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Encephalopathy after High-Dose Ifosfamide

A Retrospective Cohort Study and Review of the Literature

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Abstract

Background: Encephalopathy occurs in 10–40% of patients treated with high-dose ifosfamide. Proposed risk factors for encephalopathy include hepatic or renal dysfunction, brain metastases, electrolyte imbalances and drug-drug interactions.

Objective: The purpose of this retrospective cohort study and literature review was to estimate the prevalence of encephalopathy, identify characteristics associated with encephalopathy and evaluate the effectiveness of methylthioninium chloride (methylene blue) in its prevention.

Study design and methods: A total of 19 patients received high-dose ifosfamide for soft tissue sarcoma during a 4-year period at our medical centre. Eight patients developed encephalopathy based on adverse drug event (ADE) reports submitted by a clinical pharmacist. These reports incorporate the Naranjo probability scale, which is used to assess the likelihood that a change in clinical status is the result of an ADE rather than the result of other factors, such as progression of disease. The demographics, concurrent medication therapy, co-existing illnesses and laboratory parameters were documented from the medical records. We also conducted a review of the literature by searching MEDLINE (1996–October 2007).

Main outcome and results: A total of 19 patients received high-dose ifosfamide; eight patients experienced encephalopathy (group I, 42%) and 11 patients did not experience encephalopathy (group II, 58%). More women than men developed encephalopathy (group I, 87.5% vs group II, 27.3%). Serum albumin (group I, 3.1 ± 0.3 vs group II, 3.6 ± 0.3 g/dL), haemoglobin (10.5 ± 1.5 vs 12.4 ± 1.7 g/dL) and total bilirubin (0.5 ± 0.2 vs 0.8 ± 0.3 mg/dL) levels were substantially lower in patients with encephalopathy, whereas the ratio of actual bodyweight to the ideal bodyweight (1.4 ± 0.3 vs 1.1 ± 0.2) was substantially higher in these patients. Five (62.5%) patients received a subsequent cycle of high-dose ifosfamide; all of these patients received methylthioninium chloride to minimize the risk of encephalopathy. All of these patients developed encephalopathy. Other reports have found that hypoalbuminaemia is associated with encephalopathy and that methylthioninium chloride does not prevent ifosfamide-induced encephalopathy.

Conclusions: In summary, female sex, low total bilirubin, albumin and haemoglobin levels, and obesity appear to be associated with ifosfamide-induced encephalopathy. Methylthioninium chloride did not appear to prevent encephalopathy with subsequent doses of high-dose ifosfamide.

Background

Ifosfamide is an akylating agent used to treatment many solid tumours, including soft tissue sarcomas. However, its use is limited by the onset of encephalopathy, which develops in 10–40% of patients receiving high-dose ifosfamide.[1-3] The symptoms associated with the encephalopathy include confusion, stupor, seizures, hallucinations and blurred vision. The encephalopathy typically develops within 12–146 hours of starting ifosfamide and wanes within 48–72 hours of discontinuing the drug. However, some reports indicate a much more prolonged duration.[4-6] Serious, long-term outcomes rarely occur, but include coma and death.[7] Management includes discontinuing ifosfamide, monitoring by electroencephalogram and administering benzodiazepines or haloperidol. Methylthioninium chloride (methylene blue) can also be administered to treat the encephalopathy.[8,9] It is unclear if it improves outcomes, since the encephalopathy can spontaneously resolve upon stopping the drug. Methylthioninium chloride may also be administered with subsequent doses of ifosfamide to decrease the risk of encephalopathy; however, it is also unclear if this reduces the risk of encephalopathy.[6,10,11]

