Support Care Cancer (2014) 22:1461–1466
DOI 10.1007/s00520-013-2106-y

ORIGINAL ARTICLE

Incidence of infusion-site reactions associated with peripheral intravenous administration of fosaprepitant

Jordan D. Lundberg · Brooke Sorgen Crawford · Gary Phillips · Michael J. Berger · Robert Wesolowski

Received: 24 September 2013 / Accepted: 12 December 2013 / Published online: 9 January 2014

Abstract
Purpose Fosaprepitant is known to cause infusion-site reactions. However, there is limited data regarding these reactions including the effect of peripheral intravenous administration or other potential factors on their incidence. This single-institution retrospective study was undertaken to investigate the incidence of infusion-site reactions with single-dose intravenous (IV) fosaprepitant when given through a peripheral line prior to administration of chemotherapy. Risk factors for the development of infusion-site reactions with fosaprepitant were also explored.
Methods Medical records of patients with cancer receiving IV fosaprepitant through a peripheral line were reviewed. The primary objective of this study was to estimate the incidence of infusion-site reactions at our institution. Data collection included demographics, fosaprepitant infusion information, and grading of reactions.
Results We found a 15 % incidence of infusion-site reactions among all peripherally administered doses of fosaprepitant. The 50 reactions occurred in 43 unique patients representing an incidence per patient of 28.7 % (43/150; 95 % confidence interval (CI) 21.6–36.6). Factors found to be associated with infusion-site reactions included age [odds ratio (OR) 0.97 (95 % CI 0.94–0.99)], location of IV line [OR forearm vs. hand 0.41 (95 % CI 0.20–0.85); OR antecubital fossa vs. hand 0.31 (95 % CI 0.11–0.87)], and simultaneous maintenance IV fluid rate ≥100 mL/h during fosaprepitant infusion [OR 0.19 (95 % CI 0.08–0.44)].
Conclusions The incidence of infusion-site reactions with peripherally administered fosaprepitant as seen in this study is higher than that reported in the package insert. Risk factors for developing infusion-site reactions in our patient population include age, location of IV line, and simultaneous maintenance IV fluid rate of <100 mL/h.

Keywords Fosaprepitant · Infusion-site reactions · Peripheral intravenous administration

Background

Despite progress in the management of chemotherapy-induced nausea and vomiting (CINV), this problem still remains among the most troubling side effects of chemotherapy. Without appropriate antiemetic prophylaxis, more than 90 % of patients who receive highly emetogenic chemotherapy (HEC) will experience vomiting. With the selection of appropriate antiemetics prior to HEC, that number can be reduced to approximately 30 % [1–3]. Prevention of nausea, however, remains challenging as evidenced by the results of a recently published phase III trial in which only 38 % of patients receiving the standard antiemetic regimen were without nausea for the overall period (0–120 h post-chemotherapy) [4].

With the advent of the neurokinin-1 (NK1) antagonist aprepitant and the intravenous (IV) prodrug fosaprepitant, CINV has become even more manageable. Two phase III trials of patients receiving HEC compared standard antiemetic therapy (ondansetron and dexamethasone) to standard antiemetic therapy plus aprepitant. These studies demonstrated a 10–15 % absolute reduction of acute emesis and a 20 % absolute reduction of delayed emesis [5, 6]. Another phase III trial involving patients treated with HEC demonstrated that

J. D. Lundberg (✉) · B. S. Crawford · M. J. Berger · R. Wesolowski
The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute at The Ohio State University, 410 W 10th Ave, 368 Doan Hall, Columbus, OH 43210, USA
e-mail: jordan.lundberg@osumc.edu

G. Phillips
Center for Biostatistics, The Ohio State University, Columbus, OH, USA

a single dose of IV fosaprepitant was non-inferior to the standard 3-day oral regimen of oral aprepitant [7]. This single-dose regimen of fosaprepitant may be an attractive treatment option due to its convenience, cost, and similar efficacy.

