HHS Public Access

Author manuscript

Support Care Cancer. Author manuscript; available in PMC 2015 April 02.

Published in final edited form as:

Support Care Cancer. 2015 January ; 23(1): 55–59. doi:10.1007/s00520-014-2326-9.

An analysis of fosaprepitant-induced venous toxicity in patients receiving highly emetogenic chemotherapy

Livia T. Hegerova,
Department of General Internal Medicine, Mayo Clinic, Rochester, MN 55905, USA

Alexis D. Leal,
Department of General Internal Medicine, Mayo Clinic, Rochester, MN 55905, USA

Darryl C. Grendahl,
Division of Medical Oncology, Mayo Clinic, Rochester, MN 55905, USA

Drew K. Seisler,
Department of Biomedical Statistics, Mayo Clinic, Rochester, MN 55905, USA

Kristine M. Sorgatz,
Division of Medical Oncology, Mayo Clinic, Rochester, MN 55905, USA

Kari J. Anderson,
Division of Medical Oncology, Mayo Clinic, Rochester, MN 55905, USA

Crystal R. Hilger, and
Division of Medical Oncology, Mayo Clinic, Rochester, MN 55905, USA

Charles L. Loprinzi
Division of Medical Oncology, Mayo Clinic, Rochester, MN 55905, USA

Livia T. Hegerova: hegerova.livia@mayo.edu

Abstract

Purpose—Fosaprepitant is an antiemetic used for chemotherapy-induced nausea and vomiting. We recently reported increased infusion site adverse events (ISAE) in a cohort of breast cancer patients receiving chemotherapy with doxorubicin and cyclophosphamide (AC). In this current study, we evaluated the venous toxicity of fosaprepitant use with non-anthracycline platinum-based antineoplastic regimens.

Methods—A retrospective review was conducted of the first 81 patients initiated on fosaprepitant among patients receiving highly emetogenic chemotherapy, on or after January 1, 2011 at Mayo Clinic Rochester. None of these regimens included an anthracycline. Data collected included baseline demographics, chemotherapy regimen, type of intravenous access and type, and severity of ISAE. Data from these patients were compared to previously collected data from

Correspondence to: Livia T. Hegerova, hegerova.livia@mayo.edu.

Disclosures: No financial disclosures

patients who had received AC. Statistical analysis using χ^2 and univariate logistic regression was used to evaluate the association between treatment regimen, fosaprepitant, and risk of ISAE.

Results—Among these 81 patients, the incidence of ISAE was 7.4 % in the non-anthracycline platinum group. The most commonly reported ISAE were swelling (3 %), extravasation (3 %), and phlebitis (3 %). When stratified by regimen, fosaprepitant was associated with a statistically significant increased risk of ISAE in the anthracycline group (OR 8.1; 95 % CI 2.0–31.9) compared to the platinum group.

Conclusions—Fosaprepitant antiemetic therapy causes significant ISAE that are appreciably higher than previous reports. Patients receiving platinum-based chemotherapy appear to have less significant ISAE than do patients who receive anthracycline-based regimens.

Keywords

Fosaprepitant; Phlebitis; Neurokinin-1 receptor antagonist; Highly emetogenic chemotherapy

Introduction

Patients with advanced cancer often struggle with chemotherapy-induced nausea and vomiting (CINV); therefore, advances in prevention of CINV are paramount to improving quality of life 1, 2. Achievement in research on new antiemetics has led to updated recommendations for antiemetic regimens from the American Society of Clinical Oncology (ASCO), Multinational Association of Supportive Care in Cancer (MASCC), European Society of Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN).1, 3–5 All four major groups recommend use of a multi-drug regimen including a neurokinin-1 receptor (NK-1R) antagonist with dexamethasone and a serotonin receptor antagonist in patients receiving highly emetogenic chemotherapy (HEC). The introduction of the NK-1R antagonists has particularly reduced the incidence of delayed CINV 6, 7. The oral agent aprepitant, and its intravenous pro-drug fosaprepitant, are the NK-1R antagonists currently approved for clinical use in the USA.

