoided in phases of acute nausea.
- Offer lots of smaller varied meals throughout the day.
- Meals should be served appetizingly.

- Mildly flavoured, low-odour, maybe preferentially cold food.
- Fruits and vegetables should be consumed only if ripe; possibly juice may be tolerated better.
- Eating should take place in another room than cooking.
- Provide distraction for the meals (music, conversation).
- Avoid set mealtimes. Eating should take place according to the level of hunger, even at night.
- Stockpiling should be highly diversified.
- Arrange small bowls with snacks as «seducing» appetizers.

If normal food does not allow for sufficient calorie intake, an assortment of drinks and special foods should be provided complementary or solely. Potable food in small packaging units and with a wide diversity of flavours will be tolerated by the patient sooner than bottles containing 500 ml. Some products can be consumed not only undiluted but also mixed into warm and cold foods. Manufacturers provide stimulating recipes. Often, the possible applications of potable foods are not being exploited to their fullest before tube feeding is used, even if that would be more pleasant for the patient.

Food can be enriched with products such as maltrodextrin which is a tasteless corn starch product containing easily absorbable carbohydrates. It can be mixed into drinks, sweets and soups and is suitable for gram calorie enrichment in case of patients developing a distaste for fatty meals. In case of protein deficiency, protein powders are indicated. Further fat can be added e.g. by using cream instead of milk and potentially butter.

Therapy pauses between the cycles in particular should be utilized for stabilization of weight.

Parenteral nourishment is indicated in case when an oral or enteral food uptake of less than 500 kilo-calories pro day over a period of more than five days must be expected (5).

Nutritional requirement / Special nutrients

A tumour patients requires, according to the disease, 20 to 35 large calories per kilogram standard weight per day (2). For tumour patients, nutrient composition is based on whole foods for healthy people. I.e., approximately 50 percent of the absorbed energy should come from carbohydrates. In case of an energy demand of, e.g., 2,000 large calories per day this is approximately 270 g. 30 %of the energy should be from fat, this corresponds to approximately 67 g. In tumour patients, this portion may be higher. The rest should be absorbed in form of proteins (approximately 95 g).

Increased energy requirements are only one aspect of supplying tumour patients with food. Systemic inflammation develops probably due to tumour products and substances secreted by the immune system of the body, such as e.g. cytokines. Omega (Ω)-3 fatty acids have a positive antiinflammatory effect. They are found mostly in fish high in fat, e.g. mackerels, herrings, tunas and salmons, as well as in cod liver oil and in linseed oil.

In different tumour diseases, micro-nutrient demands are increased, too. There are no objections against taking a supplementary preparation based on the micro-nutrient demands of a healthy person. Taking particular high dosed substances must be, however, tested in each case. For example, in tumour patients selenium blood levels are reduced and their demands for selenium as a part of glutathione are increased. It has been suggested that selenium may reduce the nephrotoxicity which may occur after administration of cisplatin [6,7].

There are no data documenting that enrichment of the diet with immunomodulatory substances or glutamine have any effects on the nutritional condition of tumour patients; with regard to omega (ù)-3 fatty acids, data are controversial (2).

Prevention

In cancer prevention, there are diets that may have a positive effect. This applies primarily to tumours of the intestine. One example here is the widely supported campaign called «5 pro day incorporated society». It must be expected that the positive effects will be due to the plurality of substances absorbed. Regarding use of individual substances, evidence for cancer preventive effects is still lacking so far.

For most people, enjoying meals is an important factor for enjoyment of life. Nutritional consultation must, therefore, necessarily consider the diet of the patient.

Sources of information for consultation:

Diets in Cancer; German Cancer Aid, The Blue Advisors 46

Dietary guidelines in patients with intestinal cancer, German Cancer Aid Association

World Cancer Research Fund (WCRF) Report

References:

1 Zürcher, G.: Ausreichende Energie- und Nährstoffzufuhr – Ernährungsstrategien beim Tumorpatienten [Sufficient Energy and Nourishment Supply – Nourishment Strategies In Case Of Tumour Patients]; www. thieme-connect. com (2004)

2 Arends J, Bodoky G, Bozetti F, et.al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology Clinical Nutrition 2006, 25: 245-259

3 Ramos EJ, Suzuki S, Marks D, et al.: Cancer anorexia-cachexia syndrom [sic]: cytokines and neuropeptides. Curr Opin Clin Nutr metab Care 7 (4): 427-34, 2004

4 Münstedt, C. Ratgeber unkonventionelle Krebstherapien Ecomed, 2. Auflage [Guidebook for unconventional cancer therapies Ecomed, 2nd Edition] 2005, ISBN 978-3-609-16329-1

5 Arends J, Zürcher G, Leitlinie parenteral Ernährung der DEGM Kapitel 19 Nicht-Chirurgische Onkologie [Guideline Parenteral Nourishment of DEGM, Chapter 19 Non-chirurgical oncology], Aktuel Ernaehr Med 2007; 32, Supplement 1

6 Keller, U.: Physische und biochemische Charakteristika der Tumorkachexie. [Phisical and Biochemical Characteristics of tumour cachexia] In Schauder, P. (Ed.) Ernährung and Tumorerkrankungen [Nourishment and Tumour Diseases] .Basel, Karger (1991) 213-222

7. Keller, U.: Von der Katabolie zur Anabolie, Stoffwechselmediatoren und Therapieansätze, Aktuelle Ernährungsmedizin [From Catabolism to Anabolism, Mediators in Metabolism,Current Nutritional Medicine] 2001;26:148-152

Internet links:

http://www.5amTag.de

http://www.dge.de

http://www.wcrf.org

http://www.krebsgesellschaft.de/ernaehrung_bei_krebs_mangelernaehrung.html http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition

http://www.dgem.de/material/pdfs/ 19%20Nichtsurgicale%20oncology.pdf

http://www.nw-suppo.de/index.php?locid=150 http://www.medinal.de/f/kachexie.html

5.2.7. Undesirable Drug Effects on the Dermis

The pharmacist should be able to classify undesirable drug effects on the dermis as well as to provide recommendations for treatment.

Kerstin Bornemann, Nordheim

The skin is one of the organs most frequently affected by side effects of antineoplastic therapy: Because of the wide variety of toxicity forms, their cause and partly substance specific measures, we can give here a synopsis only.

In case of skin problems in oncological therapy, one must discriminate between conventional chemotherapy, radiotherapy and the newer EGFR-antagonist tumour therapies which may cause dermatological side effects completely different in type and degree.

Side effects by conventional chemotherapeutics

Chemotherapeutics can cause several kinds of skin alterations e.g. erythemas, flush, pruritus, nail or pigment alterations or allergic reactions.

Allergic cutaneous reactions due to cytostatics can be mainly caused by asparaginase, azathioprine, anthracyclines, alkylating agents and taxanes.

Erythemas may be caused by various chemotherapeutic substances.

Hyperpigmentation can typically be caused by bleomycin, busulfan, cisplatin, cyclophosphamide and 5-fluorouracil.

Nail alterations due to cytostatics can be growth alterations, pigmentation anomalies (hyperpigmentation caused by doxorubicin, cyclophosphamide, melphalan and methotrexate) and nail ablations (onycholysis, substances: adriamycin [doxorubicin], bleomycin, docetaxel, 5-FU, hydroxyurea).

A particularly severe and painful skin reaction is the «hand-foot syndrome», also called palmar-plantar erythrodysaesthesia – an erythematous skin alteration

on the palms of the hands and soles of the feet, many times associated with local sensitivity to pressure and paraesthesia. Severe cases are accompanied with vesication and skin ablation. Depending on the degree, the patient is handicapped slightly to severely in everyday life. Inducers can be the purine antagonists 5-fluorouracil and capecitabine, but also conventional anthracyclines with liposomal preparation or PEG-ylated liposomal doxorubicin.

Side effects of EGFR-specific tumour therapies

Cutaneous reactions are among the most frequent side effects of this substance group. EGFR inhibitors (tyrosine kinase inhibitors such as erlotinib, antibodies such as cetuximab and panitumumab).

Skin alterations mostly appear in a mild to moderate form as acneiform exanthemas, dry skin and less commonly as paronychias. The clinical presentation of these skin reactions, the involvement of visible areas (mostly face, scalp, nape, thorax and spine) and the accompanying symptoms such as itching, burning ache or pain, undoubtedly stress the patient. The persons affected often feel stigmatized, and avoid others.

Most of the skin reactions develop within the first week of treatment but regress, as a general rule, spontaneously after the end of therapy.

Here, for the attending physician it is very important to know whether the ongoing tumour therapy must be interrupted or cancelled because of the severe clinical presentation of the skin alterations.

If acneiform lesions appear, a gradual schema similar to that used in case of acne or rosacea is suggested.

In about one-third of patients, after several weeks of therapy in the area of he pre-existing exanthema there occurs a dry desquamating eczema which is frequently associated with strong pruritus and often subject to bacterial superinfections over the further course of the disease.

Further undesirable effects of the substances may include paronychias (inflammations of the nail bed, e.g. in case of cetuximab) and hair alterations.

Side effects of radiation therapy

Skin conditions caused by irradiation occur during the first weeks and affect the entry and exit sited of the ionizing rays. Depending on manifestation, they are classified into four stages, the possible complaints depend on the total dosage administered. Reddening, desquamation, vesication, pain, alopecia, necroses and irreversible damage may occur.

The so-called «recall phenomenon» can occur even years after irradiation in the context of cytostatics application, in particular of daunorubicin, dactinomycin, methotrexate and paclitaxel. Here in a pretreated skin area previously without pathological signs after administration of the respective substance a skin reaction occurs which can range from slight erythema to necrotic ulcerations.

Particular attention must be paid to the combination of radiation therapy and EGFR inhibitors, which may result in very marked reactions (e.g. cetuximab).

Pharmaceutical counseling

Because of the wide variety of possible side effects, the oncology pharmacist should be informed about the individual substances and in particular measures in case of problems. Since the pharmacist will often be the first contact person, (s)he should be able to estimate skin reactions or associate them with the therapy.

