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A phase 2 study of fosaprepitant combined with high-dose dexamethasone for Japanese cancer patients receiving highly emetogenic chemotherapy

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Abstract

Purpose: Combination therapy of fosaprepitant, dexamethasone (DEX) and a serotonin (5-HT$_3$) receptor antagonist is a standard antiemetic prophylaxis for patients receiving highly emetogenic chemotherapy (HEC). However, the appropriate dose of DEX has not been established in Japan. This study determined the efficacy and safety of triplet antiemetic prophylaxis in Japanese patients receiving HEC when administered the same doses of DEX as those given in a previous international phase 3 study on this drug.

Methods: To assess the efficacy and safety of a sufficient dose of DEX (12 mg on day 1, 8 mg on day 2, 16 mg on days 3 and 4) in combination with intravenous fosaprepitant and granisetron, we prospectively examined patients receiving HEC including cisplatin ($\geq$50 mg/m^2). The primary endpoint was to determine the percentage of patients who had achieved a complete response (CR), which was defined as no vomiting and no rescue therapy during the entire treatment course.

Results: Between February 2013 and January 2015, 44 patients were enrolled with a median age of 65 years (range, 30–75). There were 34 males (77.3%) in the study. Most of the patients had upper gastrointestinal cancers. The CR rate during the treatment course was 70% (95% confidence interval [CI]: 55%–83%) in the overall phase and 91% (95% CI: 78%–97%) in the acute phase and 70% (95% CI: 55%–83%) in the delayed phase. Appreciable severe toxicities related to the antiemetic therapy were not observed.

Conclusions: These results suggest that a sufficient dose of DEX in combination with fosaprepitant and granisetron is optimal as an antiemetic prophylaxis for Japanese patients receiving HEC.

Abbreviations: 5-HT$_3$ = serotonin, CC = complete control, CI = confidence interval, CINV = chemotherapy-induced nausea and vomiting, CR = complete response, DEX = dexamethasone, HEC = highly emetogenic chemotherapy, NK$_1$ = neurokinin type-1, PS = performance status, ULN = upper limit of the normal.

Keywords: cisplatin, dexamethasone, fosaprepitant, high emetic chemotherapy

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a harmful adverse event in patients receiving cancer chemotherapy. Without adequate antiemetic treatment, more than 90% of patients develop nausea and vomiting during highly emetogenic chemotherapy (HEC), which includes cisplatin. Therefore, the appropriate control of CINV can lead to better chemotherapy efficacy and an increased quality of life. Current guidelines for the management of CINV in patients receiving HEC recommend triplet antiemetic prophylaxis consisting of a serotonin (5-HT$_3$) antagonist, dexamethasone (DEX), and a neurokinin type-1 (NK$_1$) receptor antagonist,[1] including the oral aprepitant and fosaprepitant.

Fosaprepitant is a water-soluble phosphoryl pro-drug of aprepitant and is administered intravenously. In the international double-blinded, placebo-controlled, randomized phase 3 trial (EASE trial), the antiemetic efficiency of single-dose fosaprepitant (150 mg on day 1) was equivalent to that of a 3-day course of oral aprepitant (125 mg on day 1, 80 mg on days 2 and 3 in patients receiving HEC.[2] In a Japanese phase 3 trial of the triplet antiemetic therapy consisting of fosaprepitant, granisetron and DEX, antiemetic triplet therapy including fosaprepitant was superior to doublet therapy consisting of a 5-HT$_3$ antagonist and DEX in patients receiving HEC.[3] Because NK$_1$ receptor antagonists suppress DEX metabolism, the concentration of DEX reaches high plasma levels when used in combination with NK$_1$ receptor antagonists.[4] It is recommended that doses of DEX be reduced on days 1 and 2 when fosaprepitant is administered on day 1. However, the appropriate doses of DEX on days 3 and 4, when used in combination with fosaprepitant, have not yet been determined in Japan. While doses of DEX given in the EASE trial were 12 mg on day 1, 8 mg on day 2, and 16 mg on days 3 and 4,[2] the doses of DEX employed in the Japanese phase 3 study were 10 mg on day 1, 4 mg on day 2, and 8 mg on day 3.[3] The efficacy of antiemetic triplet therapy, which was assessed by the rate of complete response (CR) in the acute phase (0–24 hours after chemotherapy) and delayed phase (24–120 hours after chemotherapy) were 94% and 65%, respectively, in the Japanese phase 3 study and 89% and 74.8%, respectively, in the EASE trial. Thus, it is possible that reduced antiemetic effects in Japanese patients depend upon the doses of DEX.

In this single-arm phase 2 study, we explored the efficacy and safety of antiemetic prophylaxis consisting of fosaprepitant, a 5-HT$_3$ antagonist, and sufficient doses of DEX in Japanese patients receiving HEC when administered the same doses of DEX as those given in the EASE trial.