Fosaprepitant is a water-soluble, phosphorylated derivative of aprepitant and is rapidly converted to aprepitant after intravenous administration. Aprepitant has been shown to be effective for prevention of CINV over a broad range of chemotherapy regimens 8, 9. A large, randomized non-inferiority trial showed that a single dose of intravenous fosaprepitant on day 1 of chemotherapy was similar to the standard 3-day oral aprepitant regimen 10. This shorter, more convenient dosing schedule provides a simplified treatment option for CINV while ensuring medication adherence 1. Additionally, the safety and tolerability of fosaprepitant had been reported to be similar to those of aprepitant, because it is quickly converted to aprepitant following infusion 11. In light of this, Mayo Rochester incorporated fosaprepitant into its practice guidelines for use with highly emetogenic chemotherapy in January 2011.

Shortly after implementation of these new supportive care guidelines, more frequent infusion site adverse events (ISAE) were observed with fosaprepitant administration by Mayo Rochester chemotherapy nurses. They noted that such were particularly problematic

in the large number of patients receiving doxorubicin and cyclophosphamide (AC) chemotherapy. Pursuant to this observation, Mayo antiemetic guidelines were changed so that patients receiving AC chemotherapy were given oral aprepitant, instead of IV fosaprepitant. A subsequent retrospective analysis of Mayo experience was performed, identifying an incidence of venous toxicity related to IV fosaprepitant in 34.7 % of patients receiving AC versus only 2.3 % in such patients receiving oral aprepitant 12. Of note, venous toxicity was noted to be more common in the IV fosaprepitant arm of a randomized trial by Grunberg et al., but the incidence of such was reportedly low (2.7 versus 34.7 % in our study) 10.

After reviewing the results of our study regarding the very high incidence of fosaprepitant-associated venous toxicity with AC regimens, the current study was developed to look at fosaprepitant-associated venous toxicity with non-anthracycline chemotherapy regimens.

Materials and methods

To assess whether platinum-based chemotherapy regimens are associated with increased infusion site adverse events when used with fosaprepitant antiemetic therapy, we conducted a retrospective cohort study of the first 81 patients newly initiated on fosaprepitant after January 1, 2011, who received platinum-based chemotherapy that did not include an anthracycline. Patients were identified using a chemotherapy administration database.

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

Infusion site adverse events were defined as any recorded pain or other adverse events observed at the infusion site and in blood vessels at or near the infusion site, as was done in the previous study with AC 12. Patient records were reviewed for type and severity of adverse events, including all inpatient and outpatient information from the first fosaprepitant infusion to the last documented patient encounter. The study protocol was approved by the Mayo Clinic Institutional Review Board. All patients provided written informed consent for use of their electronic medical records for medical research. Descriptive statistics were used to summarize overall demographics and adverse events.

Additionally, we compared the venous toxicity incidences of those who had received AC in the previous study 12 to patients receiving platinum-based chemotherapy in the current study. Statistical analysis using χ^2 and univariate logistic regression was used to evaluate the association between treatment regimen, fosaprepitant, and risk of ISAE.

Results

There were 81 patients included in this study. The incidence of ISAE in the current study group was 7.4 %. The six patients that had ISAEs were receiving the following chemotherapy regimens: bleomycin-etoposide-cisplatin (n = 1), etoposide-cisplatin (n = 2), gemcitabine-cisplatin (n = 2), and vinorelbine-cisplatin (n = 1). The most commonly reported ISAE were swelling (3 %), extravasation (3 %), and phlebitis (3 %). All infusion-

site reactions were of mild or moderate intensity and were self-limiting. Three patients experienced more than one type of ISAE and three patients changed from fosaprepitant to an alternative antiemetic for at least some of the subsequent chemotherapy doses.

Among the 81 study patients, 64 initially had peripheral IV access and 17 had central venous access. Only one patient with peripheral IV access transitioned to central venous access. All ISAE in the platinum group were associated with peripheral IV access, thus the incidence of ISAEs was 9.4 % in the patients who had peripheral IV access.

