Case Report

The interaction of ifosfamide and aprepitant in gynecologic malignancies

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Introduction

Ifosfamide, an analog of cyclophosphamide, is an active agent in gynecologic cancers, especially sarcomas (Dusenbery et al., 2005; Kanjeeval et al., 2005). Its activity in ovarian and uterine malignant mixed mesodermal tumors (MMMT) has been demonstrated in multiple studies (Homesley et al., 2007; Mano et al., 2007; Rutledge et al., 2006). Unfortunately, it is commonly associated with neurotoxicity in patients with protein malnutrition. Its metabolism is primarily within hepatic enzymes (cytochrome p450) with excretion through the urinary tract. Ifosfamide requires activation through 4-hydroxyifosfamide to ifosforamide to exert cytotoxicity. Deactivation of ifosfamide leads to the release of the potentially neurotoxic chloracetaldehyde (Kerbusch et al., 2001).

Aprepitant is a novel and selective antiemetic that antagonizes substance P/neurokinin 1 (NK1) receptors with high affinity. Its mechanism of action is distinct without cross-over from the common targets used to prevent chemotherapy-induced nausea and vomiting: the serotonin (5-HT3), dopamine, and corticosteroid receptors. It is metabolized by the cytochrome p450 system and is a moderate dose-dependent CYP3A4 inhibitor (Anon, n.a.).

We describe, in this report, the interaction of these two medications and how that interaction precipitated neurotoxicity in two patients in whom neurotoxicity was not anticipated due to normal albumin levels.

Case report

Case 1

A sixty-seven year-old woman underwent complete cytoreduction including total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy, infragastric omentectomy, splenectomy, and diaphragm tumor ablation for a stage IIIc ovarian cancer. Final pathology revealed a homologous ovarian MMMT.

The patient had Gynecologic Oncology Group (GOG) performance status of one. Her pre-chemotherapy laboratory values were all within normal limits including an albumin level of 3.5 g/dL (normal: 3.4–5.4 g/dL). During cycles 1–3, the patient received cisplatin 20 mg/m² along with ifosfamide 1.5 g/m² daily over 90 min with concurrent mesna on days 1–4. Her premedications included ondansetron 32 mg and dexamethasone 10 mg. For four days after chemotherapy, she received dexamethasone 8 mg every morning with metaclopramide 20 mg every 8 h, and ondansetron for refractory nausea and vomiting. She had no neurologic toxicities with her first 3 cycles but experienced neutropenic fever as well as severe nausea and vomiting with her third cycle. For her fourth cycle, her doses were adjusted as well as her premedications and post-chemotherapy anti-emetics. For her fourth cycle, she was to receive cisplatin 20 mg/m² with ifosfamide 1 g/m² daily over 90 min with concurrent mesna on days 1–4. His albumin at this time was 3.6 g/dL, and her premedications included aprepitant 125 mg and dexamethasone 10 mg. For four days after chemotherapy, she received dexamethasone 8 mg every morning with metaclopramide 20 mg every 8 h, and ondansetron for refractory nausea and vomiting. She had no neurologic toxicities with her first 3 cycles but experienced neutropenic fever as well as severe nausea and vomiting with her third cycle. For her fourth cycle, her doses were adjusted as well as her premedications and post-chemotherapy anti-emetics. For her fourth cycle, she was to receive cisplatin 20 mg/m² with ifosfamide 1 g/m² daily over 90 min with concurrent mesna on days 1–4. His albumin at this time was 3.6 g/dL, and her premedications included aprepitant 125 mg and dexamethasone 10 mg. Her post-chemotherapy regimen was adjusted to add aprepitant 80 mg each morning along with dexamethasone 8 mg each morning for two days.