Ifosfamide is a racemic mixture that undergoes stereoselective and regioselective metabolism with <20% of the parent drug excreted unchanged.[12,13] It undergoes detoxification in the liver by cytochrome P450 (CYP) 3A4 and CYP2B6 to form several dechloroethylated metabolites (as well as several active metabolites).[13-15] These dechloroethylated metabolites undergo further metabolism to form chloroacetylaldehyde, which is structurally related to chloral hydrate and acetaldehyde and appears to be associated with the development of the encephalopathy.[14,16,17] Proposed predisposing factors for encephalopathy include hepatic or renal dysfunction, brain metastases, pelvic disease, electrolyte imbalances and drug-drug interactions;[11,18-22] these factors could affect the production or elimination of the dechloroethylated metabolites.[17] Other potential risk factors include an oral dosage regimen and short infusion times, although a clear dose-toxicity relationship has not been identified.[23,24] Some factors demonstrating a statistically significant relationship with encephalopathy are hypoalbuminaemia, pelvic disease (secondary to urinary obstruction) and renal dysfunction.[1-3]

Although the encephalopathy is often readily reversible, rare but serious complications can persist. Since high-dose ifosfamide remains an integral part of treatment for sarcomas and other solid tumours, the development of encephalopathy substantially limits the treatment options for these patient populations and, therefore, negatively impacts their long-term outcomes. In this paper, we identify several possible risk factors for ifosfamide-induced encephalopathy by comparing the characteristics of patients with and without encephalopathy. We also evaluate whether the use of methylthioninium chloride prevented ifosfamide-induced encephalopathy with additional ifosfamide administration following the development of encephalopathy, and provide a review of the literature regarding the risk factors for ifosfamide-induced encephalopathy. We anticipate confirming the predictive value of these possible risk factors in a prospective study.

Methods

A total of eight patients at the University of Illinois Medical Center at Chicago (Chicago, IL, USA) diagnosed with soft tissue sarcoma developed encephalopathy following high-dose ifosfamide from January 2000 to December 2004 (group I, patients with encephalopathy). These patients were identified by reviewing the adverse drug event (ADE) reports; these reports are completed by a clinical pharmacist and are based on the Naranjo probability scale. The medication administration records at the Medical Center were then reviewed to identify all adult patients who received high-dose ifosfamide for soft tissue sarcomas during this same time period. The medical records of all these patients were then studied retrospectively to identify those patients who did not develop encephalopathy. Eleven patients were identified (group II, patients without encephalopathy). Data were reviewed and extracted for patients from cycle one of high-dose ifosfamide until they stopped chemotherapy, including demographics, concurrent medications, co-existing illnesses and laboratory parameters (e.g. comprehensive metabolic profile, complete blood count with differential and hepatic function tests). The

encephalopathy was graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (v3.0). The University of Illinois at Chicago (UIC) Cancer Center Protocol Review Committee and the Institutional Review Board at the UIC approved the study. The mean ± standard deviation is reported for continuous data and number and percentages are reported for categorical data.

Results

A total of 19 patients received high-dose ifosfamide for soft tissue sarcoma; eight patients experienced encephalopathy (group I, 42%) and 11 patients did not experience encephalopathy (group II, 58%) [table I]. The ADE reports, which all incorporate the Naranjo probability scale, indicated that the encephalopathy was probably associated with ifosfamide and not due to other medications or medical conditions. Two patients received prior treatment with high-dose ifosfamide (one in group I and one group II). The median individual ifosfamide dose was 2.0 g/m^2 (range, 1.0–2.5 g/m^2) over 1–2 hours every 12 hours for 3–5 days. For two patients with encephalopathy, the infusion time was increased to 24 hours for all subsequent doses. The patients with encephalopathy received about 62% ± 22% of the planned doses, whereas the patients without encephalopathy received about 82% ± 38%. These estimates refer to the entire treatment course, including doses received after the onset of the encephalopathy.

Table I. Study population

Demographic	Patients with encephalopathy (group I) [n = 8]	Patients without encephalopathy (group II) [n = 11]
Age (years [mean ± SD])	43.4 ± 12.0	42.1 ± 19.4
Sex [n (%)]		
men	1 (12.5)	8 (72.7)
women	7 (87.5)	3 (27.3)
Race/ethnicity [n (%)]		
White	5 (62.5)	5 (45.5)
Black	3 (37.5)	4 (36.4)
Hispanic		2 (18.2)
Anthropomorphics (mean ± SD)		
mean height (cm)	165.7 ± 6.5	173.2 ± 8.7
ABW (kg)	79.5 ± 17.9	74.6 ± 14.5
IBW (kg)	58.2 ± 5.6	67.5 ± 8.9
ABW : IBW ratio	1.4 ± 0.3	1.1 ± 0.2
body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2
Stage of disease [n (%)]		
1	2 (25)	5 (45)
2	2 (25)	
4	4 (50)	6 (55)
Previous treatment [n (%)]		
surgery	7 (87.5)	9 (81.8)
chemotherapy	1 (12.5)	2 (18.8)
radiation		3 (27.3)

ABW = actual bodyweight; **IBW** = ideal bodyweight; **SD** = standard deviation.