In order to compare the incidence of venous reactions in patients receiving AC from our recent report 12 versus those receiving platinum-based regimens, a detailed description of patient demographics in these two groups is illustrated in Table 1. The treatment groups had similar baseline demographics, except for a few differences including gender and primary cancer site. Specifically, all but two patients in the AC group were women with breast cancer. Among the platinum group, most patients were men (61.7 %), were older than 55 (median age 56±13), and were Caucasian (95.0 %). In contrast to the AC group, where all patients had breast cancer, the most common malignancies in the platinum group were lung (25 %), head and neck (21 %), and reproductive or genitourinary cancers (19 %).

Table 2 portrays the incidence of infusion site adverse events among the patient population grouped by chemotherapy regimens.

When stratified by regimen and adjusted for gender, fosaprepitant was associated with a statistically significant increased risk of ISAE in the AC group (OR 8.1; 95 % CI 2.0–31.9) compared to the platinum group ($p<0.001$). In patients who had peripheral IV access, the rates of ISAE were 37.9 and 9.4 % in the AC and platinum-chemotherapy group, respectively. ISAE in the anthracycline group occurred on average 22 days (range 0–61) from initial exposure. ISAE in the platinum group tended to occur later in the chemotherapy course, on average 52 days after initial exposure to fosaprepitant. One of the six patients (16 %) receiving platinum-chemotherapy who had any venous toxicity had it with the first dose of chemotherapy, compared to 11 of the 33 patients receiving AC (33 %). The majority of ISAE in the non-anthracycline platinum group occurred during the second (50 %) and third chemotherapy cycles (33 %).

Discussion

This report supports that fosaprepitant is associated with significantly higher infusion site adverse events when given with AC, as compared to platinum-based, chemotherapy regimens. The results from our experience are in synch with results recently presented by Fujii et al., supporting the hypothesis that fosaprepitant use is associated with venous toxicity differentially between chemotherapy regimens 13. Fujii et al. reported that in 120 patients on fosaprepitant, the odds of an ISAE increased significantly when patients were receiving fosaprepitant in conjunction with an anthracycline regimen, with an odds ratio of 12.1. They did not see any increased risk of vascular toxicity events in a group of patients given fosaprepitant and cisplatin (OR 1.04), when compared to fosaprepitant non-users.

The current study shows that fosaprepitant antiemetic therapy causes significant infusion site adverse events that are appreciably higher than some early reports 10, 14. Merck & Co., Inc. described an incidence of only 3 % in 1,143 patients using fosaprepitant 15. In 2007, a phase I study of 106 healthy participants found that fosaprepitant was well tolerated at doses up to 150 mg 14. However, emerging data from two phase III trials, as well as clinical experience, are suggesting more frequent infusion site adverse events 10, 12, 16. In the Grunberg study, venous toxicity was more common with fosaprepitant than with aprepitant in the first cycle of therapy (2.7 vs. 0.3 %, respectively).10. Saito et al. reported a significantly high rate of adverse events, 24 % in 174 patients receiving fosaprepitant with cisplatin compared to placebo 16. One plausible explanation for the increased rate of adverse events in recent reports, compared to previous tolerability studies, is the time to event. In the current experience involving patients receiving cisplatin, venous toxicity did not occur very often with the initial exposure to fosaprepitant, and many of the early studies did not give repeated fosaprepitant doses for prolonged study periods.

With regards to the severity of the venous toxicity, most reactions in patients receiving non-anthracycline therapy were mild or moderate and clinically manageable. The type of predominant events seen here are similar to reports by Saito et al., which showed pain (15.5 %), erythema (5.2 %), swelling (3.4 %), and phlebitis (2.3 %) as being the most common 16. These events did not appear to delay administration of cancer chemotherapy.

It is noteworthy that the venous toxicity of fosaprepitant is associated with peripheral administration of the drug, as opposed to administration through central venous access. This may partially be responsible for the marked differences in reported infusion reactions among studies, since there are differences between chemotherapy centers, some mainly using peripheral venous access versus central venous access.

