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Fosaprepitant-induced Phlebitis: A Focus on Patients receiving Doxorubicin/Cyclophosphamide therapy

A. D. Leal¹, K. C. Kadakia¹, S. Looker², C. Hilger², K. Sorgatz², K. Anderson², A. Jacobson², D. Grendahl³, D. Seisler⁴, T. Hobday², and C. L. Loprinzi²

¹Department of Internal Medicine, Mayo Clinic, Rochester, MN, U.S.A.

²Division of Medical Oncology, Mayo Clinic, Rochester, MN, U.S.A.

³Department of Pharmacy, Mayo Clinic, Rochester, MN, U.S.A.

⁴Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, U.S.A.

Abstract

Purpose—The purpose of this study was to investigate the incidence of fosaprepitant-associated infusion site adverse events (ISAEs) among a cohort of breast cancer patients receiving doxorubicin/cyclophosphamide (AC) chemotherapy.

Methods—A retrospective review of electronic medical record (EMR) data was performed for all patients who were initiated on AC from January 2011 to April 2012. Data collected included baseline demographics, antiemetic regimen, documentation of ISAEs and type of intravenous (IV) access. Descriptive statistics (mean and standard deviation or percentages) were summarized overall, by type of IV access and initial antiemetic given.

Results—Among the 148 patients included in this analysis, 98 initially received fosaprepitant and 44 received aprepitant. The incidence of ISAEs associated with fosaprepitant administration was 34.7% ($n=34$), while the incidence of aprepitant-associated ISAEs was 2.3% ($n=1$). All ISAEs were associated with peripheral IV access. The most commonly reported ISAEs were: infusion site pain ($n=26$), erythema ($n=22$), swelling ($n=12$), superficial thrombosis ($n=8$), infusion site hives ($n=5$) and phlebitis/thrombophlebitis ($n=5$). Twenty-six patients experienced more than one type of ISAE.

Conclusions—The incidence and severity of ISAEs associated with fosaprepitant administration among a group of patients receiving AC chemotherapy is significant and appreciably higher than what has been previously reported.

Keywords

fosaprepitant; chemotherapy induced nausea and vomiting; adverse event; vein toxicity

Introduction

Nausea and vomiting are among the most distressing side effects of chemotherapy, affecting more than 70% of patients in the absence of an antiemetic [1]. Aprepitant, a neurokinin-1 receptor antagonist (NK1-RA), is effective at helping to prevent both acute and delayed

Corresponding Author: Charles L. Loprinzi Division of Medical Oncology Mayo Clinic 200 1st Street SW Rochester, MN 55905 U.S.A. Tel +1-507-284-2511 Fax +1-507-284-1803 clopinzi@mayo.edu.

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chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly-emetogenic chemotherapy (HEC) and moderately-emetogenic chemotherapy (MEC), when administered with a serotonin receptor antagonist (5HT3-RA) and dexamethasone [2-5]. Based on this efficacy, aprepitant is recommended in national guidelines for patients receiving HEC and MEC [6] and it has been a part of Mayo Clinic Rochester practice guidelines for several years.

Fosaprepitant dimeglumine, a phosphorylated analog of aprepitant, is rapidly converted to aprepitant after intravenous (IV) administration. A large randomized control trial concluded that a one-time IV infusion of fosaprepitant was non-inferior to a three-day regimen of oral aprepitant when combined with dexamethasone and ondansetron [7]. Based on these results and patient convenience, IV fosaprepitant became the recommended version of this drug at Mayo Clinic Rochester, as of January 1, 2011.

Upon making this change, from oral aprepitant to IV fosaprepitant, Mayo Clinic chemotherapy nurses noted that infusion site adverse events were a prominent and substantial problem for a significant number of patients. These nurses reported multiple cases of infusion site erythema and pain either during or shortly after, chemotherapy infusions. It was noted that patients receiving doxorubicin/cyclophosphamide (AC) seemed to have an increased incidence of venous toxicity compared to those receiving alternative chemotherapy regimens. Additionally, they noted an increased rate of potential doxorubicin-induced extravasations with fosaprepitant, noting 7 extravasations within a 6-month time frame, six of which were associated with doxorubicin while one was associated with epirubicin, compared to eleven extravasations over the course of the preceding two years (2008 to 2010). As a result of these findings, Mayo Clinic Rochester guidelines were changed, on November 21, 2011, with recommendations for oral aprepitant to be administered with AC, rather than fosaprepitant.