The symptoms associated with the encephalopathy are summarized in table II. The patients with encephalopathy experienced grade 2 (25%) or 3 (75%) encephalopathy. The symptoms subsided within 3 days with the mean duration of ~1.75 days. Five patients experienced more than one episode of encephalopathy, because they received at least one subsequent cycle of ifosfamide. Most patients developed encephalopathy during cycle one or two. However, three patients did not develop encephalopathy until later (cycle three, n = 2 and cycle five, n = 1). The average cumulative dose from the start of treatment to the development of encephalopathy was 18.5 g (range 8–39 g) for the patients who developed the encephalopathy after cycle one or two and 56 g (range, 46.2–65 g) for patients who developed the encephalopathy after receiving a minimum of three cycles. A helical computed tomography scan was completed in three of the eight patients with encephalopathy; the impression from these scans indicated normal appearance of the brain and head.

The management of the encephalopathy included discontinuing ifosfamide, altering the subsequent infusion schedule and/or the administration of methylthioninium chloride. Ifosfamide was stopped for all eight patients and methylthioninium chloride was administered to five of these eight patients (62.5%) at doses of 50 mg four to six times daily as an intravenous bolus. The number of doses ranged from 3 to 21 with most patients receiving three doses; the total number of doses could not be verified for two patients. As stated earlier, the mean duration of symptoms was ~1.75 days; the duration of symptoms was similar between the three patients who did not receive methylthioninium chloride

Table II. Neurological symptoms reported for patients with encephalopathy

Description of encephalopathy	Number (%)
Confusion/agitation/delirium	7 (87.5)
Lethargy/somnolence	5 (62.5)
Psychiatric disturbances	4 (50.0)
Muscle twitching/tremor	3 (37.5)
Hallucinations	2 (25.0)
Incontinence	1 (12.5)

(~1 day) and the five patients who received methylthioninium chloride (~2.2 days). Five patients received additional cycles of chemotherapy that included ifosfamide. The dose was reduced for one of these five patients and the infusion schedule was changed for two of these five patients (from fractionated to continuous infusion). These five patients received methylthioninium chloride to minimize the risk of encephalopathy with the subsequent doses of high-dose ifosfamide. Encephalopathy recurred in all of these patients despite receiving multiple doses of methylthioninium chloride.

More women developed encephalopathy compared with men (87.5%). The mean ideal bodyweight (IBW) was substantially lower and the ratio of the actual bodyweight (ABW) to the IBW was substantially higher in the patients who developed encephalopathy. The mean total bilirubin was lower in the patients with encephalopathy (table III and figure 1a). Similarly, the albumin and the haemoglobin levels were lower in these patients (figures 1b, 1c and table III). No other laboratory parameters demonstrated substantial differences between the patients with and without ifosfamide-induced encephalopathy, including the liver transaminases.

The average change in total bilirubin was less and the average change in the white blood cell counts was greater during ifosfamide treatment in patients with encephalopathy than in patients without encephalopathy from baseline to the last dose of ifosfamide administered immediately before the onset of encephalopathy (table III). The mean change in other laboratory parameters did not appear to be substantially different. No differences in other toxicities, including haematological, gastrointestinal, urological toxicities or rates of infection, were observed.