General suggestions for care can be offered to every patient before the start of the therapy:

- During chemo- or radiation therapy, then skin should not exposed to direct sunlight, and even in the shadow, sufficient light protection should be used and headgear be worn.
- Moisturising lotions and sufficient uptake of liquids should be used to protect the skin from drying out.
- In washing, lukewarm water and mild soaps must be used; gentle drying must be recommended.
- Any mechanical irritation must be avoided.

Many treatment centres have heir own recommendations for care. In the interest of interdisciplinary cooperation, it is expedient to coordinate them in order to increase the patient's compliance.

Treatment strategies in the individual stages under therapy with EGFR antibodies can be learned from the ASO guideline or, in individual cases, from the manufacturer.

References:

Hartmann JT, Ugurel S, Ulrich J, Dörr W Hauttoxizität, ASO-Leitlinie, September 2007

Wacker B, Nagrani T, Weinberg J, Witt K, Clark G, Cagnoni PJ, Correlation between Development of Rash and Efficacy in Patients treated with the Epidermal Growth Factor Receptor Tyrosins Kinase Inhibitor Erlotinib in Two Large Phase III Studies, Clin Cancer Res 2007, 13: 3913-3921

Dirschka T, Management kutaner Reaktionen im Rahmen EGFR-spezifischer Tumortherapien, Journal Onkologie 2007, 02: Sonderdruck

Bokemeyer C, Dermatotoxizität antineoplastischer Substanzen, in: Kompendium Internistische Onkologie, Band 1, 3.Auflage, S. 1411-1419, Springer Verlag Berlin 1999

Goldinger A, Strahleninduzierte Hautveränderungen, PZ Prisma, 2007, Teil 1 S. 5-20, Teil 2 S. 112-119

Höckel, Heckl, Nagel, Der Krebspatient in der Apotheke, 2003, S. 254-257, Deutscher Apotheker Verlag Stuttgart

Westfeld M, Liekweg A, Bornemann K, Scharfenberg H, Jaehde U, Maligne Erkrankungen in: Manuale zur Pharmazeutischen Betreuung, 2006, Govi Verlag Eschborn, S.56-57

5.2.8. Unconventional Remedies in Cancer Therapy

The oncology pharmacist also provides information about complementary and alternative medicine (CAM) for treating cancer patients and advises on unconventional remedies if requested to do so. These are medicines or methods which are not recognised by orthodox medicine, but which must be amenable to scientific investigation. For protection of the patient it is essential to assess whether use of these products or methods involves a health risk for the patient and/or whether its is a quack treatment. Interactions with existing therapeutic regimens must be checked and excluded. It is the pharmacist's duty to take patients seriously who «want something extra», to inform them of the importance of orthodox treatment of their disease, and to analyse the desire for alternative remedies.

Michael Höckel, Eisenach

Unconventional remedies in cancer medicine – also known as methods for cancer treatment without proven effect – are summarised by the term «complementary and alternative medicine» (CAM). Here «complementary» means additional use of unconventional remedies, and «alternative» use of these instead of orthodox medical treatment. There is considerable need for information about complementary medicine among patients, their family members and the physicians giving treatment. The number of patients who want to receive orthodox medicines and methods in combination with unconventional remedies is increasing. Only the pharmacist with internet access to relevant literature and sources of data will be able to provide competent answers to questions concerning the use and safety of such remedies. The crucial issue in giving advice is to discriminate, on the one hand, unconventional but reputable preparations for which the therapeutic process is intelligible to the pharmacist, from dubious remedies (quackery) on the other. Some examples of unconventional remedies are:

- mistletoe
- phytotherapeutics
- enzymes
- organ preparations
- thymus preparations
- homoeopathy
- selenium
- vitamins, minerals and trace elements

These remedies must be distinguished from products and methods which can be recognised, e.g., by the lack of information provided by the manufacturer or vendor/supplier of these products. Case reports of outstanding therapeutic results are often used in advertising. Doubtful information about the alleged efficacy of the remedies or methods is disseminated via newspapers and magazines. Some products are even offered as alternatives to conventional therapy. In these cases, particular caution is mandated because of the risk that patients may become confused and refuse or discontinue orthodox medical treatment. As a general rule, advice should be given not to use remedies and methods associated where data are limited or absent.

The counseling pharmacist should analyse the desire for unconventional remedies and strengthen the patient's confidence in orthodox medical treatment by his advice. When answering specific questions by patients about unconventional remedies, the pharmacist gives advice and recommends the patient to discuss the issue further with the attending physicians. With the patient's agreement, consultation with the attending physician may be expedient. After approval by the attending physician, the pharmacy attends to safe use of the remedy prescribed, e.g. in the case of subcutaneous injection of a mistletoe extract. The sequence of advice is based on the consultation concerning conventional, orthodox drugs.

Internet addresses as sources of information:

Biological Cancer Therapy Study Group at the Klinikum Nürnberg Nord: http://www.agbkt.de/ Medline plus informations on unconventional remedies: http://www.nlm.nih.gov/medlineplus/canceralternativetherapies.html

Information on unconventional medicine, including interactions with chemotherapy, Stanford Center for Integrative Medicine http://www.cancersupportivecare.com/complementary.html

Office of Cancer Complementary & Alternative Medicine, National Cancer Institute, Bethesda, USA http://www.cancer.gov/cam/

MD Anderson Cancer Center Complementary & Integrative Medicine, University of Texas http://www.mdanderson.org/departments/cimer/

References:

Münstedt, C. Ratgeber unkonventionelle Krebstherapien Ecomed, 2. Auflage 2005, ISBN 978-3-609-16329-1

Münstedt C, Thienel P, Patientenratgeber Krebs: alternative Therapien medizinisch bewertet, Droemer/Knaur, 2008 ISBN-13: 978-3426644706

5.2.8.1. Homoeopathy in the Treatment of Cancer

Inge Koch, Gießen

General principles of homoeopathy

Homoeopathy is a **holistic** treatment method which was established some 200 years ago by the physician Samuel Hahnemann. According to the **law of similars** «similia similibus curentur», a potentised (= diluted and «succussed» in accordance with special prescriptions) remedy is administered, which in the healthy person would induce a condition as similar to that of the patient as possible (simillimum).

The patient's symptoms are interpreted as an expression of his **life force** being out of tune. Here not only physical complaints but also emotional, psychical and mental state of the patient and above all unusual («peculiar») symptoms are decisive for the selection of the appropriate homoeopathic remedies and the assessment of the healing process.

Administration of the potentised remedy re-balances the life force, thereby activating the body's **self-healing abilities** to overcome complaints on all levels.

Homoeopathy is an **energetic** treatment approach, and the mode of action cannot be elucidated with currently available methods.

For some people it is unimaginable that a homoeopathic remedy can have any effect at a potency where according to mere arithmetics not one molecule of the initial substance is present. One can accept homoeopathy only by overcoming the idea of an effect on a purely material basis at this point.

In so-called «**classic homoeopathy**» where the simillimum (see above.) is administered as a single substance, the following treatments are discriminated:

- **constitutive treatment:**

  In a **comprehensive session** taking several hours and followed by elaborating, the homoeopath (physician or healer) records the various complaints of the

patient in their entirety. (S)He administers a remedy at a suitable potency (for high potencies, often a single dose only). In subsequent sessions, the patient's emotional, psychical and physical reaction (= effect of the remedy) is evaluated, and the healing process is further supported homoeopathically.

- **acute treatment:**

  In the treatment of acute conditions, the anamnesis is much shorter, and a remedy tried for the respective *disease* and frequently prescribed is used. This procedure has been described in many self-help guidebooks as well.

«**Complex homoeopathy**» must be discriminated from this. Here several widely-used acute remedies at low potency are mixed and administered, in accordance with common orthodox indication, frequently.

Prerequisites for the efficacy of homoeopathic remedies

The first important prerequisite for a homoeopathic treatment to have effect is sufficient life force of the patient, both to produce suitable symptoms according to which a homoeopathic remedy may be selected (often very difficult in long-term, chronic diseases treated with allopathic drugs) and to be able to react to the remedy administered.

Similarly decisive is the selection of the correct (=«most similar») homoeopathic remedy (which is frequently difficult, with more than 2000 different homoeopathic remedies).

If an improper remedy is administered, either nothing happens at all, or new symptoms occur which provide a clue to the right remedy. If the remedy is only partially appropriate, only some of the complaints will be assuaged, and after evaluation of the complete reaction of the patient a more appropriate remedy must be administered.

The effects of homoeopathic remedies may be disturbed (weakened or antidoted) by strong ethereal oils, allopathic drugs and conditions repeatedly weakening the life force.

The limits of homoeopathic treatment are reached where the life force is no longer sufficient for a healing reaction, or where irreversible physical changes have already occured. Here healing is no longer possible, but palliation still is.

Homoeopathy in the treatment of cancer

The homoeopaths' perspective on cancer differs from that of many orthodox physicians in particular in that cancer is considered not a local but a systemic disease and thus to be treated holistically. Thus, local therapy (e.g. by surgical removal of a tumour) may relieve the body of the tumour load, but the inclination to form cancer is not reduced, no more than by chemotherapy or radiation therapy.

Therefore homoeopathic therapy aims at strengthening the body's life force – if necessary, also after surgical measures – and thereby enabling it to help itself to ideally overcome cancer like any other disease or at least to reduce it so far that the patient achieves a stable balance with his cancer condition. As cancer usually develops on the basis of long-term weakening of the life force, treatment is markedly more difficult and tedious than that of other diseases

Palliative treatment

Most tumour patients consulting a homoeopath present with the desire for treatment of general weakness and lack of energy caused by the advanced disease and/or chemo- or radiation therapy. Further frequent complaints include persistent nausea, loss of appetite, pain, mucosal damage, anxiety and insomnia.

