Ifosfamide Neurotoxicity in Pediatric Patients: A Multi-Institutional Case Series Report

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**Background:** Ifosfamide is a frequently used nitrogen mustard chemotherapeutic alkylating agent that is available commercially in either an aqueous or powder formulation. Documented toxicities related to ifosfamide include a unique neurotoxicity that has been associated with hypalbuminemia, previous or concurrent administration of other neurotoxic agents, and renal dysfunction. Although data regarding ifosfamide neurotoxicity are available in adult medical oncology literature, studies regarding pediatric neurotoxicity are limited.

**Objective:** To review the clinical and pharmacologic characteristics of ifosfamide-induced neurotoxicity associated with the use of aqueous ifosfamide in pediatric patients.

**Methods:** Retrospective chart review was used to identify cases of ifosfamide-induced encephalopathy at 5 pediatric oncology centers.

**Results:** This multi-institutional case series evaluates 13 pediatric cases of ifosfamide-induced encephalopathy. The patients exhibited confusion, lethargy, aphasia, incontinence, and auditory hallucinations. Less than half of the patients had hypalbuminemia, and none had renal dysfunction at the onset of neurotoxicity that was associated with ifosfamide administration. Three patients had previous exposure to cisplatin. New anecdotal evidence presented in this study suggests that the aqueous formulation of ifosfamide may be associated with higher incidence of neurotoxicity than the powder formulation. A total of 5 patients were rechallenged with the powder formulation, without recurrence of neurotoxicity.

**Conclusion:** Our observation lends credence to the clinical opinion that the aqueous formulation of ifosfamide may be a risk factor for neurotoxicity.
Ifosfamide Neurotoxicity in Pediatric Patients

Methods
This retrospective chart review of patients diagnosed with ifosfamide-induced neurotoxicity was conducted at 5 pediatric oncology centers—Children’s Hospital of Alabama, Birmingham; Wolfson Children's Hospital, Jacksonville, FL; Sacred Heart Children's Hospital, Pensacola, FL; Florida Hospital, Orlando; and University of Kansas Hospital, Kansas City. Pertinent data reviewed for this study included patient age, diagnosis, treatment regimen, ifosfamide dose and formulation, description of neurotoxicity symptoms, concurrent use of aprepitant, cisplatin exposure, serum albumin levels, serum creatinine, and the use of methylene blue, an electron acceptor.

Results
We reviewed 13 cases of ifosfamide-induced neurotoxicity in children and teens aged 4 to 19 years who were diagnosed between 2002 and 2010 (Table). The predominant diagnosis was sarcoma (N = 11), although 2 other patients received ifosfamide as therapy for pre-B-cell acute lymphocytic leukemia (ALL) and primitive neuroectodermal tumor. All patients initially received the aqueous formulation of ifosfamide.

Daily dosages of ifosfamide ranged from 1.8 g/m² per dose to 3.5 g/m² per dose. Only 1 patient received concurrent therapy with aprepitant. All patients exhibited multiple symptoms of neurotoxicity: confusion (N = 7), lethargy (N = 5), aphasia (N = 4), and incontinence (N = 4). One patient experienced auditory hallucinations. Data were analyzed for possible organic predisposing factors for neurotoxicity.

Of the 13 patients, 9 received intravenous methylene blue as treatment, and all patients experienced abatement of symptoms within 5 days. After the resolution of neurotoxicity, 5 patients who had previously received the aqueous compound received subsequent dosing with the powder formulation of ifosfamide, without further recurrence of neuropsychiatric symptoms.

Discussion

Incidence of Ifosfamide-Induced Neurotoxicity
Approximately 10% to 40% of pediatric and adult patients who receive ifosfamide experience encephalopathy. Although widely reported in adult medical oncology literature, this phenomenon is less frequent in the pediatric population. Ifosfamide neurotoxicity in the pediatric patient varies in presentation but most often consists of confusion, hallucinations, and incontinence.