Discussion and Review of the Literature

Eight of our patients developed ifosfamide-induced encephalopathy; the prevalence of encephalopathy in our population is consistent with previous reports that indicated that encephalopathy develops in 10–40% of patients following intravenous administration of high-dose ifosfamide.[1-3] Proposed risk factors for encephalopathy include hepatic or renal dysfunction, pelvic disease, brain metastases, electrolyte imbalances and drug-drug interactions.[11,18-22] Brunello et al.[25] suggests that elderly patients may be at increased risk for ifos-

Table III. Laboratory parameters measured at baseline and after stopping treatment for patients with and without encephalopathy

Parameter	Patients with encephalopathy (group I) [n = 8]	Patients without encephalopathy (group II) [n = 11]
Baseline laboratory parameters (mean ± SD)		
Sodium (mmol/L)	138.6 ± 1.7	139.4 ± 2.1
Potassium (mmol/L)	4.0 ± 0.5	4.1 ± 0.3
Chloride (mmol/L)	103.9 ± 3.1	105.1 ± 3.1
Bicarbonate (mmol/L)	27.5 ± 3.0	27.5 ± 2.3
Blood urea nitrogen (mg/dL)	10.4 ± 5.2	9.7 ± 3.8
Creatinine (mg/dL)	0.9 ± 0.5	0.9 ± 0.2
Glucose (mg/dL)	139.5 ± 44.9	101.6 ± 28.7
Calcium (mg/dL)	8.8 ± 0.5	9.0 ± 0.5
Phosphate (mg/dL)	3.7 ± 0.5	3.1 ± 0.8
Magnesium (mg/dL)	2.1 ± 0.2	2.1 ± 0.1
Total bilirubin (mg/dL)	0.5 ± 0.2	0.8 ± 0.3
AST (u/L)	21.1 ± 11.8	17.7 ± 3.3
ALT (u/L)	25.9 ± 28.2	16.7 ± 6.4
Albumin (g/dL)	3.1 ± 0.3	3.6 ± 0.6
White blood cell count ($\times 10^3/\mu L$)	11.4 ± 5.5	6.3 ± 1.6
Absolute neutrophil count ($\times 10^3/\mu L$)	8.6 ± 5.0	4.0 ± 1.2
Haemoglobin (g/dL)	10.5 ± 1.5	12.4 ± 1.7
Haematocrit (%)	31.3 ± 4.4	37.0 ± 5.0
Platelets ($\times 10^3/\mu L$)	317.9 ± 84.2	284.7 ± 90.7
Fluctuation in laboratory parameters[a] (mean ± SD)		
Serum creatinine (mg/dL)	0.19 ± 0.25	–0.02 ± 0.11
Total bilirubin (mg/dL)	0.05 ± 0.53	–0.45 ± 0.50
White blood cell count ($\times 10^3/\mu L$)	–7.1 ± 3.0	–3.0 ± 2.7

a These values represent the difference between the baseline laboratory value and the highest or lowest value achieved for the listed parameters when treatment was stopped.

SD = standard deviation.

famide-related encephalopathy secondary to the increased likelihood of dehydration, impaired renal function and hypoalbuminaemia in older adults. However, previous retrospective studies or case reports that included 20–200 patients only identified hypoalbuminaemia, poor performance status, pelvic disease and renal dysfunction as statistically different between patients experiencing encephalopathy and those not.[1-3] Goren et al.[16] proposes that pelvic disease increases the risk of encephalopathy by obstructing the urinary tract and minimizing the renal elimination of ifosfamide and its metabolites. We did not find a difference in renal dysfunction or pelvic disease. Unfortunately, performance status was not documented in the medical record for most of the patients included in this study; we did not feel it was appropriate to estimate performance status based on the information documented in the medical record. Therefore, we did not compare performance status between the patients with and without encephalopathy. Risk factors we identified included hypoalbuminaemia, anaemia and reduced total bilirubin at baseline, and increased total bilirubin and decreased white blood cell count from baseline to completion of treatment.