The patient still experienced nausea but had no emesis. After the completion of her mesna on day 3 of chemotherapy, the patient acutely developed an ifosfamide-induced coma without any precipitating events. The ifosfamide infusion was discontinued. The coma lasted less than 24 h and a methylene blue infusion was not used. Supportive care and close monitoring in the step-down unit was used. No residual neurologic toxicities were found. Interestingly, her urinalysis revealed no red blood cells at any time.
A forty-one year-old woman underwent a panniculectomy for surgical exposure with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and peritoneal washings for complex endometrial hyperplasia with atypia discovered by dilation and curettage. Frozen section revealed a probable uterine MMMT. Therefore, she underwent bilateral pelvic and para-aortic lymphadenectomy and infracolic omentectomy. Final pathology revealed a homologous uterine MMMT (stage IB).

The patient had GOG performance status of zero. Her pre-chemotherapy laboratory values were all within normal limits, including an albumin level of 4.5 g/dL. She was admitted for cycle one of her chemotherapy the same day as the patient from Case 1 was admitted for cycle four. The plan was to give cisplatin 20 mg/m² with ifosfamide 1.5 g/m² over 90 min and concurrent mesna on days 1–4. Her pre-medications included aprepitant 125 mg and dexamethasone 10 mg. Her post-chemotherapy regimen consisted of aprepitant 80 mg each morning for two days along with dexamethasone 8 mg each morning for the length of the chemotherapy (four days).

After her mesna and ifosfamide were completed on day 3 of chemotherapy, the patient was noted to have developed acute ifosfamide-induced mental status changes including—auditory and visual hallucinations and labile emotions. The mental status changes lasted less than 24 h and a methylene blue infusion was not used. She also was closely monitored in a step-down unit. No residual neurologic toxicities were found. Her urinalysis also revealed no red blood cells at any time.

Discussion

MMMT’s are a highly aggressive cancer often of uterine or ovarian origin. Ideal chemotherapy management is still not known, however, three of the most commonly used agents are cisplatin, ifosfamide, and paclitaxel. Aprepitant is a moderate dose-dependent CYP3A4 inhibitor and inducer of CYP2C9 (Anon, n.a.). It is currently recommended for use in patients receiving moderate to highly emetogenic regimens (Kris et al., 2006). Aprepitant should not be used concurrently with several medications including but not limited to terfenadine, astemizole, and cisapride. Dose-dependent inhibition of CYP3A4 may result in elevated plasma concentrations of drugs metabolized through this system. While it does affect the pharmacokinetics of dexamethasone, it does not affect the pharmacokinetics of other chemotherapy agents (Loos et al., 2007).

Ifosfamide is metabolized by CYP3A4. Some of its metabolites can cause neurotoxicity including: encephalopathy, sleepiness, dizziness, hallucinations, coma and death (Ajithkumar et al., 2007). Ifosfamide is administered as a racemic mixture of (R)- and (S)-ifosfamide enantiomers with the levorotatory enantiomer being responsible for the neurotoxic side effects. Clinical case series have shown that the duration of neurotoxic side effects can be decreased by the administration of intravenous methylene blue (Ajithkumar et al., 2007).

Malnutrition, as documented by decreased albumin, is one of several factors that can influence the development of neurotoxicity in patients receiving ifosfamide. Other factors include: the use of cisplatin, high dose ifosfamide, prolonged infusion, rapid infusion, or phenobarbital use. Both of the patients in this report had normal albumin, but received concomitant cisplatin with their ifosfamide. This combination of chemotherapies, although highly emetogenic, may be better handled with steroids and 5HT3 antagonists as opposed to using aprepitant. Although it is easy to adjust the dose of steroids used with aprepitant, it is much more difficult to adjust the dose of ifosfamide. Although some authors do not believe that interactions with intravenous chemotherapies exist, we recommend caution with the use of aprepitant in combination with ifosfamide because of the potential for the development of acute neurotoxicity until pharmacokinetic studies reveal appropriate dose adjustments of ifosfamide with aprepitant.

Conflict of interest

None of the authors have any relevant conflicts of interest to report.

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