Although there was no difference in efficacy between the two treatment options, there is an added safety risk with IV fosaprepitant due to its propensity to cause infusion-site reactions (such as pain, erythema, edema, and thrombophlebitis) when administered peripherally [7]. There is currently limited data describing the risk of infusion-site reactions with peripherally administered fosaprepitant. The incidence reported in published literature and the package insert is 2.2 to 3 % across all grades, with grade 3 or 4 infusion-site reactions occurring rarely [7, 8]. A recently published study out of Japan reported an incidence of 23.6 % in the treatment group compared to 12.4 % in the placebo group [9]. The difficulty in interpreting these data is that the number of patients receiving fosaprepitant through a peripheral line versus a central line is not reported, so the true incidence of infusion-site reactions when administered peripherally is unknown.

At The Arthur G. James Cancer Hospital at The Ohio State University, fosaprepitant became the preferred NK1 antagonist in September 2012. Since that time, some clinicians have noticed an increased incidence of infusion-site reactions. This rate is thought to be in excess of what has been reported in the literature with this agent. Therefore, this study was undertaken to investigate the incidence of infusion-site reactions with single-dose IV fosaprepitant at The James when given through a peripheral line preceding chemotherapy. Confounding factors for the development of infusion-site reactions with fosaprepitant will also be explored.

Methods

Study design

We conducted an IRB-approved, retrospective review of patients who received IV fosaprepitant through a peripheral line between September 2012 and December 2012. Patients treated with fosaprepitant were identified for inclusion using a report of fosaprepitant use during the specified time period from the inpatient records at The Arthur G. James Cancer Hospital at The Ohio State University or outpatient records at any of the outpatient infusion center locations. Based on the package insert and institutional standards, fosaprepitant was administered at a concentration of 1 mg/mL (150 mg/150 mL), compounded in Baxter® 0.9 % sodium chloride IV bags over 20 min. The IV line was then flushed with 0.9 % sodium chloride maintenance solution before chemotherapy administration. We acknowledge the possibility that some variability in infusion time and flushing procedure existed based on personal nursing practice. The information about an infusion-site reaction was extracted from the patient's medical chart based on preformatted "smart phrases" used by nurses to standardize reporting of these reactions. When appropriate, information was extracted from nursing toxicity assessments, documentation of telephone encounters, or office visits.

Inclusion criteria

To qualify for inclusion in the study, patients were required to be between the ages of 18 and 89 years of age and received fosaprepitant through a peripheral IV line during the specified time period.

Exclusion criteria

Patients who were incarcerated or pregnant were excluded from the data analysis.

Data

Data collection included gender, age, type and stage of malignancy, past and current chemotherapy regimens, past fosaprepitant exposure, location of peripheral line, duration of fosaprepitant infusion, total volume and dilution of fosaprepitant, maintenance IV fluid rate during fosaprepitant infusion, incidence of infusion-site reactions experienced by the patient, timing of the reaction in relation to the infusion of fosaprepitant and the chemotherapy, grading of the reaction by the nurse (Table 1), future administration of fosaprepitant in the event of a previous infusion-site reaction, and nursing management of patients that experienced an infusion-site reaction (use of cold compresses, placement of new IV line, referral for placement of central line, discontinuation of fosaprepitant, etc.). The charts of all patients who experienced an infusion-site reaction were reviewed by a physician (the senior author) who verified the reaction and determined the grade based on information provided in the chart. If the chart

Table 1 Grades of infusion-site reactions

Grade	Definition
1	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
2	Pain at access site, lipodystrophy and/or edema and/or phlebitis
3	Ulceration or necrosis, severe tissue damage, operative intervention indicated
4	Life-threatening consequences, urgent intervention indicated
5	Death

Common Terminology Criteria for Adverse Events version 4.03

contained insufficient information to reliably determine the grade, the nursing assessment of the grade was used.

Sample size

The primary objective of this study was to estimate the incidence of infusion-site reactions when fosaprepitant was administered through a peripheral line at our institution between September and December 2012. We estimated the rate of infusion-site reactions per number of doses as well as the rate of infusion-site reactions per number of patients treated with fosaprepitant. Using a sample of 100 subjects and assuming an incidence of infusion-site reactions of 5 %, the 95 % confidence interval will have a width of 9.7 % (actual confidence interval (CI) 1.6 to 11.3). This width is under 10 %, which is considered narrow enough for the purposes of this study.

