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Case Report

Rare Delayed Ifosfamide Encephalopathy: A Case Report of Chemotherapeutic Neurotoxicity

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Keywords

Case report · Ifosfamide toxicity · Methylene blue · Neurotoxicity · Encephalopathy

Abstract

Introduction: Neurotoxicity is a well-documented side effect of ifosfamide chemotherapy. The presentation includes hallucinations, seizures, disorientation, coma, and death. Treatment with methylene blue can shorten the duration and severity of symptoms. Ifosfamide neurotoxicity almost always happens during or shortly after drug infusion and so is usually immediately recognized. Here, we describe a case of ifosfamide neurotoxicity with onset 14 days after treatment started. ***Case Presentation:*** A 25-year-old woman with round cell sarcoma of the jaw presented to the emergency department with 2 days of encephalopathy and bizarre behavior. Antipsychotic medications and benzodiazepines produced no benefit. After consultation, oncology recommended methylene blue, hypothesizing that her symptoms could be a rare presentation of delayed ifosfamide-induced neurotoxicity, 14 days after first administration. After 4 days of methylene blue infusion, her functioning returned to baseline. ***Conclusion:*** Delayed ifosfamide-related neurotoxicity is a rare side effect of this chemotherapeutic agent and should be considered in the workup of altered mental status, even if symptoms occur after the previously accepted 5-day standard. In such patients, delayed symptomology may require extended use of methylene blue as treatment.

This case was presented as an abstract at Georgia chapter of the American College of Physicians meeting in Savannah, GA on October 14, 2022, and the Society for General Internal Medicine in Aurora, CA, on May 11, 2023, and was presented at the Emory Division of Hospital Medicine Case Conference virtually September 9, 2022.

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Introduction

Ifosfamide is used as treatment in many solid organ and hematologic malignancies. Encephalopathy is a known adverse reaction of ifosfamide therapy, occurring in 10–30% of patients [1–3]. Ifosfamide is dose-dependent with larger doses having longer half-lives likely due to saturation of the metabolic pathways [4]. The half-life of the drug has been found to be between 4 and 15 h depending on the dose [4, 5]. Most neurotoxic side effects documented in the literature occur within the first 5 days post-infusion [6, 7]. Symptoms of neurotoxicity include fatigue, drowsiness, hallucination, seizures, coma, and death [8]. This is thought to be due to the effect of ifosfamide metabolites, primarily chloroacetaldehyde and chloroethylamine, neurotoxic byproducts that are able to cross the blood-brain barrier [1, 9]. There are 3 case studies in the literature noting delayed encephalopathy following ifosfamide infusion. In 2010, Al-Momen et al. [10] described a 19-year-old female in Saudi Arabia with Hodgkin lymphoma who presented with neurotoxicity 16 days postexposure who recovered within 24 h of methylene blue administration. Yeager et al. [7] described a 21-year-old man with chondrosarcoma 10 days post-ifosfamide infusion presenting with deteriorating mental status and encephalopathy that resolved in 48 h with methylene blue administration. The authors noted that it took 10 days to administer methylene blue due to lack of knowledge about delayed presentations of encephalopathy [7]. Lastly, in 2022, Chain et al. [9] described an encephalopathy that lasted 7 months post-infusion in an 11-year-old with a non-germinomatous germ cell tumor and autism spectrum disorder, requiring continuous methylene blue administration.

Ifosfamide's potential for delayed neurotoxicity necessitating extended treatment with methylene blue is an important aspect to consider when treating patients undergoing chemotherapy as are the potential presentations of related encephalopathy. Here, we present a case of delayed ifosfamide encephalopathy and its subsequent resolution in a 25-year-old female with round cell sarcoma of the mandible. Dr Read obtained written informed consent to publish this report from this patient on June 29, 23. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535952). None of the authors have relevant conflicts of interest.

Case Presentation

A 25-year-old female with recently diagnosed round cell (non-Ewing) sarcoma of the mandible presented to the emergency department with 2 days of bizarre behavior. Her pathology was consistent with nonmetastatic, malignant small round blue cell tumor, with an archer fusion profile without a match. She had begun her first cycle of neoadjuvant ifosfamide and etoposide 14 days prior to this episode; her planned neoadjuvant chemotherapy regimen consisted of alternating vincristine, doxorubicin, and cyclophosphamide and ifosfamide and etoposide every other week as per assumed Ewings sarcoma. Other than chemotherapeutic agents, she took no medications or partook in recreational drug use (though she had used cannabis oil several months prior). She had not been sexually active in 5 months, per parental report.

She was at her baseline until 2 days before admission, when her brother noticed differences in her texting pattern, with nonsensical speech and uncharacteristic messages. The next day she had nonsensical verbal outbursts, unprovoked crying spells, and refused to follow commands. Her family brought her to the emergency department after she stopped responding to external stimuli, such as verbal commands, physical manipulation, or even name recall.

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On arrival, her vitals were within normal limits (see Table 1 for a detailed case timeline). Laboratories were significant for white blood cell count of 24 × 10^3/μL (normal range: 4.5–11 × 10^3/μL) (likely from filgrastim use), calcium of 10.2 mg/dL (normal range: 8.5–10.5 mg/dL), creatinine of 0.83 mg/dL (normal range: 0.60–1.2 mg/dL), her liver function tests all within normal limits, and a negative urine drug screen. Physical exam showed a thin young female with a 7.1 cm expansile lytic mass of the right mandibular body, fixed gaze without tracking, mild tremor, and occasional grunting.