Serum albumin levels were substantially lower in the patients with encephalopathy. Hypoalbuminaemia has been identified as a risk factor for encephalopathy in previous case reports.[6,18] The investigators of these reports proposed that hypoalbuminaemia reflects impaired hepatic function and implied that less ifosfamide undergoes metabolism to its dechloroethylated metabolites. However, ifosfamide undergoes both bioactivation and detoxification by the same hepatic enzymes;[14,15,26] if patients who develop encephalopathy also had impaired hepatic metabolism, it would suggest that these patients may also have reduced response to ifosfamide. Additionally, hepatic impairment does not affect the pharmacokinetics of intravenous ifosfamide and no dose modifications are recommended for patients with hepatic impairment.[27] However, more than 80% of ifosfamide is bound to albumin; therefore, patients with hypoalbuminaemia should have higher plasma concentrations of the parent drug. The additional parent drug would be subsequently broken down to its neurotoxic and other metabolites; these metabolites can freely cross the blood-brain barrier into the brain and cause encephalopathy.[27] Of note in the current study, hepatic function, as measured by serum aminotransaminase levels, at baseline and completion of treatment were similar between the two groups.

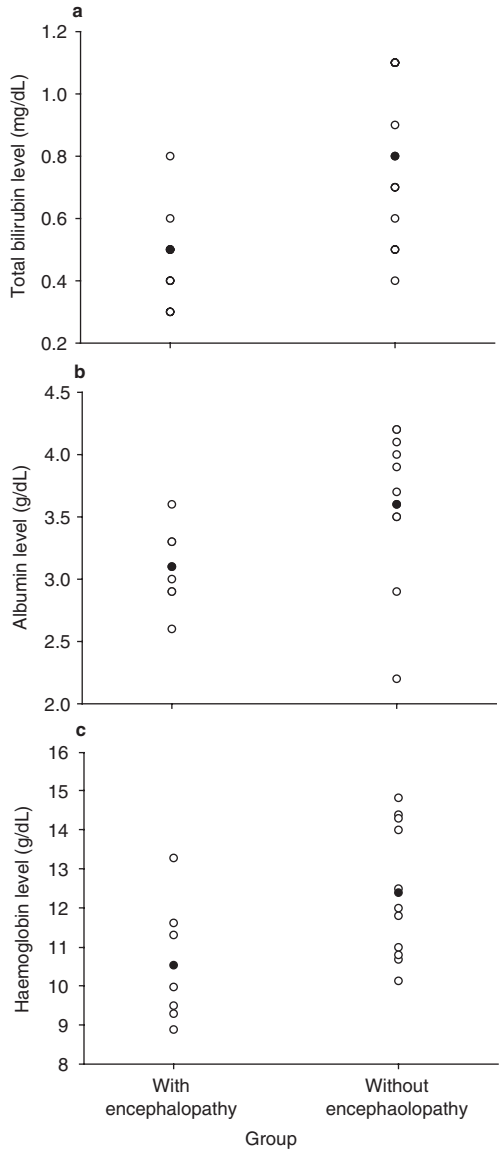

Fig. 1. Pretreatment total bilirubin (**a**), pretreatment albumin (**b**) and pretreatment total haemoglobin (**c**) levels in patients with and without ifosfamide-induced encephalopathy (group I and II, respectively). Each open circle represents one patient and the closed circle represents the mean value.

Baseline total bilirubin levels were lower in patients with encephalopathy and the average change in total bilirubin levels, from baseline to the last dose of ifosfamide, was greater in patients without encephalopathy; however, the mean total bilirubin for patients with and without encephalopathy were both within the reference interval permitting the suggestion that this difference is not clinically relevant. No previous reports have identified an association between total bilirubin and encephalopathy. The main causes of hypobilirubinaemia include hypoproliferative anaemia, malignant neoplasia and end-stage renal disease. The relationship between ifosfamide metabolism or disposition and hypobilirubinaemia is unclear at this time.

Haemoglobin levels were also substantially lower in patients with encephalopathy; no previous case reports have identified a correlation between red blood cell indices and encephalopathy. Erythrocytes have been proposed to act as transporters of the active metabolites, ifosforamide mustard or 4-hydroxyifosfamide.[27,28] The concentration of ifosfamide and these metabolites appears to be higher in erythrocytes than in plasma, with the erythrocytes responsible for the delivery of these metabolites to various tissues. We propose that patients with anaemia have fewer erythrocytes to transport these metabolites, which leads to higher concentrations of these metabolites in the plasma. The higher concentrations would saturate the bioactivation of ifosfamide and promote greater detoxification. *In vitro* studies are needed to further explore the relationship between drug transport and metabolism.