Statistical analysis

The primary analysis was done to estimate the incidence of infusion-site reactions and its associated 95 % confidence interval using exact binomial methods. The study population was described using means and standard deviations or medians and the interquartile range depending on the distribution of the continuous variable. Categorical variables were presented using frequencies and percentages. Secondary analyses used exact logistic regression methods to determine if any patient demographics or clinical characteristics were associated with an infusion-site reaction. This analysis included both univariate and multivariate analyses to identify patient characteristics associated with infusion-site reactions. All analyses were run using Stata®, version 12.1, Stata Corporation, College Station, TX, USA.

Results

During the study period, 150 patients received 333 doses of fosaprepitant through a peripheral IV line. In the study population, the incidence of infusion-site reactions was 15 % (50/333; 95 % CI 11.4–19.3) among all peripherally administered doses of fosaprepitant. The 50 reactions occurred in 43 unique patients representing an incidence per patient of 28.7 % (43/150; 95 % CI 21.6–36.6). In patients in whom infusion-site reactions occurred, there was a range of 1–3 reactions per patient with one patient experiencing 3 reactions and five patients experiencing 2 reactions. The median number of fosaprepitant doses received per patient during the study period was 2 (range 1–7). Differences seen between the group who experienced an infusion-site reaction and the group without infusion-site reactions are summarized in Table 2. All reactions were grade 2 or less according to CTCAE v4.03 criteria as determined by the nurses at the time of the reaction and later verified by a physician based on documentation of the reaction (Table 3). The discordance rate between the grading of the reaction by the physician and nurses was 14 % (7/50).

Table 2 Baseline characteristics

Variable	Reaction group (n=43)	No reaction group (n=107)
Age[a]	54 (49–62)	59 (51–67)
Female	29 (67 %)	44 (41 %)
Peripheral IV line placed in the hand	18 (42 %)	22 (21 %)
Simultaneous maintenance IV fluid rate ≥100 mL/h	6 (14 %)	53 (50 %)
Patients with breast cancer	18 (42 %)	9 (8 %)
Previous fosaprepitant exposure	28 (65 %)	16 (15 %)
Median previous fosaprepitant doses (range)	1 (0–4)	0 (0–24)
Patients receiving vesicant chemotherapy	22 (51 %)	23 (21 %)

[a] Expressed as medians with interquartile ranges

Univariate analyses (Tables 4 and 5) identified several risk factors for the development of infusion-site reactions including age [odds ratio (OR) for a 1-year increase in age 0.97 (95 % CI 0.95–1.00)], female gender [OR 2.89 (95 % CI 1.52–5.47)], diagnosis of breast cancer [OR 7.52 (95 % CI 3.10–18.3)], diagnosis of a hematologic malignancy [OR 3.32 (95 % CI 1.13–9.79)], and concurrent vesicant chemotherapy [OR 4.15 (95 % CI 2.21–7.78)]. The univariate analyses also identified several effective strategies associated with lower rates of infusion-site reactions such as infusing fosaprepitant through veins in the forearm [OR 0.41 (95 % CI 0.21–0.80)] as opposed to veins in the hand, as well as a simultaneous maintenance IV fluid rate ≥100 mL/h during fosaprepitant infusion [OR 0.19 (95 % CI 0.08–0.43)]. On multivariate analyses per episode, age [OR for a 1-year increase in age 0.97 (95 % CI 0.94–0.99)], location of IV line [OR for placement of IV line in the forearm vs. hand 0.41 (95 % CI 0.20–0.85); OR for placement of IV line in the antecubital fossa vs. hand 0.31 (95 % CI 0.11–0.87)], and simultaneous maintenance IV fluid rate ≥100 mL/h during fosaprepitant infusion [OR 0.19 (95 % CI 0.08–0.44)] remained statistically significant in their association with infusion-site reactions