Predisposing Factors
Risk factors for ifosfamide neurotoxicity, such as hypoalbuminemia, renal dysfunction, concurrent use of aprepitant, and a history of cisplatin exposure, were identified in our patient population (Table). Other less reported risk factors, such as low hemoglobin and low total bilirubin levels, were not evaluated in our study.

Currently, the greatest risk factor for neurotoxicity is hypoalbuminemia, predominantly a serum albumin level <3.3 g/dL. Recent reports show that prophylaxis with an albumin infusion has no apparent effect on the development of ifosfamide-related neurotoxicity, suggesting that hepatic dysfunction rather than albumin depletion may account for such a predisposition.

Currently, the greatest risk factor for neurotoxicity is hypoalbuminemia, predominantly a serum albumin level <3.3 g/dL. Recent reports show that prophylaxis with an albumin infusion has no apparent effect on the development of ifosfamide-related neurotoxicity.

Of the often implicated risk factors, hypoalbuminemia was the most frequently identified risk factor in our study. A total of 7 patients had hypoalbuminemia with albumin levels of ≤3.3 g/dL at the time of ifosfamide administration. In addition, 3 of the 5 patients who were rechallenged with the powder remained hypoalbuminemic but did not experience recurrent symptoms of neurotoxicity when the powder formulation was used.

Renal dysfunction was not identified as a risk factor in our patient population, because only 1 patient experienced elevated creatinine level (1.3 mg/dL) throughout the course of therapy. Only 1 patient had concurrent use of aprepitant, suggesting that this is also difficult to identify as a predisposing factor in the pediatric population.

Although 3 patients had a history of previous cisplatin exposure, they had normal renal function at the time of ifosfamide administration. Of these patients, 2 did not experience encephalopathy when rechallenged with a powder formulation. Therefore, in our population it is difficult to determine if cisplatin exposure is related to ifosfamide neurotoxicity, particularly in the setting of normal renal function.

Mechanism of Neurotoxicity
The metabolism of ifosfamide by the hepatic cytochrome (CY) P450 system results in inactive metabolites, toxic metabolites, and the active form of the drug, isophosphoramide, a nitrogen mustard. Neurotoxic effects are thought to be associated with disruption of the mitochondrial respiratory chain and the
### Table: Characteristics of Pediatric Patients with Ifosfamide Neurotoxicity

