Differential Impact of Fosaprepitant on Infusion Site Adverse Events Between Cisplatin- and Anthracycline-based Chemotherapy Regimens

TAKEO FUJII[1,2], NAOKI NISHIMURA[2], KEVIN Y. URAYAMA[3,4], HISAKO KANAI[5], HIROMASA ISHIMARU[6], JUNKO KAWANO[7], OSAMU TAKAHASHI[4], HIDEKO YAMAUCHI[7] and TERUO YAMAUCHI[1]

[1]*Division of Medical Oncology, Department of Internal Medicine, St. Luke's International Hospital, Tokyo, Japan;*
[2]*Division of Pulmonary Medicine, Department of Internal Medicine, St. Luke's International Hospital, Tokyo, Japan;*
[3]*Department of Human Genetics and Disease Diversity, Tokyo Medical and Dental University, Tokyo, Japan;*
[4]*Center for Clinical Epidemiology, St. Luke's Life Science Institute, Tokyo, Japan;*
[5]*Breast Center/Oncology Center, St. Luke's International Hospital, Tokyo, Japan;*
[6]*Department of Pharmacology, St. Luke's International Hospital, Tokyo, Japan;*
[7]*Department of Breast Surgery, St. Luke's International Hospital, Tokyo, Japan*

Abstract. *Background: Fosaprepitant may be associated with infusion site adverse events (AEs), and these adverse events possibly vary according to chemotherapy regimen. Patients and Methods: 267 oncology patients who were administered anthracycline- or cisplatin-based regimens were retrospectively studied. Multivariate logistic regression was performed in stratified analyses to evaluate potential regimen-specific effects of fosaprepitant. Results: 41.7% of patients administered fosaprepitant experienced infusion site AEs. On the other hand, only 10.9% of patients administered aprepitant experienced AEs. Multivariate analysis showed a statistically significant overall increased risk of infusion site reaction associated with fosaprepitant (p<0.001), but when evaluated separately according to chemotherapy regimen, this relationship appeared to be largely confined to patients receiving an anthracycline-based regimen (OR=12.95, 95%CI=5.74-29.20). No association was observed among patients on cisplatin-based regimens. A test for interaction was statistically significant (p=0.001). Conclusion: Fosaprepitant is associated with an elevated risk of infusion site reaction in patients receiving anthracyclines.*

Correspondence to: Naoki Nishimura, Division of Pulmonary Medicine, Department of Internal Medicine, St. Luke's International Hospital, Address: 9-1, Akashi-cho, Chuo City, Tokyo, 104-8560, Japan. Tel: +81 335415151, Fax: +81 335455939, e-mail: nina@luke.ac.jp

Key Words: Fosaprepitant, anthracycline, cisplatin, infusion site adverse events.

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse event that dramatically affects patients' quality of life. Aprepitant, a neurokinin-1 receptor antagonist administered orally over three days, combined with using a 5-hydroxythtryptamine-3 (5-HT3) and dexamethasone was shown to be effective in preventing CINV in patients receiving highly- or moderately-emetic chemotherapy (1-5). A recent study showed that fosaprepitant, an intravenous infusion type of aprepitant, is as effective in preventing CINV as aprepitant and avoids the challenges associated with patient adherence (6).

In prior studies, local reactions at infusion site of fosaprepitant were reported as adverse events (AE) with an incidence of 7-10%, but no significant difference in AE occurrence was observed between fosaprepitant and aprepitant use (6, 7). Compounding this infusion with anthracycline which in itself has reportedly been associated with 10% local infusion site reactions, through the same peripheral line may plausibly impact the risk of infusion site AEs. One retrospective study reports that the incidence of infusion site AEs associated with fosaprepitant use among patients receiving an anthracycline regimen is higher than what has been shown before (8). To our knowledge, empirical data evaluating a potential synergistic relationship between chemotherapeutic regimen and fosaprepitant use is currently not available in the published literature (9, 10).

In the present study utilizing a well-characterized series of oncology patients administered anthracycline- and cisplatin-based regimens, we evaluated whether the risk of infusion site AEs associated with fosaprepitant (*versus* aprepitant) differs between patients on cisplatin compared to those on anthracyclines.