A review of the comparative trial discussed above[7], revealed that infusion site adverse events such as pain, erythema, induration, and thrombophlebitis were noted to be infrequent, but were observed more frequently with fosaprepitant, compared to aprepitant (2.7% vs. 0.3%, respectively). A previous tolerability study, however, had reported that approximately 10% of fosaprepitant-receiving patients experienced infusion-site pain with fosaprepitant [8] while Merck & Co, Inc. reported the incidence of infusion site reactions (including erythema, pruritus, pain, induration and thrombophlebitis) in 3% of patients[9]. When the current study was initiated, there was no available information that suggested that this problem was more prominent in men versus women or in patients receiving AC chemotherapy versus other chemotherapeutic agents.

Pursuant to the above, a retrospective study was developed to investigate the incidence of venous toxicity related to fosaprepitant administration at Mayo Clinic Rochester.

Materials and methods

Following Mayo Clinic Institutional Review Board approval of this study, pharmacy records were searched to identify all patients who were initiated on AC chemotherapy who also received either aprepitant or fosaprepitant, from January 2011 to April 2012. Electronic medical record (EMR) data were reviewed on all identified patients. Data collected from the EMR included outpatient and inpatient records. Collected variables included: date of birth, gender, ethnicity, primary cancer diagnosis, presence or absence of metastatic disease, chemotherapy regimen, date of chemotherapy, prior history of chemotherapy, current use of corticosteroids, prior use of aprepitant or fosaprepitant, initial antiemetic regimen administered, presence or absence of changes to the antiemetic regimen over the course of

chemotherapy, history of prior infusion site adverse events, documentation of an infusion site adverse event, and type of IV access (peripheral versus central).

Fosaprepitant was prepared and administered per recommended manufacturer guidelines as detailed within the package insert. One hundred and fifty mg of fosaprepitant was administered intravenously over 20 to 30 minutes at a concentration of 1 mg/ml.

Infusion site adverse event details included: erythema, induration, pain, swelling, thrombophlebitis, pruritus, vein discoloration, extravasation or other local reactions at the injection site. Use of fosaprepitant and/or aprepitant was collected for each dose of chemotherapy, including whether patients switched from one to the other.

Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools [10]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Descriptive statistics (mean and standard deviation or N (%)) were summarized overall and by type of IV access and initial antiemetic given.

Results

A total of 148 patients were identified in the pharmacy database and included in this analysis. A detailed description of patient demographics is illustrated in Table 1.

Figure 1 illustrates the use of IV fosaprepitant versus oral aprepitant over time, with the first dose of AC for each patient, demonstrating that IV fosaprepitant was routinely used initially after guidelines were changed, but then oral aprepitant became routinely used following the recognition of an increased incidence of infusion site adverse events.

Table 2 portrays the incidence of infusion site adverse events among the patient population, all of which were associated with peripheral venous access, in contrast to no reactions in patients who received therapy through a central venous access device.

Infusion site adverse events associated with fosaprepitant administration were identified in 34 patients, including: infusion site pain ($n=26$), erythema ($n=22$), swelling ($n=12$), infusion site hives ($n=5$), extravasation ($n=4$), deep venous thrombosis (DVT) ($n=3$), superficial thrombosis ($n=8$), phlebitis/thrombophlebitis ($n=5$), vein discoloration ($n=1$), venous engorgement ($n=1$), venous hardening/induration ($n=4$), and local scarring ($n=1$). Among the 34 patients that experienced an infusion site adverse event, 26 experienced more than one type of event. One patient experienced two separate extravasation events. Of the 98 individual patients who started on IV fosaprepitant, 10 (10%) changed to oral aprepitant for at least some of the subsequent AC doses. The reasons for the changes were: vein toxicity ($n=4$), notation that other patients were having vein toxicity ($n=1$), alternative antiemetic management ($n=1$), no reasoning was provided ($n=3$); additionally, one patient received IV fosaprepitant initially, while awaiting prior authorization, and was changed to oral aprepitant following insurance approval.