Table 3 Observed grades of infusion-site reactions

Grade of reaction[a]	Percent	95 % CI
Grade 1	62	48–74
Grade 2	34	22–48

Grading for two reactions was not determined

[a] There were no grade 3 or 4 reactions

Table 4 Univariate analysis of infusion-site reactions per episode

Variable	Infusion-site reaction OR	95 % CI	*p* value
Age[a]	0.97	0.95–1.00	0.018
Female	2.89	1.52–5.47	0.001
Past chemotherapy	0.85	0.43–1.69	0.641
150 mg/250 mL	0.80	0.10–6.68	0.841
Previous fosaprepitant count[a]	1.01	0.90–1.12	0.919
Type			
Head and neck	0.53	0.11–2.53	0.424
Lung (referent)	1.00	–	–
Breast	7.52	3.10–18.3	<0.001
Colorectal	2.37	0.24–23.4	0.458
Gynecologic	0.81	0.21–3.13	0.765
Hematologic	3.32	1.13–9.79	0.029
Other	1.10	0.41–2.93	0.847
Stage			
I (referent)	1.00	–	–
II	1.05	0.29–3.79	0.941
III	0.79	0.23–2.71	0.712
IV	0.39	0.11–1.31	0.126
Location			
Hand (referent)	1.00	–	–
Forearm	0.41	0.21–0.80	0.009
Antecubital fossa	0.30	0.11–0.81	0.017
Duration			
20 min (referent)	1.00	–	–
30 min	0.68	0.25–1.82	0.445
40 min	1.82	0.18–17.9	0.608
Simultaneous maintenance IV fluid rate			
0 to 99 (referent)	1.00	–	–
≥100	0.19	0.08–0.43	<0.001
Current chemotherapy			
Non-vesicant/non-irritant	1.38	0.16–11.8	0.766
Irritant (referent)	1.00	–	–
Vesicant	4.15	2.21–7.78	<0.001

[a] OR is for a 1-year increase in age and for a 1-unit increase in the previous fosaprepitant count

(Tables 6 and 7). On multivariate analysis per patient, the only remaining statistically significant variable was location of IV line [OR for placement of IV line in the forearm vs. hand 0.19 (95 % CI 0.06–0.55); OR for placement of IV line in the antecubital fossa vs. hand 0.10 (95 % CI 0.01–0.84)].

Discussion

To our knowledge, this study represents the first analysis of the incidence of infusion-site reactions specifically in patients

Table 5 Univariate analysis of infusion-site reactions per patient

Variable	Infusion-site reaction OR	95 % CI	*p* value
Age[a]	0.98	0.95–1.02	0.371
Female	4.72	1.49–15.0	0.008
Past chemotherapy	0.45	0.16–1.27	0.132
150 mg/250 mL	3.58	0.31–41.6	0.307
Previous fosaprepitant count[a]	0.98	0.73–1.31	0.899
Type			
Head and neck	0.74	0.07–7.62	0.801
Lung (referent)	1.00	–	–
Breast	10.67	2.64–43.1	0.001
Hematologic	2.96	0.43–20.4	0.270
Other	0.40	0.04–4.07	0.442
Stage			
I (referent)	1.00	–	–
II	0.91	0.15–5.66	0.919
III	0.38	0.06–2.45	0.312
IV	0.12	0.02–0.86	0.035
Location			
Hand (referent)	1.00	–	–
Forearm	0.17	0.06–0.51	0.001
Antecubital fossa	0.11	0.01–0.88	0.038
Duration			
20 min (referent)	1.00	–	–
30 min	0.85	0.18–4.01	0.833
Simultaneous maintenance IV fluid rate			
0 to 99 (referent)	1.00	–	–
≥100	0.27	0.09–0.87	0.029
Current chemotherapy			
Non-vesicant/non-irritant	1.38	0.16–11.8	0.767
Irritant (referent)	1.00	–	–
Vesicant	4.15	2.21–7.78	<0.001

[a] OR is for a 1-year increase in age and for a 1-unit increase in the previous fosaprepitant count

Table 6 Multivariate analysis of infusion-site reactions per episode

Variable	Infusion-site reaction OR	95 % CI	*p* value
Age[a]	0.97	0.94–0.99	0.005
Location			
Hand (referent)	1.00	–	–
Forearm	0.41	0.20–0.85	0.016
Antecubital fossa	0.31	0.11–0.87	0.026
Simultaneous maintenance IV fluid rate			
0 to 99 (referent)	1.00	–	–
≥100	0.19	0.08–0.44	<0.001