Patients and Methods

Study population. We conducted a retrospective cohort study consisting of all adult patients (aged 18 years and older) administered anthracycline- or cisplatin-based regimens in 2011 and 2012 at the St. Luke's International Hospital, Tokyo, Japan. Patients who were injected through a central line were excluded (n=10). This resulted in a total of 267 study patients available for analysis (Table I). In 2011, aprepitant was administered as a pre-medication according to standard protocol at St. Luke's International Hospital to prevent CINV for all patients who were administered anthracycline or cisplatin. Aprepitant is an oral anti-emetic medication and is given to patients at least 1 h prior to infusion of chemotherapy and is taken once a day for an additional two days. Fosaprepitant replaced aprepitant in 2012 when becoming available on the market in Japan. It is administered intravenously once through the same infusion line as the chemotherapy. No other changes in the administering protocol were made between 2011 and 2012 pertaining to any other factor including pre- and post-hydration, other pre-medications, the kind and amount of drug solution, and injection schedule. This study was approved by the St. Luke's International Hospital Institutional Review Board and was exempted from requiring individual patient's consent.

Data collection. We accessed the electronic medical records system to obtain demographic data and clinical characteristics pertaining to cancer diagnosis, treatment regimen, and infusion site AEs such as infusion site reaction and skin induration for all eligible patients. The outcomes of interest, infusion site reaction and skin induration, were defined in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Data were collected for fosaprepitant use (*versus* aprepitant), detailed chemotherapy regimen, and additional covariates particularly age, gender, number of prior regimens administered, body mass index, and type of cancer.

Statistical analysis. Comparison of patients' characteristics between those receiving chemotherapy with fosaprepitant *versus* aprepitant was performed using the student's *t*-test for continuous variables and Chi-squared or Fisher's exact test for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariate logistic regression to examine the relationship between fosaprepitant use and infusion site AEs adjusting for potential confounders among all participants. To evaluate our main hypothesis that the risk of infusion site reaction or skin induration associated with fosaprepitant use differs between patients on cisplatin- compared to those on anthracycline-based regimens, we conducted stratified analyses by chemotherapeutic regimen. To evaluate the heterogeneity in effect by chemotherapeutic regimen, statistical tests for interaction were performed among all patients using logistic regression that included a multiplicative term representing the product of fosaprepitant use and chemotherapeutic regimen and adjusting for potential confounders. All statistical tests were two-sided and *p*-values of less than 0.05 were considered statistically significant. We used SPSS ver.19 for all analyses.

Table I. *Characteristics of patients receiving chemotherapy with and without fosaprepitant*.

Characteristics	Fosaprepitant (%)	Aprepitant (%)	*p*-Value*
Patients	120	147	
Gender			
Male	23 (19.2)	20 (13.6)	0.219
Female	97 (80.8)	127 (86.4)	
Age in years, mean (SD)	55.1 (12.8)	53.5 (11.8)	0.339
Body mass index (kg/m^2)			
<18.5	31 (25.8)	31 (21.1)	0.012
18.5-24.9	71 (59.2)	108 (73.5)	
≥25.0	18 (15.0)	8 (5.4)	
mean (SD)	21.0 (3.6)	20.7 (3.0)	0.618
Cancer type			
Breast	77 (64.2)	116 (78.9)	0.006
Lung	18 (15.0)	12 (8.2)	
Gastric	6 (5.0)	11 (7.5)	
Other†	19 (15.8)	8 (5.4)	
Chemotherapy regimen			
Cisplatin-based	43 (35.8)	31 (21.1)	0.007
Anthracycline-based	77 (64.2)	116 (78.9)	
Number of prior regimens			
0	50 (41.7)	66 (44.9)	0.596
1 or more	70 (58.3)	81 (55.1)	
Infusion site adverse events			
Infusion site reaction‡, none	75 (62.5)	133 (90.5)	<0.001
grades 1 or 2	45 (37.5)	14 (9.5)	
Skin induration‡, none	95 (79.2)	145 (98.6)	<0.001§
grade 1	22 (18.3)	2 (1.4)	
grade 2	3 (2.5)	0 (0)	

SD, Standard deviation. **p*-Values were estimated using Fisher's exact test for dichotomous variables, Chi-squared test for variable with more than 2 categories, and student's *t*-test for age and body mass index. All statistical tests were two-sided. †The "other" category comprises cancer types which were less common and included esophageal, bladder, bile duct, gynecological, and urethral cancers. ‡Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. §Fisher's exact test *p*-value evaluating the relationship between skin induration (yes/no) and fosaprepitant/aprepitant use.