The mechanism for why fosaprepitant in anthracycline-based regimens increases venous toxicity is yet to be determined. The time to maximum concentration and mean plasma levels are higher with fosaprepitant compared to oral aprepitant 11, and NK-1R antagonists can alter the metabolism of certain drugs metabolized by the CYP3A4 pathway 17. These factors may be related to the differential incidence of venous toxicity between the intravenous versus oral administration of these antiemetic agents. Interestingly, one practice, anecdotally, has started giving fosaprepitant infusion following, instead of preceding, chemotherapy infusion, and has noted a reduced rate of venous complications. This approach may require further study, including a determination of the antiemetic efficacy of fosaprepitant given in this manner. Other proposed means of limiting this toxicity have included recommendations to give intravenous dexamethasone and to dilute the fosaprepitant more, both of which could be studied.

The major limitations of this current study are those well known to retrospective study designs, including a relatively small sample size, lack of prospective reporting, and no placebo arm to estimate the nocebo effect. While it could be argued that the evaluation of venous toxicity might have picked up venous issues that are not related to fosaprepitant and that the current study did not have a control arm with which to estimate background venous

toxicity, the methodology used in the current trial was identical to that used in a preceding trial 12 whereby an oral aprepitant arm served as a background control.

In implementing supportive care guidelines, the efficacy of antiemetics must be weighed against their own drug side effects. In response to these outcomes, we recommend oral aprepitant to be administered with anthracycline-based chemotherapy that is given by peripheral venous access, rather than fosaprepitant. Mayo institutional guidelines have been changed to reflect this opinion.

Acknowledgments

Funding: This work was supported by the following United States National Institutes of Health Grant-CA 124477 (PI Charles Loprinzi MD)

References

1. Celio L, Ricchini F, De Braud F. Safety, efficacy, and patient acceptability of single-dose fosaprepitant regimen for the prevention of chemotherapy-induced nausea and vomiting. Patient Prefer Adherence. 2013; 7:391–400. [PubMed: 23687442]
2. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008; 358(23):2482–2494. [PubMed: 18525044]
3. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American society of clinical oncology clinical practice guideline update. J Clin Oncol. 2011; 29(31):418–1198.
4. Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010; 21(Suppl 5):v232–243. [PubMed: 20555089]
5. [Accessed June 24th, 2013] National Comprehensive Cancer Network: clinical practice guidelines in oncology: antiemesis, version 1. 2013. 2013http://www.nccn.org/professional/physician_gls/PDF/antiemesis.pdf
6. Van Belle SJ, Cocquyt V. Fosaprepitant dimeglumine (MK-0517 or L-785,298), an intravenous neurokinin-1 antagonist for the prevention of chemotherapy induced nausea and vomiting. Expert Opin Pharmacother. 2008; 9(18):3261–3270. [PubMed: 19040346]
7. dos Santos LV, Souza FH, Brunetto AT, Sasse AD, da Silveira Nogueira lima JP. Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. J Natl Cancer Inst. 2012; 104(17):1280–1292. [PubMed: 22911671]
8. Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer. 2010; 18(4):423–431. [PubMed: 19568773]
9. Herrington JD, Jaskiewicz AD, Song J. Randomized, placebo-controlled, pilot study evaluating aprepitant single dose plus palonosetron and dexamethasone for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Cancer. 2008; 112(9):2080–2087. [PubMed: 18327813]
10. Gnmberg S, Chua D, Maru A, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol—EASE. J Clin Oncol. 2011; 29(11):1495–1501. [PubMed: 21383291]
11. Langford P, Chrisp P. Fosaprepitant and aprepitant: an update of the evidence for their place in the prevention of chemotherapy-induced nausea and vomiting. Core Evid. 2010; 5:77–90. [PubMed: 21042544]
12. Leal A, Kadakia K, et al. Fosaprepitant-induced phlebitis: a focus on patients receiving doxorubicin/cyclophosphamide therapy. Support Care Cancer. 2013 Accepted August.