The patients are usually in a weakened condition, often beyond therapy, and the cancer in an advanced stage. In spite of these difficult conditions and the reduced life force, homoeopathic treatment may still assuage acute complaints and a marked improvement of the quality of life. On the paediatric oncological war of Dr. von Hauner's Hospital for Children in Munich, homoeopathic remedies are successfully being used as palliatives accompanying chemo- and radiation therapy (1) .

Frequently used remedies are:

Problem	Tried remedies
Nausea, vomiting after chemotherapy	Nux vomica C30, 1 – 2× 3 glob. per day
Stomatitis aphthosa (e.g. after methotrexate)	Borax C6, 3× 3 glob. per day or Calendula C6, 3× 3 glob. per day (also for prophylaxis) followed by: Phorphorus C30, Arsenicum album C30
Diarrhoea after chemotherapy	Okoubaka C6, 3× 3 glob. per day
Weakness and exhaustion	Ac. phos. C6, 3× 3 glob. per day or China C6, 3× 3 glob. per day or Chininum arsenicosum C6, 3× 3 glob. per day
Leukopenia, thrombocytopenia	Phosphorus C12, 2× 3 glob. per day for 1 week or Lachesis C12, 2× 3 glob. per day for 1 week or
Anaemia	Ferrum phosphoricum C6, 3× 3 glob. per day

Homoeopathic remedies are usually given until amelioration and is then tapered or ended.

Often, a homoeopathic constitutive treatment for prophylaxis of relapse follows (1).

In **terminal care**, an aspect frequently ignored, homoeopathic care may also be very helpful to soothe strong dyspnoea, anxiety and agitation (2).

Curative treatment

In the late 19th and early 20th century, homoeopaths treated cancer exclusively with phytotherapeutic and homoeopathic remedies (3;4;5;6).

Over the last 10 – 15 years, their approaches and insights were reviewed, developed, applied and taught in homoeopathy seminaries and published (7).

In some private hospitals, cancer is treated mainly or exclusively with homoeopathics. (8).

The chances for curing are the better, the less advanced the disease is and the less pronounced the side effects of chemo- and radiation therapy are.

These days, orthodox physicians consider a patient's decision in favour of curative homoeopathic treatment as an irresponsible violation of a taboo, even though in some typed of cancer prognosis is still very infaust in spite of new therapy options. Fortunately, over recent years open-mindedness and mutual acceptance have developed both among orthodox physicians and homoeopaths, so that patients are now no longer confronted with an «either – or» choice or conceal the respectively other treatment from either therapist.

From the perspective of a homoeopath experienced in the treatment of cancer, **linking** of both therapy approaches were optimal, such as constitutive homoeopathic treatment prior to surgery, palliative homoeopathic therapy accompanying surgery, chemotherapy or irradiation, then continuation of constitutive treatment (9;10).

Further complementation with orthomolecular medicine (11; 12) and psychological support (psycho-oncology) or visualisation according to Simonton (13) or the Wildwuchs method (14), to promote healing on a variety of levels. Problems in combining homoeopathy and orthodox medicine may result from

- symptoms by side effects of chemo- and radiation therapy being dominant, hindering identification of homoeopathic remedy appropriate for the individual patient
- high dosage chemo- and radiation therapy extremely weakening the life force and reducing the response to homoeopathy
- reaction of comprehensive homoeopathic treatment being judged differently by orthodox physicians and homoeopaths:

Excretion reactions (e.g. perspiration, diarrhoea, rashes…) may occur as relief reactions during homoeopathic treatment and should not be suppressed using orthodox medicine. occurrence of fever requires very careful, differentiated procedures: In a neutropenic phase it is threatening and must be covered using antibiotics, in a stable phase, by contrast, from a holistic perspective it may be a healing reaction if the patient generally fares better.

Over the course of the homoeopathic treatment, even symptoms existing prior to the onset of cancer may occur, in keeping with homoeopathic laws of healing. If orthodox medicine is used here («suppression»), the healing process mediated by the homoeopathic treatment may be severely disturbed. (7).

Recommendation

In the treatment of cancer, combination of therapy methods based on different approaches is expedient.

Homoeopathy is a tried and tested holistic approach to healing which may also be used accompanying orthodox medical treatments. When selecting a homoeopathic therapist (homoeopathic physician or healer), the patient should request the procedure to explained in a non-committal first talk and get a personal impression. The homoeopath should have several years of experience in classic homoeopathic treatment and have special expertise in the homoeopathic treatment of cancer.

References:

1. Kruse S, Wackerl A, Dorsci-Ulrich M, Dorsci M: Homöopathie am Dr. von Haunerschen Kinderspital www.carstensstiftung.de/wissen/hom/pdf/klin_haun_jahrbuch_band8.pdf

2. Sonnenschmidt R: Exkarnation – Der große Wandel. 2002. Verlag Homöopathie + Symbol, Berlin

3. Burnett, J.C.: Tumoren der Brust. 1997. Schriftenreihe der Clemens von Bönninghausen-Akademie,Verlag Müller & Steinicke, München

4. Burnett, J.C.: Heilbarkeit von Tumoren. 2001. Schriftenreihe der Clemens von Bönninghausen-Akademie, Verlag Müller & Steinicke, München

5. Clarke, J.H.: Die Heilung von Tumoren durch Arzneimittel. 1997. Schriftenreihe der Clemens von BönninghausenAkademie , Verlag Müller & Steinicke, München

6. Cooper, R.T. : Krebs und Krebssymptome - Fortier-Bernoville /Grimmer, A H: Die homoeopathice Behandlung von Krebs. 1996 Schriftenreihe der Clemens von Bönninghausen-Akademie Müller & Steinicke, München

7. Methner R: Die homöopathische Behandlung von Krebs (www.homeopathy.at/wiki/index.php?title=Cancer/Theorie)

8. Zeitschrift des Deutschen Zentralvereins homöopathischer Ärzte, Frühjahr 2007, Seite 2 (www.clinicasantacroce.ch/download/Homoeo0107_ClinicaStCroce.pdf)

9. Deutscher Zentralverein homoeopathicer Ärzte, Interview mit Dr. Jens Wurster, November 2004 (www.mickler.de/fallbeispiele/homoeopathie-krebs-wurster.htm)

10. Wurster, J.: Die homöopathische Behandlung und Heilung von Krebs. 2006. Verlag Peter Irl, Buchendorf

11. Kleber J.J: Naturheilkundliche Krebstherapie. 2007. Kai Kröger Verlag, Groß Wittensee

12. Sonnenschmidt R, Uricher C: Prozessorientierte Krebstherapie. 2003. Verlag Homöopathie + Symbol, Berlin

13. Simonton O.C.et al.: Wieder gesund werden. 3.Auflage 2004. Rowohlt Taschenbuch Verlag, Reinbek

14. Koppe A: Wo die Piranhas mit den Zähnen klappern (Die Kraft innerer Bilder in Selbstheilungsprozessen) 2000, Goldmann Verlag, München

6. Research and Development

The present text reflects the state of the discussion within the European Society of Oncology Pharmacy (ESOP).

In oncology, research and development should preferably be conducted in interdisciplinary fashion. Pharmaceutical-oncological services make important contributions to research activities. Results from research and development improve efficacy, suitability and quality of the offered procedures and services.

In any research environment including pharmaceutical science, qualified pharmacists should be involved in designing and conducting the trials. In research, scientific and ethic rules as well as the guidelines for the individual field of research based thereupon must be complied with.

Prior to the study, a suitable and focussed goal must be defined in writing. All research activities including the rationale must be documented completely. The necessary resources as well as their efficient utilization must be determined in advance. Responsibility for scientifically and ethically acceptable performance must rest with one individual. For quality assurance, appropriately standardized methods and procedures must be used.

Confidentiality of clinical research data is essential. The results must be documented in standardized form and filed together with the corresponding original documents in a safe and easy to retrieve way. For electronic data, special approaches are required. The results must be assessed regularly with respect to their correctness and completeness. Records from clinical trials and public health studies must be archived in conformance with the applicable national regulations.

All research results, including negative ones, must be released for verification by scientific peers and made accessible to the general public. The person in charge of research shall authorize publication and release of information. Essential contributions to planning, performance and publication of the trial are prerequisites for authorship. Detected errors should be processed by the first author, and in cases of severe errors the person in charge must retract the work. Prior to inception, written contracts relating to intellectual property rights must be concluded with the sponsors.

Per Hartvig Honoré, Copenhagen

Basics

oncology pharmaceutical services should always be based on scientific evidence and well-validated experience. Thus, for advances in oncological pharmacy, as in other medical and pharmaceutical sciences, research and development are essential. Research must be of high quality and focus on improving treatment and expanding knowledge about cancer and improving the patient's situation. Here the oath «not to do harm» is the paramount imperative. The scientific issue must be both pharmaceutically and medically relevant, be clearly worded, well structured and comprehensively documented. The results must be made accessible to the scientific community as well as to the oncology pharmacists. Performing research entails particular responsibility, hence in all projects high quality must be guaranteed and validated.

Research and development projects in oncological pharmacy are available for everyone. Support and supervision by experts for oncological pharmacy in centres of scientific excellence must, however, be guaranteed.

Research and development in oncological pharmacy

Oncological pharmacy focuses on science and knowledge relating to pharmaceutical services for oncological patients. Oncological pharmacy comprises two major fields:

- Adequate *supply with drugs* for the treatment of cancer and in particular with cytostatics must be based on solid experience but also on scientific evidence, since these drugs are particularly toxic and handling and application of their preparations require special precautions (1). In general, the relevant knowledge and expertise are limited to special departments within a pharmacy or an oncological ward run by specially trained staff with sufficient know-how in aseptic preparation of drugs and drug safety. This includes performing research trials for improving knowledge about application, mixing and stability of cytostatics and providing drugs for supportive therapy. *Dosing cytostatics* is especially awkward since there are no obvious correlations between dosage and clinically relevant response, often not even with drug plasma levels. Moreover, transport of the cytostatic into the tumour may become erratic because of poor blood supply, modulation of transporter proteins and expression of resistance mechanisms. Development of adequate and safe dosages should be supported by population-based methods. These have the advantage that the pharmacokinetic and pharmacodynamic interrelations studied in trials on small numbers of patients may be described in terms of clinical and biochemical responses, and prognostic factors may be identified considering pharmacokinetic variability.