Other possible risk factors we identified included sex and weight. In our population, more women developed encephalopathy; this risk factor has not been identified in other reports. However, one *in vitro* study found ifosfamide underwent more dechloroethylation in liver microsomes isolated from women than in those isolated from men.[29] This study suggests that sex-related differences in ifosfamide dechloroethylation exist, and women are at a higher risk of developing encephalopathy. The ratio of ABW to IBW was also substantially higher in patients with encephalopathy. However, since more women developed encephalopathy than men, and women, in general, tend to have a higher fat to muscle ratio than men, we believe these risk factors are most likely not independent of one another. Of note, the dose calculated for most chemotherapy agents, including ifosfamide, is based on body surface area (BSA). Although the BSA was similar between the two groups, the IBW was substantially lower and the ratio of the ABW to the IBW was substantially higher in the patients who developed encephalopathy. It appears that dose administration based on IBW or ABW may be more appropriate for obese patients, since the volume of distribution of ifosfamide approximates total body water[10] and the body composition is altered in obese patients with less total body water than fat tissue. However, a pharmacokinetic-pharmacodynamic study designed to measure serum or urinary metabolites is warranted before alternative dose administration calculations can be recommended in obese patients. Other studies did not identify this risk factor; however, weight as a covariate improves the predictive errors of population pharmacokinetic models for ifosfamide.[30,31]

Ifosfamide may be administered as continuous infusion or fractionated dose. A shorter infusion is a predisposing factor for encephalopathy, but this regimen provides a higher response rate than continuous infusion.[32-34] In our population, most patients received fractionated doses of ifosfamide. However, two patients who developed encephalopathy received a continuous infusion for subsequent cycles after developing encephalopathy and still experienced similar symptoms with the subsequent doses. Too few patients initially received a continuous infusion to assess if this schedule influenced the prevalence of the encephalopathy.

Ifosfamide was immediately stopped for the patients with encephalopathy. Methylthioninium chloride was administered to five of these patients as treatment. Encephalopathy resolved within 48–72 hours of discontinuing ifosfamide. It is unclear if the encephalopathy resolved independently of methylthioninium chloride treatment. Additionally, these five patients received subsequent doses of high-dose ifosfamide with methylthioninium chloride and still developed encephalopathy. Case reports describing the management of ifosfamide-induced encephalopathy include about 14 patients treated with methylthioninium chloride.[8,35-40] It is unclear in these reports if the patients received mesna; however, these

reports demonstrate minimal benefit with methylthioninium chloride. The recovery time ranged up to 72 hours and the encephalopathy occurred with subsequent doses of ifosfamide administered with methylthioninium chloride. The findings in our study are similar. These data suggest that methylthioninium chloride is not effective for the prevention of ifosfamide-induced encephalopathy. No other pharmacological interventions have been found to minimize the risk of ifosfamide-induced encephalopathy; however, pre-clinical or *in vitro* studies are currently being conducted to examine the effectiveness of glucose supplementation, thiamine and pyridoxine.[41]

Previous reports have identified predisposing factors for ifosfamide encephalopathy, but the prevalence of encephalopathy remains high in those patients without identifiable risk factors. Although our study identified several possible risk factors and supports the association between hypoalbuminaemia and encephalopathy, our findings are limited by the small number of patients included in the study and our analysis should be considered exploratory. Other limitations include the retrospective study design and other inherent flaws associated with these studies. Methylthioninium chloride did not minimize the risk of encephalopathy with subsequent doses in our patients.

Conclusion

Female sex, low total bilirubin, albumin and haemoglobin levels, and obesity appear to be associated with ifosfamide-induced encephalopathy. Methylthioninium chloride did not appear to prevent encephalopathy with subsequent doses of high-dose ifosfamide.

A prospective study evaluating the benefit of methylthioninium chloride is needed to clearly determine if this drug minimizes the risk of encephalopathy. Alternatively, different regimens that do not include high-dose ifosfamide are warranted to manage sarcoma for patients who cannot tolerate ifosfamide because of encephalopathy or other serious adverse events. We anticipate conducting a prospective study to determine the predictive value of the potential risk factors identified in our study and literature.

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