

Ifosfamide Induced Neurotoxicity Secondary to Concomitant Aprepitant Use

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Introduction

Ifosfamide is an alkylating agent, a structural analogue of cyclophosphamide. In its initial days its use was limited secondary to dose limiting hemorrhagic cystitis which was counteracted by using mesna (2-mercaptoethane sulphonate) along with it [1]. Ifosfamide has found several uses since then. One of its most important uses is in advanced soft tissue sarcomas where it is used as adjuvant chemotherapy along with doxorubicin [2,3]. The Italian cooperative trial showed 5-year overall survival estimate to be 66.0% and 46.1% for the treatment and the control groups, respectively ($p=0.04$) [4]. Ifosfamide and doxorubicin are also used with good results in advanced rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Group trial showed a complete response rate of 52% in patients treated with these 2 drugs [5]. Also, ifosfamide along with etoposide was found to be superior to vincristine and melphalan in another study for advanced rhabdomyosarcoma with an overall survival rate going up to 55% at 3 years [6]. In a study for Ewing's sarcoma, cyclophosphamide and ifosfamide were found to have similar efficacy but the former was associated with higher rate of toxicity [7]. In children with recurrent/refractory sarcoma, treatment with ifosfamide, carboplatin and etoposide (ICE) as re-induction chemotherapy produced an overall response rate of 51% with a significant improvement in overall survival at 1 and 2 years [8]. Furthermore, in patients with relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) the overall response rate to ICE was found to be as high as 70%, with a complete response rate of 25% to 30% [9]. When this regimen was combined with rituximab (R), an even better response was seen [10].

In comparison to doxorubicin, ifosfamide is less convenient to use as it has to be given over several days while doxorubicin can be given in one day. However unlike doxorubicin, ifosfamide can be given at high doses as it is not associated with dose limiting cardiotoxicity [11].

Overall, ifosfamide is a widely used chemotherapy agent and its side effects include bone marrow suppression, hemorrhagic cystitis, alopecia, nausea and neurotoxicity. The incidence of neurotoxicity or encephalopathy is 10-30% and is increased with concomitant aprepitant use as seen in a few recent case reports [12-14]. Here we present one such case along with a review of the latest literature.

Case Report

A 58-year-old female with cystosarcoma phyllodes of the left breast status post mastectomy, was found to have a left parasternal mass which on biopsy was consistent with the primary cystosarcoma tumor. The patient was admitted to the hospital for chemotherapy with doxorubicin, ifosfamide and mesna. The dose for Ifosfamide was modest at 2500 mg/m² daily for 3 days. The pre- medications included ondansetron, lorazepam, prochlorperazine, dexamethasone and aprepitant. Aprepitant was given 125 mg orally on day 1 followed by 80 mg orally on days 2 and 3. Chemotherapy was initiated at 1400 hours on day 1. The patient was tolerating it well until the morning of day 3 when she developed mental status changes with disorientation and agitation along with difficulty breathing. The patient remained oriented but was unable to lay still;

she had incessant semi purposeful movements. She had only a transient response to lorazepam. Her agitation and restlessness worsened over the next 12 hours and she developed tachypnea. The third planned dose of ifosfamide and doxorubicin was held temporarily since she could not even lay still and this led to traumatic removal of the venous access as well as incontinence and catheterization. She was treated with furosemide for potential fluid overload, since a chest x-ray showed mild interstitial prominence but with no relief. A CT thorax was obtained which indicated no pulmonary embolism but noted progression of her metastatic disease in the lungs. Additional lorazepam was administered which appeared to calm her down so she could sleep. Chemotherapy was restarted once the patient was calm. However within an hour, the patient again became agitated and then the chemotherapy was discontinued. The agitation persisted and was coupled with severe respiratory distress and acute respiratory failure requiring endotracheal intubation and mechanical ventilation. The patient was transferred to the medical Intensive Care Unit (ICU), where she was started on 1% methylene blue intravenously 50 mg every 8 hours for ifosfamide induced neurotoxicity. She received a total of 5 doses of this agent and her mental status came back to baseline. She was able to breathe spontaneously and was extubated. She was then transferred back to the oncology floor and was discharged home a week later. She received 2.5/3 of the total intended dose of ifosfamide.