- The clinical part comprises trials on the use and validation of *treatment regimens* for tumour patients. *Supportive therapy* is a central focus in oncology pharmaceutical practice. For most symptoms caused by the disease or therapy, empiric treatment methods are available but barely validated from a scientific point of view. For others, there are only very few treatment alternatives or inadequate therapies, e. g. for fatigue, for certain types of pain and, still, for vomiting. Improving therapy options requires better understanding of the biochemical causes of these symptoms. New insights in this field will extend the basis for the development of novel supportive treatment alternatives and thus increase the patients' quality of life. In this context, documentation of

patients' experiences of illness, with health care and with the contact with oncology pharmacists, with the psychological and social effects of disease and therapy as well as the effects on quality of life is of great importance and should be investigated scientifically.

A1. Studies of the pharmacokinetics and pharmacodynamics of cytostatics with population-based methods

Background

Dosage of cytostatics is mostly based upon experimental evidence but not upon medical evidence. Therapeutic drug monitoring is not routinely performed for cytostatics. There are several reasons for this, e.g. absence of established therapeutic dosage ranges and poor correlation between dosage and pharmacokinetics – and, even worse, effects – of the drug. In combination therapy using a plurality of drugs, changes in pharmacokinetics and pharmacodynamics (PK-PD) relative to monotherapy may cause problems.

In general, in the upper non-toxic range are used for the treatment of cancer dosages. For detection of over- and underdosages of the cytostatic, definition of a target plasma level would be advantageous. Beyond increasing therapeutic and avoiding toxic effects, clinical-pharmacokinetic knowledge may present further advantages in minimizing the effects of pharmacokinetic variability, adjusting dosages for patients with decreased hepatic or renal clearance or detecting drug interactions. Deeper knowledge of the PK-PD of cytostatics will therefore improve therapy and may allow to define suitable standard dosage levels («dose banding»).

Dose banding, taking pharmacokinetic variability into account, aims at treating all patients with pre-formulated dosages in a range of +/- 5% of the individually calculated and prescribed dosage. This shortens the time to delivery of the prepared cytostatics dose from the pharmacy, since most cytostatics are prepared in advance (paying attention to the stability criteria) and can thus be shipped immediately after receipt of the request by the pharmacy. Any dose banding must, however, be validated by a controlled clinical trial.

As an alternative dosing strategy, the notion of dosage intensity – defined as the dosage of the drug administered per hour – was extended to cover systemic exposition. This appears as a potentially more useful parameter, since systemic exposition can be determined from pharmacokinetic parameters such as steady-state serum levels (Css) or the area under the curve. Several trials have already been conducted for determining the relation between systemic response and successful therapeutic outcome in cytostatics treatment.

The final goal of the ongoing projects in oncology pharmaceutical practice is to improve *dosage of cytostatics by applying population parameters to pharmacokinetic-pharmacodynamic PK-PD studies and by dose banding in the pharmacy.*

Trial design

In dose banding, all patients are treated with pre-formulated dosages in a range amounting to +/- 5% of the individually calculated and prescribed dosage. This means that most cytostatics are prepared in advance (paying attention to the stability criteria) and can thus be shipped immediately after receipt of the request by the pharmacy. All in all, however, there are few scientific data on the dose banding of drugs. A scientific basis for dose banding thus remains to be developed. As mentioned above, scientific evidence relating to dosage strategies in oncology is all in all still very rudimentary. Generally, there is no close correlation between dosage and measured plasma levels of the effective substance, and the relation with concentration (and hence effects) in the tumour itself is, due to inter-individually varying blood supply to the tumour and varying biological characteristics of individual tumour cells, still less unambiguous.

The pharmacokinetic basis may be improved by including further parameters into the dosage strategy. Things to be considered here include cardiac, renal or hepatic insufficiency, age of the patient, biomarker concentrations and data relating to genetics of transporters and metabolic enzymes in a population-based PK-PD model. Thus, adequate dosage nomograms including a dose banding strategy may be developed by the manufacturing pharmacy.

On the one hand, the benefit of these research projects is that more precise dosages may be used to achieve the desired effect without a trade-off in terms

of more side effects for the patients treated with the cytostatics. On the other hand, the projects also form a basis for the pharmacies to increase their production capacity, to improve service for the wards, to reduce production errors and to make manufacture of cytostatics safer for the employees. Cytostatics to be evaluated primarily are cisplatin and 5-fluorouracil.

Impact of the results

Improved understanding of the relations between pharmacokinetic parameters or exposition parameters on the one and tumour growth or survival rate on the other hand, the efficacy of therapy and the outcome for patients may be improved by defining the first dosage *a priori* and adapting subsequent dosages *a posteriori* using population-based methods.

Thus, on the one hand the benefit of these research projects is that more precise dosages may be used to achieve the desired effect without a trade-off in terms of more side effects for patients treated with cytostatics. On the other hand, the projects also form a basis for the pharmacies to increase there production capacity, to improve service for the wards, reduce production errors and to make manufacture of cytostatics safer for the employees. Hence, patients as well as drug preparation on the ward benefit from increased capacity and economic saving.

A2. Dosage of cytostatics in reduced renal clearance

Background

Many cytostatics are excreted quickly and mostly in unmodified form through the kidneys. However, cytostatics or their metabolites may also be nephrotoxic. High dosage therapy with certain cytotoxic substances such as e.g. MTX is thus limited by their renal toxicity. Strategies presently used for avoiding the risk of renal failure include therapeutic drug monitoring and rescue therapy. Renal dysfunction may also reduce elimination, prolong exposition and thus in turn result in further reduction of renal clearance.

Cancer patients often show a wide variety of symptoms, and often it is difficult to determine whether these symptoms are caused by the underlying disease or

by stressful cytostatics therapy. It is thus important to follow the course of the renal dysfunction and to observe dosages and precautions limiting iatrogenic harm by the therapy.

For several cytostatics, suitable dosages in the individual stages of renal insufficiency are not documented well enough. Here dosage regimens remain to be defined in order to improve treatment safety.

Trial design

The eventual goal is to define a basis for the dosage of cytostatics in renal insufficiency. This research may be performed multicentrically in cooperation with the European Society of Oncology Pharmacy (ESOP). The task is to compile data from literature and clinical trials on the dosage of cytostatics in renal insufficiency. This can be done by collaborations as well as by focused trials in the individual centres. The results must be validated clinically in adequate fashion and circulated early among the oncology pharmacists.

Impact of the results

Long-term effects of cytostatics must be limited or prevented, since patients in remission ought not to be afflicted by effects of their therapy. Thus, efforts must be made to increase our knowledge of the damage, e.g. the influence of limited renal clearance on dosage or cytotoxic damage of tissues by drugs. The goal is to reduce the impact of the disease upon the patient and to increase chances for a return to working life and resumption of social activities.

A 3. Interactions between cytostatics and immunosuppressants

Background

In recipients of transplants, simultaneous application of cytostatics and immunosuppressants (e.g. cyclosporine) may become necessary. Cyclosporine and other immunosuppressants are metabolised by various subtypes of the metabolic enzymes of the CYP-450 systems, and drug interactions by stimulation or blocking of metabolic enzymes may render simultaneous application of drugs a game of pure chance. Some cytostatics are metabolised by this metabolic enzyme system as well, and the resulting changes in drug exposition may lead

to overdosage or underdosage relative to the dosage expected for the patients. Patients after bone marrow transplantation may receive both types drugs, which may lead to further unexpected difficulties in treatment.

Cancer patients often show a wide variety of symptoms, and often it is difficult to determine whether these symptoms are caused by the underlying disease or by drug interactions. Further data are required to correctly manage these complex interactions.

Trial design

Primarily, the project is a retrospective trial based on patient files of transplant recipients. The dosage of cyclosporine as well as the cytostatics therapy used and side effects which may have been caused by interactions are registered. This study presents the basis for performing a clinical trial on interactions.

Impact of the results

Though the effects of interactions are not known, they leave a feeling of uncertainty relating to pharmacotherapy. Most drug interactions are not so strongly pronounced that they become clinically relevant, and not all patients exposed show increased side effects. However, interactions between immunosuppressants and some cytostatics may potentially be consequential and even life-threatening for the patient. Thus, a clearer image of the consequences of drug interactions is required.

B. Supportive therapy for tumour patients

B.1 Fatigue

Background

The role of «Brain Derived Neurotrophic Factor» (BDNF) in stress and physical activity.

Fatigue affects 70 – 100% of tumour patients and increases during treatment. There is no effective treatment, and the cause is unknown. Fatigue is often followed by aggravation of other symptoms. More recent biochemical studies have focused on BDNF and on the effects of physical activity for combating the

worst of symptoms. BDNF may have protective function in acute stress. BDNF expression is suppressed by corticosteroids. Immediately after immobilisation stress, levels of circulating corticosteroids were increased and showed a decrease in BDNF protein. Rats which had free access to running facilities before stress exposition showed significant increase in hippocampal BDNF, and their basic corticosteroid levels likewise remained high. In animals without physical activity, BDNF levels decreased shortly after stress. Thus, corticosteroids modulated stress-induced changes in BDNF protein levels. Physical activity may possibly overcome the negative effects of stress, and it resulted in continuously high levels both of corticosteroids and BDNF. According to clinical observations and the above-mentioned study on fatigue caused by treatment of cancer and cytotoxicity, voluntary physical activity may be a simple non-pharmacological way of maintaining brain levels of neurotrophins, e.g. BDNF.

The biochemistry of fatigue should be investigated in search of new treatment alternatives.