Results

Out of the 267 patients included in the analysis, 16.1% were male and the mean age was 54.3 years. Fosaprepitant was administered to 120 (44.9%) patients and the remaining 147 (55.1%) were administered aprepitant. Descriptive examination of patient characteristics showed that the use of fosaprepitant compared to aprepitant differed by BMI, cancer type, and chemotherapy regimen (Table I).

Among fosaprepitant users, 50 patients (41.7%) developed infusion site AEs, while 16 (10.9%) experienced those AEs

Table II. *Percent of infusion site reaction in patients receiving fosaprepitant or aprepitant by chemotherapy regimen.*

Treatment regimen	Fosaprepitant		Aprepitant		*p*-Value*
	N	%	N	%	
All patients, any regimen	120	41.7	147	10.9	<0.001
All patients, cisplatin-based	43	18.6	31	16.1	0.783
Cisplatin + S-1	6	16.7	11	9.1	
Cisplatin + Pemetrexed	8	0.0	7	28.6	
Cisplatin + Gemcitabine	11	36.4	2	0.0	
Cisplatin + 5-Fluorouracil	4	25.0	5	20.0	
Cisplatin + Vinorelbine	5	0.0	1	0.0	
Cisplatin + Etoposide	2	0.0	4	25.0	
Cisplatin + Irinotecan	4	50.0	1	0.0	
Cisplatin + Docetaxel	2	0.0	0	0.0	
Cisplatin + Capecitabine	1	0.0	0	0.0	
All patients, anthracycline-based	77	54.6	116	9.5	<0.001
FEC	61	59.0	90	10.0	
AC	15	33.3	20	10.0	
EC	1	100.0	6	0	

AC, Doxorubicin + cyclophosphamide; AE, Adverse events; EC, epirubicin + cyclophosphamide; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; **p*-Values were estimated using Fisher's exact test for dichotomous variables.

Table III. *Multivariate evaluation of fosaprepitant use, anthracycline- versus cisplatin-based regimen and risk of infusion site adverse events.*

	Model 1†		Model 2†	
Analysis*	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
All patients				
Fosaprepitant (yes vs no)	7.12 (3.68 to 13.78)	<0.001	7.02 (3.55 to 13.91)	<0.001
Fosaprepitant x anthracycline interaction‡	9.69 (2.24 to 41.90)	0.002	11.95 (2.63 to 54.37)	0.001
Cisplatin Group				
Fosaprepitant (yes vs no)	1.17 (0.34 to 4.02)	0.807	0.78 (0.20 to 3.05)	0.717
Anthracycline Group				
Fosaprepitant (yes vs no)	11.89 (5.47 to 25.85)	<0.001	12.95 (5.74 to 29.2)	<0.001

*Each row represents results for a separate logistic regression analysis evaluated using 2 different models. †Odds ratios (OR) and 95% confidence intervals (CI) associated with vasculitis or skin induration were calculated using logistic regression adjusting for patients' age and gender (Model 1) and additionally for body mass index, cancer type, and number of prior regimen (Model 2). The analysis performed on all patients included chemotherapeutic regimen (anthracycline vs cisplatin) in the models. Statistical tests were 2-sided. ‡Results for the multiplicative term used in the logistic regression model to evaluate the two-way interaction between fosaprepitant use and chemotherapy regimen. The risk estimate for the interaction term is defined as the ratio of the joint effect of fosaprepitant and anthracycline regimen and the product of the individual effects [$OR_{fos+anthra}/(OR_{fos} * OR_{anthra})$]. Statistical tests were two-sided.

among aprepitant users (Tables I and II). Infusion site adverse events included infusion site reaction and skin induration. All CTCAE grades for infusion site reaction and skin induration were 1 or 2, and there were no patients with severe infusion site AEs. The occurrence of both infusion site reactions and skin indurations were significantly different between fosaprepitant and aprepitant users (Table I). Most of the infusion site reactions appeared to be grade 2 and only a small number of grade 1, however, the limitation of retrospective chart review did not allow for the clear distinction between the two. Based on medical records, there were two definite cases of phlebitis. About 17% of patients on cisplatin-based regimens experienced infusion site AEs, which appeared similar between fosaprepitant and aprepitant users. Overall, patients on anthracycline-based regimens experienced a larger proportion of infusion site AEs which was disproportionate between fosaprepitant (54.6%) and aprepitant (9.5%). There was some variation in the specific

combination of therapies administered within the cisplatin- and anthracycline-based regimen groups (Table II). The small sample size precluded our ability to make interpretable comparisons across specific combinations of therapies.