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Ifosfamide dose (liquid)</th>
<th>Concurrent use of aprepitant?/History of cisplatin exposure?</th>
<th>Ifosfamide symptoms</th>
<th>Serum albumin, g/dL</th>
<th>Serum creatinine, mg/L</th>
<th>Methylene blue</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>M</td>
<td>Clear-cell sarcoma of kidney with central nervous system relapse</td>
<td>3 g/m² × 3 days</td>
<td>No/No</td>
<td>Ataxia, vertigo, lethargy</td>
<td>3.5</td>
<td>0.7</td>
<td>Yes × 2</td>
<td>Head CT negative Neurotoxicity occurred on last cycle of chemotherapy Did not rechallenge</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Pre-B-cell ALL</td>
<td>1.8 g/m² × 5 days</td>
<td>No/No</td>
<td>Lethargy, confusion, incontinence</td>
<td>2.1</td>
<td>0.3</td>
<td>No</td>
<td>Head MRI negative Symptoms experienced after dose 4 Powder formulation used for dose 5 without recurrent symptoms</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Metastatic desmoplastic round cell tumor</td>
<td>1.8 g/m² × 5 days</td>
<td>No/No</td>
<td>Alternating agitation and lethargy, unable to ambulate, disorientation</td>
<td>3.2</td>
<td>0.8</td>
<td>Yes × 1</td>
<td>Head CT negative Dose 3 held Returned to baseline status and discharged on hospital day 5 Not rechallenged</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>Clear-cell sarcoma right medial thigh</td>
<td>3 g/m² × 3 days</td>
<td>No/No</td>
<td>Confusion, asthenia, presyncope</td>
<td>3.8</td>
<td>0.5</td>
<td>Yes × 4</td>
<td>Symptoms resolved after 24 hrs of treatment Finished proton beam therapy, transferred back to referral center Not rechallenged</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>Osteosarcoma</td>
<td>2.8 g/m² × 5 days</td>
<td>No/Yes</td>
<td>Disorientation, aphasia, new tremor, emotional lability</td>
<td>3.7</td>
<td>0.71</td>
<td>Yes × 2</td>
<td>Head CT and MRI negative EEG indicative of encephalopathy Powder formulation used on later date and no neurotoxicity</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>Rhabdomyosarcoma</td>
<td>1.8 g/m² × 5 days</td>
<td>No/No</td>
<td>Aphasia, confusion, aggression</td>
<td>2.7</td>
<td>0.8</td>
<td>No</td>
<td>MRI and LP negative Returned to baseline on hospital day 4 Rechallenged 2 months later with same regimen without recurrent symptoms</td>
</tr>
<tr>
<td>Age, yr</td>
<td>Sex</td>
<td>Diagnosis</td>
<td>Ifosfamide dose (liquid)</td>
<td>Concurrent use of aprepitant?/History of cisplatin exposure?</td>
<td>Ifosfamide symptoms</td>
<td>Serum albumin, g/dL</td>
<td>Serum creatinine, mg/L</td>
<td>Methylene blue</td>
<td>Comments</td>
</tr>
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<tr>
<td>15</td>
<td>F</td>
<td>Osteosarcoma</td>
<td>2.8 g/m² × 5 days</td>
<td>Yes/Yes</td>
<td>Incontinence, tremor, auditory hallucinations</td>
<td>2.9</td>
<td>0.6</td>
<td>Yes × 6</td>
<td>Powder formulation used on subsequent admission, no neurotoxicity</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>Osteosarcoma</td>
<td>3 g/m² × 3 days</td>
<td>No/Yes</td>
<td>Agitation, aphasia, incontinence</td>
<td>2.9</td>
<td>0.5</td>
<td>Yes × 8</td>
<td>Completed course with frequent dosing methylene blue Not rechallenged</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>Metastatic PNET</td>
<td>3 g/m² × 2 days</td>
<td>No/No</td>
<td>Aphasia, lethargy, facial twitch and myoclonic jerks</td>
<td>3.1</td>
<td>0.5</td>
<td>Yes × 1</td>
<td>Head CT negative Returned to baseline on hospital day 4 Not rechallenged</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>Osteosarcoma</td>
<td>3.5 g/m² × 5 days</td>
<td>No/No</td>
<td>Disorientation, confusion</td>
<td>3.2</td>
<td>1.3</td>
<td>Yes × 8</td>
<td>Course shortened because of symptoms Returned to baseline within 4 days</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>Undifferentiated sarcoma</td>
<td>2.8 g/m² × 5 days</td>
<td>No/No</td>
<td>Aphasia, lethargy, confusion</td>
<td>3.6</td>
<td>0.8</td>
<td>No</td>
<td>Last 2 doses ifosfamide held Returned to baseline within 5 days Rechallenged with dose reduction without recurrent symptoms</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>Alveolar rhabdomyosarcoma</td>
<td>1.8 g/m² × 5 days</td>
<td>No/No</td>
<td>Amnesia, confusion</td>
<td>4.1</td>
<td>0.7</td>
<td>No</td>
<td>Ifosfamide discontinued Switched to nonifosfamide-containing regimen</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>Spinal osteosarcoma</td>
<td>3.5 g/m² × 5 days</td>
<td>No/No</td>
<td>Disorientation, confusion</td>
<td>3.5</td>
<td>0.7</td>
<td>Yes × 8</td>
<td>Returned to baseline within 48 hrs Ifosfamide discontinued Not rechallenged</td>
</tr>
</tbody>
</table>

ALL indicates acute lymphocytic leukemia; CT, computed tomography; EEG, electroencephalogram; LP, lumbar puncture; MRI, magnetic resonance imaging; PNET, primitive neuroectodermal tumor.
The treatment of ifosfamide-induced neurotoxicity is focused on the reduction of excess electrons and restoration of the mitochondrial respiratory chain, resulting in increased metabolism of CAA.