Of the patients receiving oral aprepitant, only one had an infusion site adverse event, which was characterized as infusion site erythema following doxorubicin administration. This particular patient had a previous infusion site adverse event at the same site, which was

associated with fosaprepitant administration and, as such, this event may represent a recall reaction, rather than a true adverse event related to aprepitant administration. Of the 44 individual patients who started oral aprepitant, 2 (5%) changed to IV fosaprepitant for at least some of the subsequent AC doses. One patient was changed to try to get improved nausea management, while no reasoning was provided for the other patient.

Among the 148 patients included in this analysis, 132 initially had peripheral IV access and 16 had central venous access. Of the 132 patients with peripheral IV access, 10 were transitioned to central venous access. Documented reasons for the change in type of access included: infusion site adverse events ($n=4$), suboptimal venous access ($n=2$), patient preference ($n=1$), no documented reasoning for the change ($n=2$), and ease of administration ($n=1$). One patient initially had a peripherally inserted central catheter (PICC), which was transitioned to a peripheral IV for the last 2 doses of chemotherapy.

Discussion

This record review substantiates the nurses' perception that the incidence of infusion site adverse events associated with fosaprepitant administration was significantly higher than what had been previously reported at the time that the current study was devised. Merck & Co, Inc. [9] described the results of a controlled clinical study to evaluate the safety of patients receiving fosaprepitant ($n=1143$) and aprepitant ($n=1169$), reporting a 3% incidence of infusion site reactions in the fosaprepitant group, versus 0.5% in the aprepitant group. Grunberg, et al [7] reported significantly more cases of infusion-associated reactions with fosaprepitant than with aprepitant, but these events were only reported in 2.7% of those that received fosaprepitant. Additionally, investigator assessment in this trial concluded that only 18 of the 30 reported events in the fosaprepitant group were related to the study medication [7]. Lasseter, et al [8] conducted a study to assess the tolerability of fosaprepitant (either in 100 mg or 115 mg doses), in comparison to aprepitant, noting an increased incidence of infusion site pain in patients receiving fosaprepitant, 10% ($n=7$) for 100 mg and 8% ($n=5$) for 115 mg, in comparison to no infusion site pain in patients receiving aprepitant. The same investigators noted infusion site erythema in only 1 patient receiving 100 mg fosaprepitant and infusion site induration in only 1 patient with the 115 mg dose of fosaprepitant [8].

The incidence of venous toxicity in the current experience, however, is more comparable to that recently reported by Saito, et al [11], who conducted a placebo-controlled trial assessing the safety and efficacy of fosaprepitant ($n=174$) in patients receiving high dose cisplatin. They found a doubling in the incidence of infusion site adverse events with fosaprepitant (24%, $n=41$), as compared to a placebo (12%, $n=21$) ($p=0.0068$). Among the reported adverse events in their study, 16% ($n=27$) experienced pain at the injection site, 5% ($n=9$) developed injection site erythema, 3% ($n=6$) experienced swelling, 2% ($n=4$) developed phlebitis, and 2% ($n=3$) had extravasations [11]. Saito et al noted that only 2-3% of the infusion reactions were of moderate grade while none of them were severe, without a specific definition of what they considered as moderate or severe reactions.

While the incidence of infusion site reactions are similar in the current study and the Saito et al study, the current experience supports that the magnitude of this toxicity is more prominent than has been previously reported in any of the other trials. Many patients experienced substantial erythema, swelling, and pain, in addition to concerns regarding doxorubicin extravasations, which can cause clinically significant tissue damage. Granted that the severity of the reactions was not prospectively graded, the nursing records reveal that many of the reactions would have been moderate to severe.

Additionally, a recently presented Japanese abstract provided findings quite similar to the present report. These investigators noted a 12 fold increased risk of venous toxicity in patients who concomitantly received an anthracycline (compared to patients who received an anthracycline without fosaprepitant), but no increase in the risk of venous toxicity in patients who received fosaprepitant along with cisplatin[12].