In the overall analysis conducted for all patients, multivariate analysis adjusting for potential confounders (including age, gender, BMI, cancer type, chemotherapy regimen, and number of prior regimen) showed fosaprepitant to be independently associated with a strong statistically significant increased risk of infusion site reaction or skin induration (OR=7.02, 95% CI=3.55-13.91, $p<0.001$) (Table III). Results did not markedly differ across two statistical models which differed in the extent of adjustment for potential confounders.

To examine whether this association differed according to chemotherapy regimen, the multivariate analysis was conducted separately for patients receiving a cisplatin-based regimen and for those receiving an anthracycline-based regimen (Table III). Among patients receiving an anthracycline-based regimen, fosaprepitant use was associated with a strong statistically significant increased risk of infusion site reaction or skin induration (OR=12.95, 95% CI= 5.74-29.2, $p<0.001$). In contrast, no association was observed among the cisplatin-based regimen group (OR=0.78, 95% CI=0.20 to 3.05, $p=0.717$). A test of multiplicative interaction in a multivariate logistic regression analysis showed this heterogeneity in the effect of fosaprepitant use between the two chemotherapy groups to be statistically significant ($p=0.001$). An evaluation of potential confounding based on two different statistical models showed similar results.

Discussion

Neurokinin-1 receptor antagonists have been shown to be highly effective in reducing the emetic side-effect of chemotherapeutic agents used to treat cancer patients, but recent reports have demonstrated a potential for them, particularly fosaprepitant, to cause infusion site AEs (6, 7). In the current study, we evaluated this association among a well-characterized group of cancer patients receiving either cisplatin- or anthracycline-based chemotherapies. Our results showed that compared to aprepitant, patients receiving fosaprepitant have a higher risk of experiencing infusion site reaction, and interestingly, this increased risk is mainly limited to those on anthracycline-based regimens.

The mechanism of vascular damage by fosaprepitant and anthracycline is not clear. However, our hypothesis stems from previous studies showing venous irritation as one toxicological property of fosaprepitant suggesting the potential for vascular endothelial damage at the local infusion site (11). Anthracycline also has a potential of causing vascular endothelium damage (12). Thus, anthracycline injection through veins damaged by fosaprepitant may cause greater frequency of infusion site reaction or skin induration. In contrast, cisplatin is not believed to have this type of effect on the vascular endothelium.

Those AEs strongly interfere with patients' quality of life. In our study, some of the patients were referred to dermatologists to evaluate their infusion sites, and as a result, all patients with infusion site reaction improved spontaneously with time. The duration varies from weeks to months. However, skin induration sometimes persisted for an extended period of time and resulted in limited instrumental activity in daily life. Depending on the severity of AEs, more medical treatments may be required, including epidermization in the case of dermal necrosis. Cancer patients are already under tremendous stress and discomfort with concerns about their condition and the side-effects of chemotherapeutic treatment itself. The risk of infusion site AEs places additional burden on the patient, and in rare circumstances may even lead to the suspension of the chemotherapy which could affect prognosis. Thus, administration of a drug, such as fosaprepitant that carries with it significant risk of injection site adverse event should be given additional consideration particularly given that alternate anti-emetic options are available. At this point, when you use fosaprepitant combined with anthracycline regimens we recommend using a central catheter.

There are some limitations to our study. First of all, this is a retrospective study and we were not able to distinguish between grade 1 and grade 2 of infusion site reactions. There were no grade 3 or greater infusion site reactions. Second, we note that the anthracycline group was comprised of only females and breast cancer patients which we acknowledge influences our ability to directly interpret our findings as an anthracycline-specific effect. Although there is no prior reason to suspect a gender- or breast cancer-specific effect of fosaprepitant on risk of infusion site reaction or skin induration, we examined this in our data using additional analyses. Analyses performed only in females among the cisplatin group showed no evidence of a fosaprepitant association with infusion site AEs. Also, eight breast cancer patients not included in the analysis that were on non-anthracycline and non-cisplatin regimen, but used fosaprepitant, did not experience infusion site reaction or skin induration.