Trial design

In ongoing trials, endogenous factors for fatigue, e. g. «Brain Derived Neurotrophic Factor» (BDNF) and corticosteroids are assessed in tumour patients and during cycles of treatment with cytotoxic drugs. The effects of BDNF and physical activity on cytotoxic-induced fatigue during treatment of cancer are likewise assessed. As a result, the individual patient's fatigue risks are validated using the validated Fatigue Rating Scale in a multi-dimensional analysis including CSF, BDNF, cancer type, age, preceding physical activity etc. to select an appropriate treatment program.

Impact of trial results

The present study links the argumentative chain for serotonin-mediated regulation of BDNF activity, which was improved by simple means such as 30 minutes of walking per day in tumour patients, with fatigue induced by cytotoxic drugs. BDNF values are determined in fatigue patients before and during treatment of cancer.

From the study, a large body of important information is extracted. Elucidation of the role of BDNF in fatigue caused by cancer and treatment with cytotoxic drugs will provide instruments for developing advantageous treatment. Identification of a BDNF-regulated mechanism affecting cell repair after stress and fatigue will enable the patient to select effective treatment, e.g. physical activity for combating tantalizing symptoms and to improve everyday quality of life. Likewise, BDNF-modulating substances and drugs increasing serotonergic modulation must be assessed for positive effects. Finally, individual treatment of fatigue is indispensable, and the ways leading to this goal must be validated.

B2. Nausea

Background

Recommendations are practical tips for the clinical oncologist for assessing prescription of anti-emetics after administration of cytotoxic drugs to the individual patient for the pharmaceutical treatment plan. There are ways to individualize treatment and achieve acceptable control of the symptoms. For treatment optimization, individual cytotoxic drugs and treatment regimens are classified by severity and duration. Clinical experience shows that younger patients suffer more from nausea. By contrast, alcoholics frequently show less marked symptoms. Different persons react differently to food and other environmental influences such as heat and odours.

Nevertheless, patients do suffer from nausea, and there is still a need for further improvement. The mechanisms of nausea and vomiting induced by cytotoxic drugs, which differ from other causes for nausea, remain to be elucidated completely and to be integrated into the drug development process for more effective treatment. The project aims at improving the treatment of nausea with regard to delayed vomiting, for which a proposed mechanism is still to be validated.

Currently, efforts are ongoing to improve treatment of nausea by development of individual drug dosage regimens based on population data for the identification of risk factors. This includes plasma pharmacokinetics of selected drugs relating to treatment of cancer, anthropometric factors such as body weight, alcohol

consumption, smoking and eating habits. Further studies aim at validating, as an alternative to drugs, good measures for the therapy of nausea, such as distraction with music, images and information, and to implement simple clinical guidelines on the basis of the results for different groups. All of the three aspects named above are considered as sub-projects.

Trial design

Further trials are required for improving treatment of nausea in tumour patients. Individual dosage of the recommended drugs must be attempted, and risk factors must be eliminated. The relation between plasma concentration and effects is relatively weak, and optimal concentrations must be determined. Population data based methods identify these, but they also emphasize the relative importance for the individual patient. The results must be prospective validated in clinical trials and then implemented.

In a prospective trial an attempt is made to minimize the validated risk factors, and the new therapy is validated in a randomized, blinded, maybe cross-over trial in a selected patient cohort. An alternative treatment is tested in these selected patients in a later phase of treatment, and a proof of efficacy is required prior to further trials. A definitive goal is condensation of the knowledge into brief guidelines to be introduced into clinical practice, and which offer benefits both for the individual patient and for medical care in the hospital.

Impact of the project

Today, patients suffer from imperfect protection from nausea which impairs their daily life and in some cases make even render them unable to work. Good treatment of nausea prevents further complications such as the very stressful anticipatory vomiting. Both patients and oncological care benefit from the trial results if these are continuously updated and validated.

B 3. Pain in different cultures and influences of ethnicity

Background

Pain is an unpleasant sensation caused by tissue injury or trauma. The perception of pain is transmitted from the tissue to nerve areas in the spine.

In the thalamus, at the base of the cerebrum, the pain impulse is forwarded to centres for spatial association of pain, condensation of memory and experience and also to centres mediating various kinds of psychological states or various kinds of social anxiety. For the same type of pain, description of the perception of pain, its spatial association, its expression and its fluctuations over time are described in rather similar terms by persons from all over the world.

Perception and expression of pain as interpreted in the brain may vary between different cultures and ethnicities. Tradition, education, assumptions and meaning of the pain may influence the behaviour in case of pain. Pain is expressed differently, and other symptoms are expressed as pain. Effects of treatment likewise vary widely due to treatment traditions differing among different cultural and ethical groups. Non-pharmacological treatment may be advantageous, but close monitoring with scanning procedures and surgical interventions may affect the effects of the treatment, as can be seen from a nocebo effect.

Different gene expression in different ethnicities may also exert an influence. This is a new field. Some genetic traits affecting the perception of pain were identified. Differences among metabolic enzymes may likewise exert influence, but are better characterised in various populations.

Experience and approach of the physicians may also be influential. If the presumed needs of the patients are not fulfilled, disappointment and reduced efficacy will result. Intercultural communication problems may affect both the experience of pain soothing and the side effects of treatment. In a first phase, the trials are conducted in the form of a problem-oriented survey. The patients are questioned on the subjects of pain, analgesic treatment and social background as well as experience, perception and expression of pain and analgesic treatment.

The study results are summarised and analysed with regard to measures for improving patient care and further optimization of therapy. In subsequent trials, more special issues concerning individual patient groups or types of pain or treatments, e. g. in cancer, will be investigated.

Impact of the results

Pain is an extremely feared symptom, and patients suffer from impairments in everyday life and the inability to work and have social contacts. Thus it is most valuable fpr oncological patient care, for society and for the patient suffering from pain to have analgesic treatments continuously developed further on the basis of ideas tested in animals and transferred to clinical practice.

Improper treatment of pain may entail enormous costs to society due to sick leave and reduced ability to participate in work and daily social activities. All efforts must be taken to obtain an effective treatment. Communication problems, unmet expectations and differences of drug effects among individual patients must be investigated. The impacts of culture and ethnicity on these problems seem to be tremendous. Hence the study will furnish further information about the cause of the problems, prepare a basis for further actions and contribute to understand patients in other ways.

Conclusion

Within the ESOP, currently there are several research projects in progress, aiming at improving patient care in cancer. Any support will be appreciated. There is both responsibility and advantage in further developing and improving the scientific basis of the activities in oncology pharmaceutical practice. Die scientific basis is the basis for professional competence.

Appendix A

A. Requirements for Drug Manufacturers

Drug manufacturers are an important source of information relating to pharmaceutical products and drugs.

Their obligation pro provide essential information on safe handling (material safety data sheet) and safe application (expert information) must be complemented with further information and in particular also with measures. Partially, there is a considerable backlog, in particular regarding the provisions by the manufacturer for safe handling, which must be supplemented by the oncology pharmacist as well as by the responsible buyer.

Dr. Werner Kittlaus, Pullach

Drug manufacturers are the primary source of information relating to pharmaceutical products and drugs.

Their resulting obligation to provide essential information on safe handling (material safety data sheet) and safe application (expert information) must be complemented with further information and in particular also with measures. If information or measures should be inadequate, they must be demanded from the oncology pharmacist as well as from the responsible buyer. If there is any doubt regarding suitability of the offered product for preparation under the individual conditions in the pharmacy, it is not to be purchased.

The special role of the drug manufacturer or vendor as primary information source arises from the fact that only he knows all the ingredients of the composition, i.e. active substance(s), excipients and packaging, or has, via the producer, direct access to relevant data.

On the one hand, this concerns therapy safety – matters of course such as precision of dosages, correct labelling and batch conformity are supplemented with information on stability and compatibility. If the information provided in the printed documentation is insufficient, information on active ingredient(s) and excipient(s) allow to individually conduct further inquiries. The vendors' home pages must comprise detailed expert information. A F.A.Q.s section should cover the most frequent questions. Links to relevant data bases, technical regulations and recommendations by professional societies allow to quickly retrieve up-to-date information.

On the other hand, workplace safety issues are addressed. Thus, TRHS (Technical Rule for Hazardous Substances) 525 explicitly points out that hazard counseling based on patient information, expert information and material safety data sheets if applicable may be done by pharmacists and physicians. Material safety data sheets must relate to the individual drug, i. e. specifically to the active substance, the pharmaceutical product, the added solvent and the final preparation. Information on recommended cleansing or decontamination agents after contamination of areas or persons in particular must be specific and take into account the chemical/physical properties of of the toxic components. The same applies to information on protective clothing, in particular protective gloves. Specific examples (product, vendor) for protective gloves must be listed (see also 3.1.2. Single-use gloves for protection in the manufacture of cytostatics solutions). Here every manufacturer of cytostatics is requested to make definite statements on suitable protective products for his pharmaceutical products.

In order to be able to provide up-to-date information any time, providing a section «Working and protection materials» on the manufacturer's home page is expedient. Printed information should include the date of creation; use of icons allows for fast comprehension of information (see example). Documentation sheets for download enable the pharmacies to log information on regular manufacture and special events or incidents if applicable and to pass them back to the vendor.

The vendor should implement regulations on handling shipped but damaged goods.

Another point where environment and workplace safety are still far from satisfactory is contamination of primary packaging. In several trials, contamination of primary packaging was demonstrated [1,2,3,6]. None of the manufacturers producing cytostatics on an industrial scale are able to guarantee shipment of uncontaminated primary packaging. The reason is in the formation of aerosol during packing, breakage or dosage errors and subsequent spreading of contamination through the packaging machinery. Several vendors offer protective packaging enabling handling without contact with the primary packaging. This is an important contribution to increasing staff workplace safety [4,5]. Because of responsibility for pharmacy employees and in order to avoid possible claims for damages after suspected harm by occupational exposition, cytostatics concentrates in protective packaging should be preferred.

Cytostatics vendors offering protective packaging allow – according to the present state of the art – contamination-free handling of the vials when preparing cytostatics.