The patient's chemotherapy had begun with ifosfamide and etoposide x 5 days that were first administered 14 days prior to presentation. The patient's mother provided more history, stating that the patient had previously experienced a period of unresponsiveness once before, 6 months earlier, when her boyfriend suddenly passed away. At that time, she was given haloperidol and returned to baseline.

Because of her prior episode of unresponsiveness, conversion disorder as a reaction to her new cancer diagnosis and chemotherapy effects (e.g., hair loss) was included on the differential but was eliminated following consultation and assessment by a psychiatrist. A computed tomography scan of her head without contrast and magnetic resonance imaging of her brain were normal. Neurology was also consulted; both neurology and Psychiatry diagnosed her with encephalopathy.

Her electroencephalogram showed diffuse slowing, consistent with encephalopathy. She continued to be intermittently encephalopathic with impaired attention and limited thought content. Her behavior included pulling out her hair and eating it, pulling at room fixtures, and standing on hospital furniture.

At Psychiatry's recommendation, haloperidol, lorazepam, and scheduled olanzapine were trialed without benefit. Neurology considered doing a lumbar puncture but deferred due to lack of neurologic findings, her electroencephalogram, and nonfocal exam. Oncology was consulted and considered infectious, oncologic, and medication etiologies for her encephalopathy. The patient did not exhibit symptoms of toxicity, ruling out infection. Leptomeningeal disease, which can cause encephalopathy, was also considered but was eliminated because affected individuals generally have much more extensive cancer, signs on magnetic resonance imaging, and other neurological issues (e.g., cranial neuropathies). The oncologist then noted that the patient's symptoms strongly resembled ifosfamide toxicity, despite the long interval since its administration. Because the oncologist had heard reports from several patients about perceived "bizarre behavior" at home after discharge post-infusion of ifosfamide, they searched and found 2 case reports [7, 10] discussing delayed-onset neurotoxicity. Oncology thus recommended trial of methylene blue and thiamine for delayed ifosfamide toxicity (50 mg every 4–8 h until symptoms resolve). Her symptoms resolved after 4 days of thiamine and methylene blue administration.

The patient was discharged home with her family with plans to adjust her chemotherapy regimen. She had no recollection of the events, last recalling the day before admission. She had no lingering symptoms. Ifosfamide was abandoned and she received chemotherapy with vincristine, doxorubicin, and cyclophosphamide only, with response on imaging and 15% remaining viable tumor on mandibulectomy. At present, 1 year after the described events, she is in remission and being followed with surveillance imaging.

Discussion

Ifosfamide is metabolized by the liver into chloroacetaldehyde and chloroethylamine, which can cross the blood-brain barrier and have demonstrated neurotoxicity [1]. These neurotoxins can cause hallucinations, seizures, disorientation, coma, death, and brain damage

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Table 1. Case timeline

Hospital day	Significant events
−14	First administration of ifosfamide and etoposide with plans to alternate with vincristine, doxorubicin, and cyclophosphamide every other week
−2	Patient's brother notices differences in her written communication when texting
−1	Patient displays concerning behaviors when interacting with her family members: nonsensical verbal outbursts, unprovoked crying spells, and refusal to follow commands
0	Patient stops responding to external stimuli
	Family brings patient to ED
0–2	Haloperidol, lorazepam, and scheduled olanzapine trialed without symptom resolution
	Neurology and psychiatry consulted
	EEG performed, demonstrating diffuse slowing
	MRI obtained
3	Oncologist consulted. Conversion disorder/psychiatric, infectious, and oncologic etiologies ruled out
	Oncologist reads 2 case reports and recommends trialing methylene blue as symptoms are consistent with delayed ifosfamide encephalopathy
4–7	Initiation of 4 days of methylene blue and thiamine administration, with complete symptom improvement by hospital day 7

ED, emergency department; MRI, magnetic resonance imaging, EEF, electroencephalogram.

through direct neurotoxicity or inhibition of mitochondrial oxidative phosphorylation. Risk factors for ifosfamide toxicity are older age, female sex, low serum albumin, renal failure, and oral route of administration of ifosfamide [11]. While a clinical diagnosis, the onset of encephalopathy is known to typically occur within 2–146 h of infusion [7]. Two prior case reports have demonstrated acute-delayed neurotoxicity, at 10 days post-infusion [8] and 16 days post-infusion [10], both resolving with methylene blue administration.

Aside from hydration, thiamine [12–14], and discontinuation of the offending agent, methylene blue is the antidote for ifosfamide toxicity, often with complete resolution of symptoms [1, 3, 15]. As the neurotoxins inhibit mitochondrial oxidative phosphorylation, methylene blue is hypothesized to work by acting as an alternative electron acceptor, allowing the mitochondrial respiratory chain to function as previously [3]. Symptoms typically improve within 24 h of administration, and time to improvement may correlate with the timing of toxicity [15]. Those with a delayed onset of symptoms may also have delayed resolution with methylene blue, as was seen in our patient, who received a total of 4 days of treatment.

Conclusion

Delayed encephalopathy is a rare side effect of ifosfamide but can be fatal if not treated appropriately. Despite the small number of previous case reports in the literature, delayed neurotoxicity should be considered in encephalopathic patients who have received the drug, even if they are several days posttreatment. When considering this diagnosis, the required length of treatment with methylene blue may correlate with the length of time spent encephalopathic.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

No authors had conflicts of interest relevant to this report.

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Author Contributions

Ambika Menon, Chidiebele Enunwa, William Read, and Kyle James all were part of the patient care, preparation, writing, and editing process of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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