Additionally, both regimens were always used in combination with other cytotoxic agents (Table II). In particular, all the anthracycline-based regimens contained cyclophosphamide, and thus, we cannot rule-out the possibility of a cyclophosphamide interaction with fosaprepitant. However, cyclophosphamide is presumed to have a low potential for local infusion site reaction because it can be used intramuscularly. In addition, a previous study using casopitant, another type of NK-1 antagonist, for the

prevention of CINV in patients receiving cyclophosphamide-containing chemotherapies, reported no local site infusion reactions (13). Based on these considerations, the biological plausibility of an anthracycline and fosaprepitant interaction appears more likely. Among the 74 patients on cisplatin regimens, 6 also received vinorelbine, another drug known to have vesicant properties. Five out of these six patients used fosaprepitant, however, no infusion site AE was reported among them.

To our knowledge, a contraindication of fosaprepitant with anthracycline has not been noted, but our results strongly suggest that fosaprepitant in combination with anthracycline drugs administered through peripheral lines are associated with an excess of infusion site AEs. Although, additional studies are required to identify whether the effect is specific to a particular anthracycline, we believe this new evidence warrants consideration in further evaluations regarding the safety of fosaprepitant.

Conflicts of Interest

The Authors indicated no potential conflict of interest.

References

1 Van Belle S, Lichinitser MR, Navari RM, Garin AM, Decramer ML, Riviere A, Thant M, Brestan E, Bui B, Eldridge K, De Smet M, Michiels N, Reinhardt RR, Carides AD, Evans JK and Gertz BJ: Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. Cancer *94*: 3032-3041, 2002.

2 Cocquyt V, Van Belle S, Reinhardt R, Decramer ML, O'Brien M, Schellens JH, Borms M, Verbeke L, Van Aelst F, De Smet M, Carides AD, Eldridge K and Gertz BJ: Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. Eur J Cancer *37*: 835-842, 2001.

3 Rapoport BL, Jordan K, Boice JA, Taylor A, Brown C, Hardwick JS, Carides A, Webb T and Schmoll HJ: 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 *18*: 423-431, 2010.

4 Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, Hipple A, Evans JK, Horgan KJ and Lawson F: Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer *97*: 3090-3098, 2003.

5 Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD, Raftopoulos H, Grunberg SM, Gabriel M, Rodgers A, Bohidar N, Klinger G, Hustad CM, Horgan KJ and Skobieranda F: Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol *23*: 2822-2830, 2005.

6 Grunberg S, Chua D, Maru A, Dinis J, DeVandry S, Boice JA, Hardwick JS, Beckford E, Taylor A, Carides A, Roila F and Herrstedt J: 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 *29*: 1495-1501, 2011.

7 Lasseter KC, Gambale J, Jin B, Bergman A, Constanzer M, Dru J, Han TH, Majumdar A, Evans JK and Murphy MG: Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. J Clin Pharm *47*: 834-840, 2007.

8 Plosker GL and Faulds D: Epirubicin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cancer chemotherapy. Drugs *45*: 788-856, 1993.

9 Coukell AJ and Faulds D: Epirubicin. An updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of breast cancer. Drugs *53*: 453-482, 1997.

10 Olver IN: Prevention of chemotherapy-induced nausea and vomiting: focus on fosaprepitant. Ther Clin Risk Manag 4: 501, 2008.

11 Chow AY, Chin C, Dahl G and Rosenthal DN: Anthracyclines cause endothelial injury in pediatric cancer patients: a pilot study. J Clin Oncol *24*: 925-928, 2006.

12 Herrstedt J, Apornwirat W, Shaharyar A, Aziz Z, Roila F, Van Belle S, Russo MW, Levin J, Ranganathan S, Guckert M and Grunberg SM: Phase III trial of casopitant, a novel neurokinin-1 receptor antagonist, for the prevention of nausea and vomiting in patients receiving moderately emetogenic chemotherapy. J Clin Oncol *27*: 5363-5369, 2009.

Received August 27, 2014
Revised October 5, 2014
Accepted October 10, 2014