It is remarkable to note the difference in the incidence of infusion reactions reported in the Grunberg et al study [7] (2.7%) versus the current study. One possible explanation could be related to the relatively high number of Mayo patients who receive AC chemotherapy via a peripheral IV approach, as opposed to a central venous access device, which is used for the majority of patients receiving AC chemotherapy in many practices. Speaking against this explanation, however, is that the Grunberg et al study was conducted in many countries where implantable IVs are not commonly used. Another possible reason for the substantially higher incidence and severity of venous toxicity in the current report may be related to the regimen studied. Doxorubicin is a vesicant, in comparison to cisplatin, which is neither an irritant, nor a vesicant. All of the patients in the Grunberg study received cisplatin and they only studied patients for one cycle, which likely explains much of the difference. Further work is ongoing to investigate the incidence of fosaprepitant-induced vein toxicity in patients that are receiving non-anthracycline chemotherapy regimens.

The current study is one of the few studies to investigate the incidence of fosaprepitant-induced infusion site adverse events. The primary weaknesses of this study are relatively standard limitations associated with retrospective study designs. Data abstracted from clinical records may lead to under-ascertainment or over-ascertainment of cases of infusion site adverse events due either to under-reporting, over-reporting or inadequately documenting toxicity data. Lack of blinding to type of antiemetic administered during retrospective review could attribute to bias in determination of infusion site adverse events. Another limitation of this study is that the study population is comprised primarily of middle-aged Caucasian women who live in the United States Midwest, and therefore may not be generalizable to other patient populations.

Although fosaprepitant has been shown to be non-inferior to aprepitant in the efficacy for management of acute and delayed CINV [7], drug tolerability is also an important factor in determining an antiemetic regimen for patients. The current study supports that the incidence and severity of infusion site adverse events associated with fosaprepitant administration, in a group of patients receiving AC largely through peripheral venous access, is significantly higher than those reported in the literature. Further data are needed to determine whether certain patient populations, fosaprepitant dosing or co-administration with particular chemotherapeutic agents increases the likelihood of infusion site adverse events.

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Figure 1.
Fosaprepitant vs. Aprepitant administration rates by month

Table 1**Baseline Demographics**

	Total (N=148)
Age at time of chemo	
Mean (SD)	52.4 (10.4)
Median	53.5
Range	(28.0-76.0)
Sex	
Male	2 (1%)
Female	146 (99%)
Ethnicity	
Caucasian	130 (88%)
African American	5 (3%)
Asian	3 (2%)
Hispanic/Latino	4 (3%)
Other	5 (3%)
Unknown	1 (1%)
Primary cancer diagnosis	
Breast	148 (100%)
Metastasis	
Yes	4 (3%)
No	144 (97%)
Prior intravenous chemotherapy	
Yes	29 (20%)
No	119 (80%)
Current use of corticosteroids	
Yes	148 (100%)
Prior use of aprepitant	
Yes	1 (1%)
No	147 (99%)
Prior use of fosaprepitant	
Yes	3 (2%)
No	145 (98%)
Initial antiemetic given	
Fosaprepitant	98 (66%)
Aprepitant	44 (30%)
Other	6 (4%)
Initial type of IV access	
Implanted vascular access device	16 (11%)
Peripheral IV	132 (89%)

Table 2

Infusion Site Adverse Events

Infusion Site Adverse Event (ISAE)	Fosaprepitant (n=98)		Aprepitant (n=44)	
	No.	%	No.	%
Patients with at least 1 ISAE	34	35	1*	2
Patients with 1 ISAE	26	27	0	0
Infusion site pain	26	27	0	0
Erythema	22	22	1*	2
Swelling	12	12	0	0
Infusion site hives	5	5	0	0
Extravasation	4	4	0	0
Deep venous thrombosis (DVT)	3	3	0	0
Superficial thrombosis	8	8	0	0
Phlebitis/Thrombophlebitis	5	5	0	0
Vein discoloration	1	1	0	0
Venous engorgement	1	1	0	0
Venous hardening/induration	4	4	0	0
Local scarring	1	1	0	0

* This ISAE occurred in a patient with previous ISAE at the same site related to fosaprepitant administration, thus could possibly represent a recall reaction rather than a true aprepitant associated ISAE.