Recent reports show that prophylaxis with an albumin infusion has no apparent effect on the development of ifosfamide-related neurotoxicity, further suggesting that hepatic dysfunction rather than albumin depletion may account for this predisposition. The treatment of ifosfamide-induced neurotoxicity is focused on the reduction of excess electrons and restoration of the mitochondrial respiratory chain, resulting in increased metabolism of CAA (Figure).

Methylene blue has traditionally been used to accomplish this. Methylene blue may also reduce the formation of CAA by blocking activity of monoamine oxidases. Although not as well described, intravenous thiamine administration has been reported in the literature as an intervention for ifosfamide-induced neurotoxicity. The proposed mechanism of action has been postulated to be related to ifosfamide-induced thiamine dysfunction or reduced thiamine availability. Alternatively, attempts have been made to prevent neurotoxicity by modifying the ifosfamide molecule, altering metabolism so that CAA production is hindered.

**Patient Characteristics**

Characteristics of rechallenged patients are also shown in the Table. For several years, anecdotal observations suggesting a higher incidence of encephalopathy with the aqueous formulation of ifosfamide have been discussed among oncologists and oncologic pharmacists. In this case series, we report 5 cases in which patients who developed encephalopathy with an aqueous ifos-
Ifosfamide formulation did not experience recurrence of such symptoms when rechallenged with the powder formulation.

A 19-year-old male with undifferentiated sarcoma and an 11-year-old female with osteosarcoma experienced neurotoxicity with the liquid formulation and later during therapy received the powder formulation without adverse effects. Neither had hypoalbuminemia or renal dysfunction when encephalopathy occurred. The 11-year-old female did have a history of cisplatin exposure. Both patients had normal serum albumin levels at the time of infusion with powder formulation.

Two additional patients, a 14-year-old female with rhabdomyosarcoma and a 15-year-old female with osteosarcoma, both of whom had also had hypoalbuminemia, developed encephalopathy with the liquid formulation. Both patients were rechallenged at a later date with the powder formulation, which did not result in any adverse effect. The patients remained hypoalbuminemic at the time of infusion with the powder formulation (serum albumin levels, 3.3 g/dL and 3.1 g/dL, respectively). It is interesting to note that the 15-year-old female who was rechallenged had 3 known risk factors for ifosfamide-associated neurotoxicity—hypoalbuminemia, previous cisplatin exposure, and concurrent use of aprepitant. However, she did not experience recurrent encephalopathy with the powder formulation.

A 7-year-old male with pre-B-cell ALL experienced lethargy, confusion, and incontinence after 4 doses of the liquid formulation of ifosfamide. He was persistently hypoalbuminemic throughout his hospital course and had no history of cisplatin exposure or renal dysfunction. He was not administered methylene blue. Rather, the patient's next dose of ifosfamide was held, and his symptoms resolved within 24 hours. He was then administered the fifth dose of ifosfamide, using the powder formulation, and did not experience neurotoxicity.

Conclusion

Ifosfamide-induced neurotoxicity has been frequently reported in the literature. Our case series raises some interesting questions regarding this phenomenon. Serum albumin has been reported as a risk factor, and this was identified in patients in this pediatric case series. However, low serum albumin levels were not consistently associated with neurotoxicity. Other risk factors, such as renal dysfunction or previous cisplatin exposure, could not be identified in our small population. In addition, the lack of neurotoxicity in patients rechallenged with the powder formulation of ifosfamide suggests a possible increased incidence of ifosfamide neurotoxicity with the liquid formulation of the drug.

The current aqueous formulation of ifosfamide could be a contributing factor to neurotoxicity, and further studies are warranted to evaluate this trend. Investigation utilizing high-performance light chromatography or nuclear magnetic resonance spectroscopy to analyze possible differences in toxic metabolite formation between formulations may be helpful.

Author Disclosure Statement

Dr Parsons is on the Speaker’s Bureau of Sigma Tau Pharmaceuticals. Drs Lee, Ng, Poon, Schwartz, Smith, and Assanasen, and Mr Henry have reported no actual or potential conflicts of interest.

References