

Treatment and prophylaxis of ifosfamide-induced encephalopathy with intravenous methylene blue

To the Editor:

A 20-year-old woman was diagnosed in April 2000 with a low-grade intraabdominal leiomyosarcoma. The tumour was surgically resected. In June 2002, she presented with progressive disease in lung, liver and unresectable multiple implants in peritoneum. c-Kit (CD117) was immunohistochemically assessed in the initial surgical sample, with results negative. She received six cycles of doxorubicin iv (50 mg/m² day 1, every 21 days) plus ifosfamide iv (2 g/m² over 1 hour infusion, on days 1-3, every 21 days), with a stabilization of the tumour lesions. In March 2003, the patient presented disease progressed again with weight loss and refractory ascites. High doses ifosfamide was initiated (12 g/m² iv, over 24 hours infusion, on days 1-5, every 21 days). Antiemetic prophylaxis consisted of 8 mg iv of ondansetron prior to chemotherapy. She did not receive another drugs.

About 24 hours after the beginning of the second cycle infusion, she became agitated, confused and somnolence, with incoherence and disorientation (neurocortical toxicity grade 3 of National Cancer Institute-Common Toxicity Criteria). Peripheral blood counts and smear, electrolytes, globulin, bilirubin (total and direct), alkaline phosphatase, SGPT, SGOT and prothrombin were normal. Creatinine clearance was 60 ml/min and serum albumin 2.8 g/dl. Computed tomographic studies of the brain were normal. Electroencephalography showed diffuse slowness consistent with metabolic encephalopathy.

50 mg iv methylene blue (MB) was administered immediately to the patient, and repeated every six

hours. One day later the signs of encephalopathy disappeared. Our patient received prophylactic intravenous with MB in a dose of 50 mg four times daily for the next cycles, and no further episode of neurological toxicity was noted.

Ifosfamide is an alkylating agent used in the treatment of many solid tumors, including soft-tissue sarcomas. Its toxicity profile is characterized by myelosuppression and urotoxicity. Ifosfamide is relatively well tolerated, but has been responsible for life-threatening toxicities such as ifosfamide-induced encephalopathy (IIE)¹. This syndrome develops in 10 to 15% of patients exposed to the drug and usually disappears after stopping therapy, although some patients die without recovery².

It occurs more frequently when the drug is given at intravenous high doses with short infusion time, and in patients with poor performance status, low serum albumin and creatinine clearance³. No cumulative-dose neurotoxic effects have been reported, but re-treatment may again precipitate the same acute toxicity manifestations. The clinical picture can range from mild somnolence or agitation over confusion or hallucinations to deep coma and even the death¹.

The exact mechanisms of IIE are unknown, but one or more metabolites of ifosfamide that are in high quantities may be the cause of the toxicity. Chloroethylamine may be the principal neurotoxic metabolite involved. Chloroethylamine conjugates with cysteine forming thialysine which can be metabolized to thialysine ketimine. The latter can inhibit the electron-binding flavoproteins in the mitochondrial respiratory chain with loss of energy production⁴. The inhibition of mitochondrial respiration

may also lead to a disturbance of the intracellular NAD/NADH balance with the accumulation of NADH that avoid the dehydrogenation of aldehydes with accumulation of chloroacetaldehyde, a potential neurotoxic substance. Another important mechanism is mediated by monoamine oxidation in the extrahepatic tissues and in plasma by which chloroacetaldehyde can be formed⁵.

The experience in the management of this toxicity is limited. Previous reports confirm that methylene blue (MB) may be useful in the treatment and prophylaxis of IIE^{2-4, 6}. Several sites of action have been proposed for MB: substitute for electron transport flavoprotein enzyme, restoration of hepatic NADH oxidative function, and inhibition of extrahepatic mono-amine oxidation of chlorethylamine to chloroacetaldehyde⁷.

We describe our experience of this potential neurological toxicity due to the possible fatal outcome in some cases. In our patient, medications history was taken, and she was not taking others drugs that had possible interactions with IFOS. Brain involvement due to disease was ruled out. CNS toxicity occurred while the patient was receiving active treatment with IFOS, and the symptoms exhibited were consistent with IIE. She benefited from using MB for acute treatment. When the patient was pre-treated with MB before receiving further IFOS, the toxicity was absent compared with the previous episodes.

As a conclusion, several recommendations must be done to prophylaxis and acute treatment of this syndrome. First, physicians prescribing ifosfamide, especially in high doses, should monitor carefully patients for early signs of toxicity in order to discontinue ifosfamide administration soon enough to avoid development of mayor toxicity. Second, high risk patients should be considered to be those with creatinine levels of greater than 1.5 mg/dl or serum albumin levels of less than 3 g/dl or both, and the risks and benefits of administration of the drug should be judged accordingly. Third, MB prophylaxis at dose of 50 mg iv diluted in 100 ml of normal saline in 10 minute infusion every six hours, may be enable in previously affects patients to continue this treatment. Fourth, MB is the choice treatment for IIE until resolution or a significant improvement of symptoms is achived. MB administration does not affect IFO pharmacocinetics. Thiamin (100 mg at

same schedule that MB) may be reserved as a second therapeutic option in case a patient's condition would not improve under MB⁸.

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