Guidelines for the Use of Methylene Blue for the Treatment and Prophylaxis of Ifosfamide-Induced Encephalitis

Introduction

Ifosfamide is an alkylating agent used in the treatment of gynaecological, testicular and head and neck cancers, sarcomas and lymphomas. One of the side effects associated with the use of ifosfamide is ifosfamide-induced encephalopathy (IIE).
Some degree of central nervous system toxicity can occur in about 10–30% (mean 12%) of patients after intravenous infusion of ifosfamide. The incidence of CNS toxicity may be increased to 50% after oral administration of ifosfamide because of differences in the preferential route of metabolism between the two routes.

Objectives

The objectives of these guidelines are to promote consistent clinical practice in relation to the use of MB in the treatment of ifosfamide induced encephalopathy.

Scope

This guideline is relevant to:
• Oncology doctors
• Oncology nurses
• Pharmacists
• Other staff involved in the administration of ifosfamide

Guidance

Manifestation of IIE

- Confusion is the most common symptom of IIE, ranging from transient lethargy or increased drowsiness to frank delirium
- Hallucination or psychosis occurs in up to 30% of patients
- Incontinence and muscle twitching are present in about 9% of patients
- Less common manifestations (<5% of patients) include extrapyramidal symptoms, cranial nerve abnormalities, seizures, mutism, dysarthria, amnesia, blurred vision, hearing loss and asterixis
- Time to onset varies between 12-192 hours from the start of the Ifosfamide infusion

Cause and risk factors attributed to development of IIE

Cause:

- The exact mechanism for IIE is not known. Various metabolic pathways have been suggested. The most widely accepted hypothesis is that encephalopathy is caused by one or more of the ifosfamide metabolites, particularly chloroacetaldehyde.

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- Chloroacetaldehyde is produced when ifosfamide (a pro-drug) undergoes hepatic activation. It is capable of crossing the blood-brain barrier. Chloroacetaldehyde and other neurotoxic metabolites of ifosfamide are excreted renally.

Patients with IIE who have subsequently had a CT scan show no focal lesions but EEGs have captured irregular slowing of impulses, which appear to correlate with the grade of IIE (Watkin 1989, Ajithkumar 2007).
Risk factors:
Pre-treatment parameters which increase the risk of severe encephalopathy:

- Low serum albumin (may indicate hepatic insufficiency and increase circulating levels of neurotoxic, protein-bound metabolites of ifosfamide)
- High serum creatinine
- Presence of pelvic disease (may lead to obstructive nephropathy, potentially impairing the clearance of these metabolites)
- Previous cumulative dosages of cisplatin
- Prior CNS disease
- Hypokalaemia
- Hyponatraemia

There is no evidence of dose: toxicity relationship.

Rationale for use of methylene blue

There is little conclusive evidence to support the use of MB in IIE. It is thought to act as an electron acceptor to prevent the formation of chloroacetaldehyde. Without MB treatment, the reported recovery time from encephalopathy ranges from 2 to 29 days. A review of published studies shows that the time to recovery from encephalopathy with MB varies from 10 minutes to 8 days.

Alternative treatments (only to be considered following neurological/ICU review)
The neurological features of ifosfamide are considered akin to Wernicke's encephalopathy. As a result research has suggested intravenous thiamine could be considered as an alternative to methylene blue. Intravenous albumin has also been suggested as a treatment for IIE. Albumin is thought to act by binding chloroacetaldehyde, thereby preventing its entry into the CNS.

Grading of ifosfamide induced encephalopathy
The severity of IIE can be graded using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grading for neurocortical toxicity (Turner et al. 2003.) (see table 1)
Table 1: NCI common toxicity criteria: neurocortical toxicity.

	Grade				
Symptoms	0	1	2	3	4
	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence, agitation, confusion, disorientation, or hallucinations	coma, seizures, toxic psychosis

Treatment of IIE

a) Grade 1 encephalopathy
   Monitor neurological status
   Ensure the ifosfamide infusion is running no faster than 1g/m2/hour
b) Grade 2 encephalopathy
   As for grade 1 and:
   Commence MB 50mg i.v. - 4 hourly.
   Continue MB until encephalopathy has resolved to grade 0.
   Consider prophylactic MB for subsequent cycles of ifosfamide.
   If neurotoxicity deteriorates to >grade 2, discontinue ifosfamide (see below).
c) Grade 3-4 encephalopathy
   Stop ifosfamide infusion (NOTE: mesna should be continued as per protocol even after stopping the ifosfamide infusion)
   Commence MB 50mg i.v. – 4 hourly
   Consider other supportive measures/ITU review
   Monitor neurological status
   Continue MB until encephalopathy has resolved to grade 0

Further treatment with ifosfamide should be avoided.

Prophylaxis of IIE

The use of prophylactic MB should be considered for patients with:

- Patients with previous IIE
- Patients with serum creatinine >150 umol/L or serum albumin <30.
- Administer MB 50mg i.v. 6 hourly for the duration of the ifosfamide infusion.

a) Dose of MB
   Treatment of Ifosfamide-induced encephalopathy:
   Adults: 50mg – 4 hourly
   Children <50kg: 1mg/kg/dose – 4 hourly
   Prophylaxis of Ifosfamide-induced encephalopathy:
   Adults: 50mg – 6 hourly
   Children <50kg: 1mg/kg/dose – 6 hourly
b) Administration of MB
   Either as a slow IV bolus (undiluted) – given over 5 minutes, or in 50ml 5% glucose over 15-30 mins.
   The MB should be filtered before use using a 0.2micron filter
c) Contra-indications

- Glucose-6-phosphate dehydrogenase deficiency
- Pregnancy & Lactation
- Known sensitivity to the drug
- Severe renal impairment (GFR <30mls/min)

d) Side Effects
   Potentially life threatening effects:

- Occasionally: hypotension and cardiac arrhythmias
  Symptomatic Adverse Effects
- I.V. administration may cause abdominal pain, headache, dizziness, tremors, apprehension, confusion, chest pain, dyspnoea, tachycardia, and sweating.
- Nausea, vomiting, diarrhoea, and dysuria have been reported with oral administration
- If MB is injected subcutaneously or extravasation occurs, necrotic abscesses may result
- Blue discolouration of urine, stools and saliva.

e) Drug Interactions
   No significant Interactions have been reported.

f) Monitoring During Treatment
   Standard monitoring of neurological status.

g) Availability
   Methylene Blue is available in the UK as a generic preparation. It comes as 10ml ampoules containing methylthioninium chloride (Proveblue) 5 mg/ml solution for injection

6.0 References

Key reference materials used in the development of this guideline are as follows:

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