13. Fujii T, Nishimura N, et al. Impact of fosaprepitant use on dermal and vascular adverse events in anthracycline-based regimens administered through peripheral lines. J Clin Oncol. 2013; 31(suppl; 9629)

14. Lasseter KC, Gambale J, Jin B, et al. Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. J Clin Pharmacol. 2007; 47(7):834–840. [PubMed: 17525168]

15. EMEND (fosaprepitant dimeglumine) for injection [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.;

16. Saito H, Yoshizawa H, Yoshimori K, et al. Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. Ann Oncol. 2013; 24(4):1067–1073. [PubMed: 23117073]

17. Rogers MP, Blackburn L. Use of neurokinin-1 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy. Clin J Oncol Nurs. 2010; 14(4):500–504. [PubMed: 20682506]

Table 1

Baseline demographics

Baseline demographics by type of chemotherapy or patients receiving fosaprepitant

	AC (*N*=99)	Platinum (*N*=81)	Total (*N*= 180)	*p* value
Age at time of chemo				0.0266[a]
N	99	81	180	
Mean (SD)	53.3 (9.7)	56.4 (13.2)	54.7 (11.5)	
Median	55.0	57.0	56.0	
Range	(31.0–74.0)	(22.0–77.0)	(22.0–77.0)	
Gender				<0.0001[b]
Male	2 (2.0 %)	50 (61.7%)	52 (28.9 %)	
Female	97 (98.0 %)	31 (38.3 %)	128 (71.1 %)	
Ethnicity				0.2069[b]
White	91 (91.9%)	77 (95.1 %)	168 (93.3 %)	
Black	2 (2.0 %)	0 (0.0 %)	2 (1.1 %)	
Asian	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)	
Hispanic	3 (3.0 %)	1 (1.2 %)	4 (2.2 %)	
Other	3 (3.0 %)	0 (0.0 %)	3 (1.7%)	
American Indian	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)	
Middle Eastern	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)	
Primary cancer diagnosis				<0.0001[b]
Breast	98 (99.0 %)	4 (4.9 %)	102 (56.7 %)	
Lung	0 (0.0 %)	20 (24.7 %)	20 (11.1 %)	
GI	0 (0.0 %)	12 (14.8%)	12 (6.7%)	
Reproductive or genitourinary	1 (1.0 %)	15 (18.5 %)	16 (8.9%)	
Other	0 (0.0 %)	7 (8.6 %)	7 (3.9 %)	
Endo	0 (0.0 %)	6 (7.4 %)	6 (3.3 %)	
Head	0 (0.0 %)	17 (21.0%)	17 (9.4%)	
Prior history of chemo				<0.0001[b]
No	84 (84.8 %)	40 (49.4 %)	124 (68.9 %)	
Yes	15 (15.2%)	41 (50.6 %)	56 (31.1 %)	
Metastasis				<0.0001[b]
Yes	2 (2.0 %)	22 (27.2 %)	24 (13.3 %)	
No	97 (98.0 %)	59 (72.8 %)	156 (86.7%)	
Corticosteroid use				0.3644[b]
No	1 (1.0 %)	0 (0.0 %)	1 (0.6 %)	
Yes	98 (99.0 %)	81 (100.0 %)	179 (99.4 %)	
Prior use of fosaprepitant				_[b]
No	99 (100.0 %)	81 (100.0 %)	180 (100.0%)	
Prior use of aprepitant				<0.0001[b]

Baseline demographics by type of chemotherapy or patients receiving fosaprepitant

	AC (*N*=99)	Platinum (*N*=81)	Total (*N*= 180)	*p* value
No	98 (99.0 %)	57 (70.4 %)	155 (86.1 %)	
Yes	1 (1.0 %)	24 (29.6 %)	25 (13.9 %)	

AC anthracycline-cyclophosphamide

[a] Kruskal Wallis

[b] Chi-Square

Table 2

Infusion site adverse events

Infusion site adverse events				
	Platinum group (*N*=81)		**Anthracycline-cyclophosphamide group (*N*=99)**	
Infusion site adverse event (ISAE)	Number	%	Number	%
Patients with no ISAE	75	93	65	66
Patients with at least 1 ISAE	6	8	33	34
Patients with >1 ISAE	3	4	26	27
Infusion site pain	0	0	26	27
Erythema	0	0	22	22
Swelling	2	3	12	12
Infusion site hives	0	0	5	5
Extravasation	2	3	4	4
Deep venous thrombosis	1	1	3	3
Superficial thrombosis	0	0	7	7
Phlebitis/thrombophlebitis	2	3	5	5
Vein discoloration	1	1	1	1
Venous engorgement	0	0	1	1
Venous hardening/induration	0	0	4	4
Local scarring	0	0	1	1
Warmth sensation	1	1	0	0