

# IFOSFAMIDE INDUCED ENCEPHALOPATHY: PROPHYLAXIS AND THERAPY WITH METHYLENE BLUE.

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## BACKGROUND

Ifosfamide is an alkylating agent effective in young patients affected by sarcoma. Its use is limited due to severe side effects: haemorrhagic cystitis, prevented with mesna; neurotoxicity is currently its worse adverse effect. Hepatic conversion of ifosfamide to chloroacetaldehyde seems to be the main pathophysiologic mechanism responsible for development of ifosfamide induced encephalopathy (IIE). There are sporadic case reports suggesting the use of methylene blue as effective treatment for this dose limiting side effect.

## OBJECTIVES

The aim of the study was to evaluate benefit derived from use of methylene blue (MB) for treatment and prophylaxis of Ifosfamide-Induced-Encephalopathy (IIE) in paediatric and young adult patients.

These subjects are more sensible to a neurologic damage, irreversible in some cases.

## METHODS

We conducted a retrospective analysis of 74 patients (range: 1-25 years), most of which affected by rhabdomyosarcoma (75,67%, 56/74).

Out of these 56, 24 had a parameningeal neoplasia.

Patients were divided into three groups based on methylene blue administration:

- **Group A (36,48%, 27/74):** Primary prophylaxis group;
- **Group B (24,32%, 18/74):** Control group (Methylene Blue not used);
- **Group C (39,19%, 29/74):** Methylene Blue used "on demand", after acute episode of neurotoxicity or as secondary prophylaxis.

All were treated, between 2010 and 2015, with regimen including ifosfamide at an average dose of 9,1 g/cycle.

The 75% of patients were at high risk of developing IIE due to specific comorbidities.

Control group had not same risk factors as other two groups (as shown in Figure 1), and this was the reason why MB was not used.

## RESULTS

- 23% (17/74) of patients developed neurotoxicity Grade 1 or more (NCI-CTC). Toxicity incidence was for each group was: 22,2 % group A; 16,7 % group B; 27,6 % group C.

Comparing the prophylaxis (Group A) and non-prophylaxis (Group C) groups, homogenous for risk factors, there was a difference of 5,4% of incidence of IIE (see Table 1).

- 14/17 (82,35%) were treated with MB at a dose of 3 x 50 mg day-1 intravenously, and all recovered.

- 3/17 (17,65%) patients spontaneously recovered.

- 13/17 (76,47%) patients continued ifosfamide cycles with MB as secondary prophylaxis and didn't manifest other neurologic symptoms.

- Otherwise patients at high risk, prophylactically treated with MB before the beginning of chemotherapy, manifested neurotoxicity of lower grade, compared to patients with same risks but without prophylaxis (see Table 2).

## CONCLUSIONS

Methylene blue is an efficacy and low cost antidote to treat and prevent Ifosfamide-Induced-Encephalopathy in patients at major risk to develop it.

MB has potential use in primary prophylaxis in patient with risk factors for neurotoxicity; it also can be used in secondary prophylaxis and acute treatment. Another important result is that MB enabled our patients to continue further ifosfamide chemotherapy.

Figure 1- Risk Factors & Comorbidities

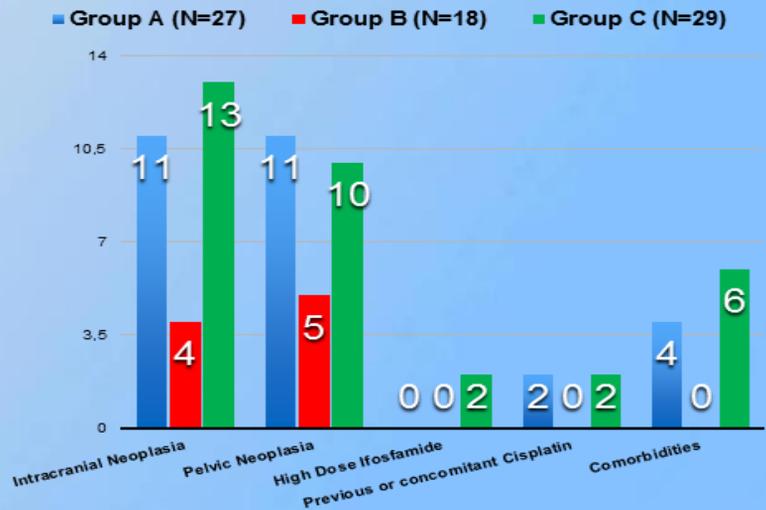


Table 1 - Neurotoxicity cases

	Group A (N=27)	Group B (N=18)	Group C (N=29)	Total Cases	Incidence based on tumour
Pelvic Sarcoma	2	0	1	3	17,65%
Parameningeal Sarcoma	3	3	4	10	58,82%
Other Sarcomas	1	0	3	4	23,53%
<b>Total Cases</b>	<b>6</b>	<b>3</b>	<b>8</b>	<b>17</b>	
<b>Incidence for each group</b>	<b>22,20%</b>	<b>16,7%</b>	<b>27,5%</b>		

Table 2 – Number of case/Severity of IIE related to each group

	Group A (N=27)	Group B (N=18)	Group C (N=29)	TOTAL
<b>Grade 1</b>	4	2	1	7
<b>Grade 2</b>	2	1	4	7
<b>Grade 3</b>	0	0	1	1
<b>Grade 4</b>	0	0	2	2
<b>TOTAL</b>	<b>6</b>	<b>3</b>	<b>8</b>	<b>17</b>