[a] OR is for a 1-year increase in age

Table 7 Multivariate analysis of infusion-site reactions per patient

Variable	Infusion-site reaction OR	95 % CI	*p* value
Location			
Hand (referent)	1.00	–	–
Forearm	0.19	0.06–0.55	0.022
Antecubital fossa	0.10	0.01–0.84	0.034

receiving fosaprepitant through a peripheral line. We observed an overall incidence of 15 % (95 % CI 11.4–19.3) per episode and 28.7 % (95 % CI 21.6–36.6) per patient, which is severalfold higher than that reported in the package insert [8]. To date, there have been no identifiable explanations for why these reactions occur. Potential explanations for the propensity of fosaprepitant to cause infusion-site reactions could be the pH of the fosaprepitant infusion solution (8.3), the concentration or rate of the solution, and lastly, the polysorbate 80 content of the formulation. Infusion reactions to polysorbate 80, however, are mostly systemic anaphylactic-type reactions as opposed to reactions at the site of infusion as seen with fosaprepitant [10].

We also examined potential risk factors for patients experiencing infusion-site reactions with peripherally administered fosaprepitant. On univariate analyses, these risk factors included age, female gender, peripheral IV lines placed in the hand rather than in the forearm or antecubital fossa, simultaneous maintenance IV fluid rate <100 mL/h, patients with breast cancer or a hematologic malignancy, and concurrent vesicant chemotherapy. On multivariate analyses per episode, the only risk factors that continued to show association with infusion-site reactions included age, location of IV line (IV lines placed in the hand showed the second highest association with infusion-site reactions), and simultaneous maintenance IV fluid rate (rates of <100 mL/h showed the highest association with infusion-site reactions). Breast cancer patients in the reaction group were all female which could explain why the higher percentage of breast cancer patients seen in the reaction group did not remain statistically significant on multivariate analysis. Of the 19 breast cancer patients in the reaction group, 14 (74 %) had peripheral IV lines placed in the hand and 17 (89 %) had a simultaneous maintenance IV fluid rate <100 mL/h. Another risk factor identified on univariate analysis that did not remain statistically significant on multivariate analysis was concurrent vesicant chemotherapy. The reason for this is not fully clear but perhaps precautions (i.e., avoiding joints where the IV catheter could be bent or extravasate; using larger veins as opposed to smaller veins; close attention to adequate blood return before, during, and after infusion; using heat packs/pads to keep veins dilated; and using higher maintenance IV fluid rates to keep veins patent) that are normally instituted prior to administration of vesicant chemotherapy agents through a peripheral line may also be effective in reducing the fosaprepitant-related infusion-site reactions. Of the 27 patients in the reaction group that received vesicant chemotherapy following fosaprepitant administration, 25 (93 %) were female, 16 (59 %) had peripheral IV lines placed in the hand, and 24 (89 %) had a simultaneous maintenance IV fluid rate <100 mL/h. Another possible explanation could be that the type of subsequent chemotherapy following administration of fosaprepitant is irrelevant when it comes to the risk of developing fosaprepitant-related infusion-site reactions. On multivariate analysis per patient, the only remaining statistically significant variable was location of IV line. A possible explanation for this difference could be the smaller sample size when analyzing variables per patient as opposed to analysis per episode, limiting power to detect associations with variables.

Observed management strategies for the treatment of infusion-site reactions included placing new IV lines and the use of warm protocol (applying warmth to the affected area for 15–20 min at least four times per day for the first 24–48 h), which seemed to help alleviate the patients' discomfort. Placing new IV lines, particularly in patients with breast cancer, presents a challenge due to the fact that many of these patients have had axillary lymph node dissections, leaving only one viable arm for IV infusions. Observed management strategies for the prevention of future infusion-site reactions included switching to oral aprepitant, switching to an alternative antiemetic regimen (i.e., olanzapine-containing regimen [4]), prolonging the fosaprepitant infusion duration, further dilution of fosaprepitant to 0.6 mg/mL for the next administration, and even placement of implanted ports. Switching to oral aprepitant or to an alternative antiemetic regimen will avoid the potential for infusion-site reactions altogether, and this was observed in 18.6 % (8/43) of patients in our study. There were only four patients that were switched to the more dilute fosaprepitant infusion (150 mg in 250 mL) after experiencing infusion-site reactions. All four of these patients did not experience an infusion-site reaction following the use of a more dilute formulation of the agent. One of these patients experienced infusion-site reactions twice prior to receiving the more dilute fosaprepitant. The second infusion-site reaction in this patient consisted of standard concentration fosaprepitant (150 mg in 150 mL) given through a peripheral line in the antecubital fossa over 40 min with a simultaneous maintenance IV fluid rate of 300 mL/h. Fourteen patients underwent port placement after experiencing an infusion-site reaction. It is presumed that these patients were protected from future infusion-site reactions. However, future administrations were not examined in these patients as data collection only included peripheral administrations. Therefore, it is not known for certain if these patients experienced any additional infusion-site reactions when fosaprepitant was administered through a port.