1 Wilken A. Beobachtungen zur Außenkontamination der Primärverpackungen von Zytostatika. Krankenhauspharmazie 1997;18(7):37-9.

2 Hepp R, Gentschew G. Untersuchungen zur Außenkontamination der Primärverpackungen von Zytostatika. Krankenhauspharmazie 1998;19(1):22-7.

3 Delporte JP, Chenoix P, Hubert Ph. Chemical contamination of the primary packaging of 5-Fluorouracil rtu solutions commercially available on the Belgian market. European Hospital Pharmacy 1999;5:119-21.

4 Bokemeyer,C; Schmoll; H.J.; Treatment of testicular cancer and the development of secondary malignancies. J.Clin.Oncol. 13 (1995); S. 283-292

5 Burgaz, S; et.al.: Urinary cyclophosphamid excretion and micronuclei frequencies in peripheral lymphocytes and in exfoliated buccal ephithelial cells of nurses handling antineoplastics. Mutant. Res. 439 (1999), S. 97-104

6 Pethran, A.; et.al.: Untersuchungen einer möglichen Gesundheitsgefährdung durch berufliche Exposition gegenüber Zytostatika (UGEZ). Schlussbericht. Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie, Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege, Bundesunfallkasse, München 1998

Exemplary icon (source: FDA)

Appendix B

B. Return Consignments to the Manufacturer

Remands, e. g. of hazardous drugs, to the manufacturer must be coordinated with the recipient. The packaging must ensure safe transport and withdrawal. The consignment must be labelled in accordance with the legal regulations and marked with the Yellow Hand.

Ludwig Metz, Burglengenfeld

Remands of hazardous drugs to the manufacturer must be coordinated with the latter. Possibly, the manufacturer provides a precise procedure for processing of complaint on his web page. In any case it is necessary to ring up the manufacturer's responsible contact person and settle the details.

Which points relating to the drugs and the procedure, inter alia, need clarification?

- What is complained about?
  Name and batch number, package size, dosage, way of purchase (wholesale etc.)
- Reason for complaint?
- Where is it to be sent to?
  Is it to be returned at all?
- Does the manufacturer offer a return kit with complaints form sheet?
- Is the drug collected by the manufacturer?

After clarification of the aforementioned points, the drug to be returned must be packaged safely by the sender. Tight liquid and solid products, e. g. vials, are packaged into a cardboard box shrink-wrapped twice and concussion-proof. Leaky liquid products should not be returned to the manufacturer, since in handling special precautionary measures are required for sender, transporter and receiver. If the manufacturer should insist, the cytostatic must be packaged safely to exclude any hazard. Moreover, the sender must affix a stamp, address the package correctly and label it in accordance with applicable legal regulations. In addition, cytostatics shipments must be labelled with the Yellow Hand. If quality is complained about, this must likewise be noted on the outside of the parcel so that the manufacturer may forward this as quickly as possible to the competent department to enable immediate processing. Accompanying letters must be attached on the outside.

Appendix C

C. Living Will

In the context of pharmaceutical counseling, the pharmacist may be approached for possibilities how to arrange things in situations when the patient is, e.g. due to old age dementia, illness or handicap, no longer able to decide about his own affairs. The pharmacist should be able to provide contact addresses and suitable examples for a living will.

Barbara Köster, Pinneberg

When the pharmacist is addressed with regard to the above questions, he should emphatically advise the patient to make provisions in due time, namely at a time when the aged or diseased person is still able to arrange effective regulations for the future.

This may be done by a ***health care power of attorney*** as well as by a ***living will***.

A health care power of attorney allows anybody to determine who shall represent him/her in case nursing should be required and how this is to occur, when his/her own affairs can no longer be attended to. With respect to its particularly confidential nature, the health care power of attorney is usually granted to the spouse or a close relative. It can be implemented to be a general power of attorney or a power for specified legal acts only. Basically, a health care power of attorney is effective also without specific form. However, it should absolutely be documented in writing as a probative expression of the individual will with definite instructions (How should the custodian otherwise prove that he has indeed been duly authorized?).

If the power of attorney is intended to extend to real estate transactions, certification by a notary public is mandatory.

Some banks also require presentation of a power of attorney certified by a notary public to be able to ascertain that e.g. in financial transactions a third party is empowered to do this in the name of the patient, and that everything is legally regular. For certification, the notary verifies the identity of the person he is facing.

A ***living will*** serves to document a person's individual desires relating to medical treatment and care in most severe, hopeless illness, particularly in the terminal phase of life. Therein, issues such as refusal of total parenteral nutrition or life-support measures in in case of most severe illness are addressed. Notaries advise about the form in which these statements must be documented and what else must be done to ensure that these statements are recognized in the fullness of time. In particular, the notary shall advise about the consequences of these statements and the best wording of such statements in order to assert the patient's true will. Moreover, the task of the custodians is facilitated, since they know the patient's wishes. As they assume great responsibility, the patient should discuss the contents of the living will with the custodian early enough.

For considerable time there has been a register of authorizations allowing registration of the wills. Prior to appoint a stranger as custodian, the courts of law are obliged to check with this register whether a private statement relating to these issues as been filed. This ensures that the patient will not be confronted all of a sudden with a complete stranger deciding about his affairs. The patient should personally write down the individual powers or wills (manually or using a computer), otherwise it may later be difficult to find out whether the patient has really wanted certain alternatives, since with a form sheet it cannot be excluded that third parties cancel out something if there are alternatives.

Where to get advice?

For reasons of economy, anybody desiring professional service should directly consult a notary, not a lawyer first, since this would double the costs. Certification by a notary is not mandatory but strongly advisable.

Certification by a notary is mandatory if there is real estate which the custodian must manage, e.g. if there is a house to be sold because the person in custody is in the nursing home and needs the money from the sale of the house. The banks likewise demand certification when dispositional to an account a person's identity must be verified.

For a small fee, privately written health care powers of attorney can be registered with the Central Register of Public Notaries in Berlin. Since July 1st, 2004, the courts have been obliged to first enquire there whether the person in question might have deposited a private power of attorney there prior to ordering custody. Privately granted health care power of attorney excludes judicially ordered custody. The address is as follows:

Bundesnotarkammer (National Association of Notaries)
Central register of authorizations
P. O. Box 08 01 51
D-10001 Berlin
phone +49-1805-35 50 50
Email info @ vorsorgeregister.de

Results of the Conference for Standardisation in Oncology Pharmacy, September 2008 in Luxembourg and the continuing Workshop at the 6th EU NZW-Conference in Hamburg, January 2009

1 Technical Aspects

ad 2.1. Working Rooms for Preparation of Cytotoxic Drugs vs Biologicals

The problem still remains how to handle compounds with different classes of toxicity in patient-oriented procedures?

The ideal situation would be the use of an appropriate separate equipment as described previously for:

- Cytotoxic and monoclonal antibody (mab) for cancer patients
- Mab for non cancer patients
- Vaccins (active)
- Gene medicine

Each institution which can not achieve the ideal situation should perform a risk analysis according to the rooms and equipments available, local guidelines and lows comprising the following points must:

- Safety for the product
- Safety for the patient
- Safety for the personal handling the drugs

According to the results, specification of the necessary measures must be established. Examples of measures are listed below.

Cytotoxics and mab for cancer patients

- Cytotoxics and mab for cancer patients can be prepared in the same equipments as described previously.

Mab for non cancer patients

- The first step is to define the toxicity of the mab: some have CMR activities and some have not.
- Mab, which have CMR activities and are used for non cancer patients, should be prepared in a different equipment as the one used for the preparation of cytotoxic drugs.

⇒ If the ideal situation can not be achieved, the mab with CMR activities for non cancer patients can be prepared in the same equipment as the one used for the preparation of cytotoxic drugs. However, specification of the necessary measures must be established such as an appropriate cleaning before and after the preparation.

Vaccines (active)

- Some studies have demonstrated the risk of cross contamination with the use of BCG vaccine and so it is recommended that BCG vaccine is NOT prepared in the same ventilation tool as cytotoxics which will be administered to immuno-compromised patients. The use of one cabinet to prepare cytotoxics and BCG vaccine is not recommended [1].

⇒ If there is no other adequate equipment available, specification of the necessary measures must be established such as:

- The place dedicated to prepare BCG vaccine.
- The required protective material for the preparation.

Gene Medicine

- Cytotoxics and gene medicine must be prepared in different dedicated rooms and equipments.
- Standard operating procedure (SOPs), biosafety cabinets and adequate disposal methods are required for their use [2].
- The guidance on the Pharmacy handing of gene medicines describes the minimum requirements and covers the storage, transportation, preparation, dispensing, administration and disposal of gene medicines, as well as decontamination and accidental exposure procedures for these agents [3].

References:

1. ISOPP Standards of Practice: Section 11-Checking procedures 2007, p52
2. S. Ylä-Hertuala. Principles of gene medicines. EJHP 2007:13;18-19
3. Vulto AG, Stoner N, Balásová H, Cercos AC, Hoppe-Tichy T, Genestar JLV, et al. European Association of Hospital Pharmacist (EAHP): Guidance on the pharmacy handing of gene medicines. EJHP 2007;13:29-39

ad 2.2. Ventilation and Air Conditioning Systems

To address the technical aspects associated with the compounding of cytotoxics, we have to distinguish two categories of sterile drugs:

- Parenterals, prepared with terminal sterilisation
- Parenterals that must be aseptically prepared, because a terminal sterilisation is not possible.

The conditions of preparation and the related standards strictly depend on this classification e.g. the assignement of working procedures to different clean areas. The sterile preparation is considered to be a high risk procedure. Therefore, it is consequent to set the strongest requirements for the preparation of individualized sterile products such as cytotoxics, which are aseptic preparations

Sterile preparations should be carried out in clean dedicated areas. Clean areas for the preparation of sterile products are classified in four grades (A, B, C and D) according to the required characteristics of the environment: a maximum permitted number of airborne particles at rest / in operation and limits for microbiological monitoring in operation for each of the four grades. As sterile filtration and terminal sterilisation of aseptically prepared products e.g. cytotoxics is not feasible, GMP-Guidelines (PIC, EU) recommend for aseptic activities a working environment grade A in combination with a background environment grade B if a LFC/BSC is used.