Discussion

Ifosfamide induced neurotoxicity is one of the rarer side effects seen with this drug [15], with a few cases showing increased incidence with aprepitant use [12-14]. Aprepitant is a neurokinin-1 inhibitor which is used as an antiemetic. As per the latest NCCN guidelines for antiemesis aprepitant is indicated for moderate to highly emetogenic chemotherapeutic regimens [16]. Ifosfamide is included in moderate to highly emetogenic chemotherapy depending on the total dose being less than or greater than 10 g per meter square [17]. Aprepitant is a moderate inhibitor of CYP3A4, an enzyme responsible for numerous drug metabolism pathways [16]. Ifosfamide is a prodrug that requires hepatic activation to its cytotoxic metabolite, ifosfamide mustard. The latter is hydroxylated through CYP3A4 to active alkylating agents, ifosforamide mustard and 4-hydroxy-ifosfamide. Ifosfamide is also converted by CYP3A4 to inactive, neurotoxic metabolites: the 2- and 3-dechloroethylifosfamide and chloroacetaldehyde. Competition with 4-hydroxylation is the major oxidative pathway that causes the dechloroethylation and

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the formation of the neurotoxic metabolites chloroacetaldehyde and 2-and3-dechloroethylifosfamide. The potential inhibition of CYP3A4 by aprepitant [18] may increase the levels of ifosfamide metabolites resulting in accumulation and further risk of encephalopathy and other side effects like hemorrhagic cystitis or neutropenia [14].

The exact pathophysiological mechanisms responsible for the development of ifosfamide-induced encephalopathy are not known. Küpfer et al. [19] presented possible pathways by which Ifosfamide metabolites can induce neurotoxicity. These hypotheses were based on the finding of glutaric acid and sarcosine in the urine of a patient with ifosfamide-induced encephalopathy. The same products are also found in the urine of patients with congenital glutaric aciduria [19]. In these patients a metabolic dysfunction is caused by the absence of glutaryl CoA (type 1) or by a lack of electron transferring flavoproteins in the mitochondrial respiratory chain (type 2). Further investigations showed a relation between glutaric aciduria and chloroethylamine but not with any of the other metabolites of ifosfamide. This led to the conclusion that chloroethylamine may be the principal neurotoxic metabolite of ifosfamide [19]. Chloroethylamine conjugates with cysteine, thus forming thialysine, which can be metabolized to thialysine ketimine. The latter can inhibit the electron-binding flavoproteins in the mitochondrial respiratory chain. Thialysine ketimine could have CNS effects on its own. The inhibition of the mitochondrial respiratory chain may also lead to a disturbance of the intracellular NAD/NADH balance with the accumulation of NADH. This in turn prevents the dehydrogenation of aldehydes, such as the ifosfamide metabolite chloroacetaldehyde, which need NAD for their oxidation [20]. Chloroacetaldehyde is a potential neurotoxic substance. It is closely related to chloral hydrate, a known hypnotic, and to acetaldehyde which is the neurotoxic metabolite of ethanol. Ifosfamide and its metabolites can penetrate the blood brain barrier. Another important pathway may be mediated by monoamineoxidase in the extrahepatic tissues and in plasma by which chloroacetaldehyde can be formed.

Durand et al. [13] reported a case of acute encephalopathy following an ifosfamide infusion that they believed was triggered by aprepitant. A pharmacokinetic evaluation was performed in the patient who received ifosfamide and aprepitant and presented with marked sleepiness, dizziness, visual and auditory hallucinations. It revealed an increase in the neurotoxic metabolites- 2- and 3- dechloroethyl ifosfamide by 66.7% and 37.3%, respectively. Both are metabolized by CYP3A4. There was also an increase in 4-hydroxy ifosfamide an active form of ifosfamide, by 28.1% at 2 hours and 27.7% at 4 hours post infusion [13]. This pharmacokinetic data supports the increase in accumulation of toxic metabolites by a drug-drug interaction of ifosfamide and aprepitant. Other risk factors which have been implicated to increase the risk of ifosfamide induced neurotoxicity include hypoalbuminemia and elevated creatinine [20].

Conclusion

Increased incidence of ifosfamide induced neurotoxicity secondary to concomitant aprepitant use is being increasingly seen as depicted in this case. The treatment for this is methylene blue which can also be used for secondary prevention. It has been shown to shorten the duration of neurotoxicity. It is used at a dose of 50 mg IV every 4-8 hours. It can be taken orally for prevention [21]. Clinicians need to be aware of this increased incidence of neurotoxicity and avoid the use of these drugs at the same time to prevent this life-threatening complication.

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