The infusion-site reactions were usually short-lived and resolved in minutes to hours; however, 24 % (12/50) of the infusion-site reactions were longer lasting with a median duration of 14 days (interquartile range 6.25–15 days).

Given the high incidence of infusion-site reactions, patient discomfort, and nursing dissatisfaction observed at our institution, the standard fosaprepitant administration procedure was amended. The dilution of fosaprepitant was changed to 250 mL of 0.9 % sodium chloride base solution, which was to be administered over 30 min for all patients regardless of venous access device. For patients who were to receive fosaprepitant peripherally or who had experienced a previous infusion-site reaction to fosaprepitant, providers were also encouraged to consider the use of oral aprepitant or the use of a different antiemetic regimen, such as olanzapine combined with dexamethasone and palonosetron [4]. These changes went into effect near the end of our study period, and it is not yet clear whether they will help lower the rate of fosaprepitant-related infusion-site reactions. We plan to conduct an additional analysis to determine the impact of the above changes.

There are several limitations to our study. First, the study was conducted in a single center and represented a small sample size, although the analysis included a wide variety of patients with multiple different cancer types, making these results more generalizable. Second, patients were analyzed retrospectively, creating the possibility of information bias. We relied on nursing documentation for much of our data collection and therefore encountered several instances of missing information; in particular, the grading of the reaction was often not documented. In order to improve accuracy, a physician reviewed the charts of all the patients with documented infusion-site reactions and verified the diagnosis and grading with a discordance rate of 14 %. Lastly, to maintain consistency with previously published literature [7, 9], we chose to include infusion-site reactions that occurred during chemotherapy and beyond. Forty-eight percent of all reactions occurred after administration of fosaprepitant, but the lack of a comparator arm (a chemotherapy arm that did not receive fosaprepitant) makes it difficult to determine whether these reactions were due to the combination of fosaprepitant and chemotherapy or chemotherapy alone. Based on our previous institutional experience, infusion-site reactions were very uncommon prior to the use of intravenous fosaprepitant, even in patients treated with vesicant chemotherapy.

Conclusions

The incidence of infusion-site reactions with peripherally administered fosaprepitant as seen in this study is much higher than that reported in the package insert. Fortunately, all reactions were mild to moderate in severity and resolved quickly, confirming that IV fosaprepitant should remain a valuable agent in nausea prevention prior to HEC. Risk factors for developing infusion-site reactions include age, location of IV line, and simultaneous maintenance IV fluid rate of <100 mL/h. More robust prospective trials are needed to confirm these findings.

Disclosures None

References

1. Herrstedt J (2008) Antiemetics: an update and the MASCC guidelines applied in clinical practice. Nat Clin Pract Oncol 5:32–43
2. Hesketh PJ, Kris MG, Grunberg SM et al (1997) Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 15:103–109
3. Roila F, Herrstedt J, Aapro M et al (2010) 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 21(Suppl 5):v232–v243
4. Navari RM, Gray SE, Kerr AC (2011) Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 9(5):188–195
5. Hesketh PJ, Grunberg SM, Gralla RJ et al (2003) The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin. J Clin Oncol 21:4112–4119
6. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD et al (2003) Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 97:3090–3098
7. Grunberg S, Chua D, Maru A et al (2011) 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(11):1495–1501
8. EMEND® for Injection [package insert] (2012) Merck & Co., Inc
9. Saito H, Yoshizawa H, Yoshimori K et al (2012) 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 24:1067–1073
10. Coors EA, Seybold H, Merk HF, Mahler V (2005) Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. Ann Allergy Asthma Immunol 95(6):593–599