The discussion about clean areas is often reduced to considerations about the number of airborne particles neglecting the process of preparing individualized parenterals, which is always characterized by intensive manual working. In fact, the personnel himself act as the main risk factor for this type of preparation. Microbiological monitoring close to the product (media fills, contact plates, settle plates, glove prints etc.) is an excellent tool to assess the risk of microbiological contamination and is prefered to the monitoring of airborne particles. As a consequence, focus must be on microbiological validation of aseptic procedures.

The goal for microbiological monitoring of cleans areas in operation should be according to PIC grades A and B. A useful validation-procedure has been proposed (Baumann et al., 2003) with a systematic, standardized media-fill-process regarding aseptic preparation of parenterals in individual dosage. These procedures might demonstrate a high quality level according to GMP demands.

In addition to the proposed method, other methods may be also a valid approach as long as the results obtained are the same and comply with the standard's needs. Guidelines such as PIC recognize that "there are acceptable methods, other than those described in this guide, which are capable of achieving the principles of the guide. The guide is not intended to place any restraint upon the development of alternate systems, new concepts or new technologies, which provide a level of Quality Assurance at least equivalent to those set out in this guide." (PIC/S Chapter A.2)

Reference

Baumann L., Maurer, J.: Retrospective Validierung – Der Schlüssel zur mikrobiologischen Validierung der aseptischen Herstellung Krankenhauspharmazie 2003, 24: 471-479),

ad 3.4.1. Validation of Aseptic Technique and Production Process

The production of cytostatics in a safety cytostatic workbench or isolator is aseptic drug preparation whose production process must be validated. Compliance with the European Pharmacopoeia in respect of agents for parenteral use is mandatory. Validation is only possible through inspection of the entire work process and the circumstances under which production takes place, i.e. the following items must be taken into account:

1. The rooms with respect to air classification, cleaning and hygiene
2. The safety workbench (LAF, laminar air flow) or isolator
3. The work materials
4. The starting materials
5. The aseptic technique
6. The production method
7. The operating staff

Each operator should be individually validated for both aseptic working technique as well as proper compounding (the production method).

Methods for microbiological validation of the rooms and workbench

Microbiological monitoring of the surfaces in the rooms, the air in the rooms and the environment in the workbench should be performed using appropriate methods. Wipes or prints of the surfaces as well as air tests during compounding should be made regularly. These tests should be inspected for micro-organisms capable of reproduction.

Methods for validation of aseptic technique

Microbiological validation of the aseptic technique should be performed using media fills – i.e. the compounding of cytostatics in the workbench must be simulated using an appropriate medium (broth). Each staff member should be validated initially with a simulation of the worst case (i.e. the most complex preparation). The validation must be repeated at least annually, however, the number and frequency of such a procedure should be oriented on the situation in the particular pharmacy. A study protocol needs to be established.

Methods for validation of the production method

Proper compounding should be validated for each staff member using an appropriate simulant that can be quantified in the end product, for example a dye or a fluorescent. Again, the worst case should be simulated. For example, the worst case could be a compounding procedure including a dilution and filtering step, or the compounding of a combination of drugs in a single infusion bag, syringe or pump. The validation should be performed initially and repeated at least annually.

2 Quality Management

Quality Management

If it is not documented, it hasn't happened.

Clear standards need to be set and, ideally, these should be achievable, although in some instances they may need to be aspirational. Once the highest standards are agreed and set, there is a need for constant monitoring arrangements to maintain these standards to preserve and enhance the ability of the oncology pharmacy staff to meet the needs of the cancer patient.

It is the duty of the pharmacy department to ensure that the treatment the patient receives is safe, effective and timely. The products used, whether manufactured, reconstituted or purchased as a licensed product do not place the patient at a higher risk than those inherent to their expected activity. There must be a comprehensive system of quality assurance, which is correctly implemented to ensure standards are maintained. **All processes should be fully documented and their effectiveness monitored and action taken when necessary.**

An approved, comprehensive documentation system must be prepared. Documents within the pharmacy should have a standardised style and presentation. All documents should be clear and detailed and be regularly reviewed at defined intervals. Superseded documents should be identified and retained.

1. Policy

- A mission statement together with a document stating the objectives of the facility must be available.
- A quality policy must be in place.
- Capacity planning is important and a document stating the current capacity and available measures for handling changes in workload must be available.
- A complete quality manual must be available.

- Arrangements must be in place for emergency dispensing.

2. Personnel (refer QUAPOS chapter 1)

All sections in the pharmacy department should have a documented organisational structure (organigram) that clearly indicates the responsibilities and accountability of each member of staff.

A register should be held of those persons qualified to prescribe, including those qualified to prepare and release the completed preparation. Where an electronic prescribing is used, protected passwords should be used.

There should be a named independent quality assurance person for internal audit and also for external audit.

Each member of staff should have an individual training record.

There should be tailored training programme for each member of staff.

There should be regular staff evaluation, and each member of staff should have a development programme.

A capacity plan must be available, and workload figures regularly reviewed against this plan. Action must be taken where appropriate.

Standard Operating Procedures (SOP's)

Training.

Records

Record personnel workload, together with exposure to neoplastic agents
Record accidents and injury at work
Keep absence due to reported sickness records

3. Preparation site. (refer : QUAPOS chapters 2 & 3)

A detailed contingency plan should be available to cover any unforeseen shutdown or suspension of the service.

Standard Operating Procedures (SOP's) for:

Isolator/LAFC cleaning, decontamination and sterilisation
Facilities
Equipment

Records

Operation, cleaning, maintenance and fault logs on facilities and equipment.

Planned preventative maintenance and breakdown maintenance should be recorded.

Environmental records should be maintained and a programme of sessional, daily, weekly, monthly quarterly and annual testing should be in place with all results documented and retained. These should include:

Microbiological: Finger dabs
Settle plates
Surface samples
Active air sample

Physical: Pressure differential between rooms
Pressure differential across HEPA's
Particle counts
Air changes
HEPA filter integrity
Isolator glove integrity
Isolator leak test
Isolator alarm test.

Original construction specifications and validation documents should be retained for inspection.

4. Production and Dispensing (refer QUAPOS 3, 4)

Standard Operating Procedures **SOP's)** for:

Generic substitutions
- Additions and changes to prescription form, paper or electronic
- Approval of addition and changes to prescription form
- Prescription check and verification
- Change or alteration of prescription
- Final check of finished product
- Final check of completed prescription
- Release

Worksheet preparation
- Worksheet check
- Assembly and check of raw materials
- Assembly and check of disposables
- Transfer
- Labels and labelling
- Use of protective clothing
- Entering and leaving clean room.
- Packaging and storage of finished products
- Delivery of the finished products

Spillage
- Training records

Waste
- Packaging etc
- Process waste
  - Re-use
  - Disposal
- Recovered unused preparations
  - Re-use
  - Disposal

Starting materials
- Ordering
- Receipt

Storage
Disposal

Stability and shelf life

Disposables e.g. syringes, needles, gloves, closed-systems, etc.
Processes
Computer software and hardware

Records

A record of all adverse incidents and near missed should be kept and of investigation and actions taken. A summary report should be produced at regular intervals.

A record of all complaints received, from staff, patients or their relatives, should be maintained as well of investigations and action taken. A report should be produced at regular intervals.

5. Clinical Pharmaceutical Support (QUAPOS 4, 5 & 6)

Prescription and final check should made by suitably qualified person
Clinical pharmacy practice should be defined and documented.

Standard Operating Procedures (**SOP's**) for:
Formulary compilation, alterations, additions and removals
Protocols compilation, alterations, additions and removals
Formulary and protocol compliance and report
Clinical trials
Information and counselling

Records

A record of all adverse incidents and near missed should be kept and of investigation and actions taken. A report should be produced at regular intervals.

A record of all complaints received, from staff, patients or their relatives, should be maintained as well of investigations and action taken. A report should be produced at regular intervals.

6. Audits

There should be a named independent quality assurance person for internal audit and also for external audit.

A system of quality assurance should be fully documented and be continually reviewed to ensure agreed standards are maintained.

Internal audits, and audits of any off-site testing must be carried out on a regular basis and deficiencies must be investigated and rectified.

Audits of off-site manufacturers of 'specials' e.g. compounding organisations, must be available.

Audit involving all areas in the above must be undertaken on a regular planned basis. This is to monitor implementation and compliance with the agreed standards.

Audit will involve inspection of facilities and equipment. Detailed examination of documentation, clinical processes, production and quality control measures, validation and training are included. Adverse incidents and complaint records should also be examined, together with recalls.

Observations made during audits should be recorded together with any recommendations for corrective measures. Corrective measures must be reviewed at the next audit, or if serious, as soon as possible.

The audit report should be submitted to the Director of Pharmacy and a timescale agreed to remedy any deficiencies. The final report should submitted to the Chief Executive of the hospital or clinic.

There must be a regular programme of internal audit.

3 Pharmaceutical Care

Pharmaceutical Care

According to the statement adopted by the Council of the International Pharmaceutical Federation (FIP) at its Council meeting in The Hague, The Netherlands on 4th September 1998, pharmaceutical care is defined as followed.

"Pharmaceutical Care is the responsible provision of pharmaco-therapy for the purpose of achieving definite outcomes that improve or maintain a patient's quality of life. It is a collaborative process that aims to prevent or identify and solve medicinal product and health related problems. This is a continuous quality improvement process for the use of medicinal products"

In the field of cancer, ESOP considers that pharmaceutical care is an essential mission of oncology pharmacists and, therefore, is fully included in the treatment plan of cancerous patients.

The goal of pharmaceutical care in oncology is to improve the response to treatment and the quality of life.

To fulfil this mission, the following recommendations should be followed.

1- General recommendations

- Oncology pharmacist is a full member of the multidisciplinary team managing the chemotherapy and supportive care
- Oncology pharmacist has full access to all relevant data to support high level pharmaceutical care.
- European oncology pharmacists strongly support the recommendations from ECCO that all chemotherapies are prescribed according to a previously defined protocol
- Oncology pharmacist insures that chemotherapy prescriptions comply with validated standards such ESMO standards

- Oncology pharmacist assess patient information requirements both for inpatients and outpatients

2- Factors to be considered in care planning for all patients:

- A complete patient drug history is obtained before initiation of therapy
- A particular attention is given to patient with possible compliance issues:
    - Young people
    - Different ethnicities
    - Poor educational level
    - Psychotropic drug users
    - Disabilities: poor vision, dementia…
- Since individual life habits are considered as aggravating factors for poor compliance and/or potential interaction problems such as abuse of psychoactive drugs, cannabis use, alcohol, smoking, abnormal diet, a specific attention is given to patient exhibiting one or several aggravating factors.
- Particular attention is given to problems linked to the transition between IV route and oral route
- Patients with organ dysfunctions (such as renal or hepatic dysfunctions) require specific care such as:
    - Dose ajustement
    - Replacement of initial drugs by alternative drugs
- Particular attention is given to patients taking complementary or alternative medicine (herbal medicine) and complete list of intakes is obtained to assess any potential interactions with prescribed treatments.

3- Factors to be considered in care planning for patients according to their specific situation:

3-1-Patients having received previous chemotherapies:

- Pharmacist reviews both side-effects and related management of the previous course of chemotherapy.

- A careful review of blood tests and relevant complementary examinations are of particular importance before the initiation of the next course.
- Complete information is obtained from patient regarding previous experience with chemotherapy, particularly by collecting data on tolerability, compliance and quality of life.

3-2- Naïve patient:

- Particular attention is given to care planning for patient going to receive the first cycle of the course of chemotherapy.
- Pharmacist insures that prevention of side-effects such as emesis, pain, organ toxicities is covered by adequate supportive therapy.
- Pharmacist verifies that correct dose, route or administration and regimen timing follow the prescribed therapeutic plan.
- Any pharmaceutical problems concerning formulation additives, administering device, and compatibility are avoided.

4 Research and Development

Oncology Pharmacist and Research

Most patients have never met an oncology pharmacist. However, in the eyes of the patients having met one, he/she is another professional informing on treatment, with more focus on global management including co-morbidities (not only cancer) that will increase the patient´s knowledge on treatment and give him/her a feeling of safety to the given drugs.

Oncology pharmacists are often newcomers in clinical research but their achievements may increase quality of cancer treatment, will be time saving and will enable more efficient treatment, as well as a more rational use of resources (money, beds). Dissemination of the project and its results into other departments in other countries will benefit many patients and will give the oncology pharmacist the opportunity for better communication to patients and between professionals

The oncology pharmacist in research must continuously improve her/his knowledge and competence. Further there is a need for quality management of activities using the quality circle e.g. analyze-plan-implement-validate. To withhold the new position, he/she should initiate continuous scientific validation and continue to conduct other scientific studies.

The start of oncology pharmacy research

The prerequisites for conducting active research are to find resources and sponsors. Those can be found among:

- Drug companies
- Governmental funding
- International funding
- Private funding
- Patient organisations

Patient organization

A good way to start collaboration with a selected patient organization in a country is to invite the organization to the National Oncology Pharmacy Meeting and to ask them to give a talk on patient perspectives and expectations from oncology pharmacists. Working connections can be established in a small group for discussions on projects. After finding the resources it is of high value to start early presentations of aims, objective and conduction of a project, both to the patient organization, and to oncology pharmacists around.

Research can be carried in several areas, out of which some are not expensive to conduct

- Literature survey on best treatment (on evidence based treatment)
- Observational studies (on e.g. emesis)
- Focus group studies
- Clinical trials (efficacy and cost benefit)
- Comparative trials carried together with patient organizations around Europe
- (Sophisticated studies – PK-PD)

Research with oncology nurses and other professionals

Local engagement might be very fruitful. Oncology nurses are one category with a similar interest in oncology pharmacy. The steps to achieve a good collaboration and a successful result are as follows:

- Search good relations with local professionals
- Present the idea in seminars to the ward
- Get support for the project in all categories of health professionals
- Get resources for the project
- Present results early in the local hospital
- Present results in a scientific journal
- Disseminate results during conferences
- Start further and continuing studies

There are a number of common interests as:

- Safety in preparing and administration of cytotoxic drugs.
- Support treatment (collaboration with MASCC)
- Analysis and validity guidelines for care plans
- Compliance and adherence to therapy with cytotoxic drugs
- Emesis, pain, fatigue, nutrition surveillance
- Comparative trials on drug therapy
- Information via leaflets - validate
- Monitoring of extravasation
- Treatment suggestions and intervention in drug therapy of the care plan
- Prospective quality assessment

International studies

Internationally there are several organizations that may support research in cancer and cancer treatment. Among those there are:

- ISOPP (research grants, www.isopp.org)
- ECCO
- The suborganisations of ECCO
- International suborganisation (ASCO)
- WHO (international surveys, directed studies)
- EU commission
- (Selected university institutions)

To start with it is important to find a good project which might be fruitful, e.g a project that has a good chance for financial support. You must search international collaborators in the oncology pharmacy community, but also other potential partners who may have beneficial input into the project. The application to the selected founder might be elaborative and should include aim, objectives, ethics, planning, conduction, documentation, agreement, budget planning, etc. Usually some kind of lobbying might be necessary to get funding.

The results must be disseminated in several ways (scientific journals, conferences, EJOP, www.esop.eu etc)

The study design can be the same as on the national level but should be comparative to other countries results. The comparative observational studies can be very valuable for highlighting differences between countries. International funding make also possible formation of platforms for studies on e.g cancer support therapy with several active centres in other countries with different focus.

Benefits to oncology pharmacy

The most important beneficiant of oncology pharmacy research is patient.

However, the oncology pharmacist will also get

- More personal contacts and relations with other professions.
- Increased knowledge and competence (possible PhD-studies)
- Knowledge and interest on the project around the hospital
- Information on oncology pharmacy to others
- Scientific merits to oncology pharmacy and ESOP

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UNITY IN DIVERSITY

The European Society of Oncology Pharmacy

European Society of Oncology Pharmacy (ESOP)

The European Society of Oncology Pharmacy, founded in 2000 in Prague, is the largest organization of oncology pharmacists in the world with a membership of nearly 2000 members from 33 countries. Each country has one vote in the delegate assembly. The ESOP is full member of the European Cancer Organisation (ECCO).

Aim and Objectives

The aim of ESOP is to support optimal treatment for cancer patients.

The objectives are to develop and promote clinical and oncology pharmacy practice through:

1. Education and training,
2. safe handling and administration of drugs,
3. quality management,
4. research and development and
5. pharmaceutical care.

In addition further objective is to make information on knowledge and achievements in cancer treatment and activities available to the public.

Cooperation – The Oncology Team

The pharmacy as coordination Center of Cytostatic Therapy implements the quality management of the oncology pharmacy service and takes responsibilities in patient care and personnel protection regarding all areas of cytostatic therapy.

The pharmacy collects and processes all medical and toxicological data relevant to cytostatics, as well as accompanying and supportive measures if possible. The situation of the oncology patient must be viewed on as a whole. The needs and desires of the patients play an important role in oncology pharmacy and made us aware that focusing on the cytostatic treatment alone was not enough. We realise, that we also need to focus on a variety of other things, such as the appropriate diet, an adequate analgesic medication and the correct anti-emetic scheme. We understand that we cannot ignore the social and psychological problems that the patient may experience by his or her situation.

In view of the fact that financial resources have become limited, it is necessary to intensify our pharmaceutical services in order to increase cost-effectiveness, to help ensuring adequate medical treatment and to prevent quality loss. Thus, we promote the application of the following instruments:

- Epidemiology
- Chronooncology
- Pharmacoeconomy
- Pharmaceutical Care

Our common goals – the Ljubljana Declaration 2006

"The close co-operation between oncology physicians and oncology pharmacists is vital for optimal patient care. The multidisciplinary approach will deliver best practice to patients within a clinical governance framework. Professional, close & timely collaboration will in particular ensure economic use of resources and improved patient safety."

Our goals: Quality Standards, Continuous Education and Certification

Since the first publication in 1996 the fourth edition of Quality Standards for the Oncology Pharmacy Service (QuapoS) – translated into 21 languages – presents the considerable changes which have taken place not only in Germany with respect to the positioning of this service. ESOP has discussed Quality standards on Oncology Pharmacy Service (QuapoS) at three conferences 2001, 2004 and 2008 at the EU-commission in Luxembourg. They are in use as well as to promote the standardisation of national principles and to speak with one single voice in Europe. In some European countries it is possible to obtain certification as "Oncology Pharmacist".

It is not only a logical consequence that certification of the producing pharmacies on the basis of these quality standards is now organized, but it is also a necessary step in order to emphasize to our healthcare partners the capabilities of the pharmacy in the field of oncological therapy.

The beneficiary of these efforts will always be the patient who will surely appreciate.

Specific activities

ESOP yearly invites to a Master Class in oncology pharmacy practice in order to provide continuing education in oncology for interested pharmacists. The demands on oncology pharmacy duties require expertise in cytotoxic drug preparation, handling and administration including risk management. Clinical pharmacy needs ensure them to give patients the best possible care and support. A panel of experienced oncology pharmacists from Europe serves as teachers and supervisors.

Quality communication calls provide news of national activities as well as scientific papers in order to serve the demands for better communication and education. The scientific and information journal of ESOP, European Journal of Oncology Pharmacy (EJOP) have been launched with the mission to satisfy these desires and to open new horizons. The 33 European countries that together form ESOP now get another sharp weapon to fight for more rapid and quality development in oncology pharmacy.

www.esop.eu

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