2. Materials and methods

2.1. Objective and study design

This was a multicenter, phase 2 study conducted by the Kyushu Medical Oncology Group. The objective of this study was to assess the efficacy and safety of antiemetic prophylaxis consisting of fosaprepitant, granisetron (5-HT$_3$ antagonist), and high-dose DEX in Japanese patients receiving HEC. The primary endpoint was to estimate the CR rate, which was defined as no vomiting or retching episodes and no use of rescue medication in the treatment phase, defined as the period from the start of cisplatin administration to 120 hours after the administration. The secondary endpoints were CR rates in the acute phase (defined as the period from the start of cisplatin administration to 24 hours after its administration) and the delayed phase (defined as the period from 24 to 120 hours after the start of cisplatin

administration), and the rate of complete control (CC), which was defined as no vomiting, no rescue therapy, and no episodes of moderate-to-severe nausea, in the overall, acute, and delayed phases. Other endpoints were alterations in dietary intake on days 2–6 and the incidence of adverse events. Nausea and vomiting that occurred within 24 hours of cisplatin administration were defined as acute CINV, and nausea and vomiting that occurred after 24–120 hours were defined as delayed CINV. This study was approved by the Ethics Review Board of 4 participating institutions, and patients were informed of the investigational nature of the study and provided their written informed consent before registration in the study. This clinical trial is registered in the UMIN registry system (No. 000012202).

2.2. Patient inclusion and exclusion criteria

Patients who were scheduled to be treated with systemic chemotherapy including cisplatin ($\geq$ 50 mg/m^2) were eligible. The main eligibility criteria included histologically or cytologically confirmed solid cancer, age $\geq$20 years, Eastern Cooperative Oncology Group performance status (PS) of 2 or less, neutrophil count $\geq$1000/mm^3, platelet count $\geq$75,000/mm^3, hemoglobin $\geq$8.0 g/dL, aspartate transaminase and alanine transaminase $\leq$2.0 × the upper limit of the normal (ULN) range in the institution, total bilirubin $\leq$2.0 × ULN, and creatinine clearance estimated by the Cockcroft–Gault equation $\geq$ 60 mL/min. Patients were excluded if they required oral intake of aprepitant more than 4 days, were pregnant or breastfeeding, had brain metastasis, had hypercalcemia, had a large amount of pleural effusion or ascites, or had uncontrolled diseases other than malignancy. Patients taking the following drugs were excluded: CYP3A4 inhibitors and inducers, CYP3A4, or CYP2C9 substrates.

2.3. Antiemetic prophylaxis

Fosaprepitant (150 mg) and granisetron (1 or 3 mg) were administered intravenously 30 minutes before anticancer drugs were administered on day 1. For DEX, 12 mg on day 1, 8 mg on day 2, and 16 mg on days 3 and 4 were given intravenously.

2.4. Assessments

The efficacy of antiemetic therapy was continuously evaluated by patients' self-assessment in the treatment phase. Patients recorded vomiting or retching episodes, rescue therapy (defined as medication for nausea/vomiting), and nausea ratings at about noon on days 2–6 in a symptom diary. For nausea, patients recorded the most intense bout of nausea during the past 24 hours period based on a 4-level scale: none, mild (food and water can be ingested), moderate (only water can be ingested), and severe (neither food nor water can be ingested). For rescue therapy, the investigator or nurse recorded the date and time of therapy, name and dose of drug, and reasons for use. The assessment period was divided into 2 phases: acute phase and delayed phase. Adverse events during the 2 weeks from the initiation of chemotherapy were recorded. Each adverse event was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (version 4.0), and the investigator reported the worst grade of toxicity.

2.5. Statistical analysis

We set the true CR rate in the treatment phase to be 72% according to the EASE trial,[2] and determined whether the value

of point estimation of the CR rate of our data was not greatly inferior to 72%. If the point estimation of the CR rate exceeded 67% in the treatment phase without being 5% inferior to the pre-set value, we considered our result to be equivalent to a true CR rate. There was an 80% probability that this was realized in less than 40 cases. Efficacy analyses were performed on the full analysis set, which consisted of all patients with confirmed eligibility who were receiving both chemotherapy including cisplatin ($\geq$50 mg/m^2) and the protocol antiemetic treatment. Safety analyses were performed in all of the patients who were administered fosaprepitant. A time-to-treatment failure curve was estimated by the Kaplan–Meier method.

3. Results

3.1. Patient characteristics

Between February 2013 and January 2015, 45 patients from 4 institutions were screened for inclusion of this trial. Among the 45 patients, 1 was excluded due to deviance from the eligibility criteria. Therefore, a total of 44 patients were assessable in the intention-to-treat analysis, and these patients were included in the safety analysis. Patient characteristics are summarized in Table 1. The median age was 65 years, with a range of 30 to 75 years. A total of 34 males and 10 females were included in the study. The number of patients with a PS of 0 and 1 was 39 (88.6%). Twelve patients (27.3%) had received chemotherapy before this study, seven of whom had a history of taking aprepitant. Thirty-nine patients (88.6%) had upper gastrointestinal cancers (Table 1).

3.2. Administration of chemotherapy and antiemetic prophylaxis

All of the patients were treated with cisplatin-based combination chemotherapy. Thirty-seven patients (84.1%) received cisplatin plus fluoropyrimidines including S-1 (tegafur, gimeracil, and oteracil potassium), capecitabine, and fluorouracil (5-FU). Seven patients (15.9%) were treated with a combination therapy of 5-FU, cisplatin, and docetaxel, and 3 patients with esophagus

Table 1

Patient characteristics.

Characteristics		Number (n = 44)	%
Age	Median (range)	65 (30–75)	
Sex	Male	34	77.3
	Female	10	22.7
Performance status	0	18	40.9
	1	21	47.7
	2	5	11.4
History of prior	Yes	12	27.3
Chemotherapy	No	32	72.2
Confirmed alcohol intake	Yes	25	56.8
	No	19	43.2
Simultaneous irradiation	Yes	3	6.8
	No	41	93
Primary site of tumor	Stomach	21	47.7
	Esophagus	16	36.4
	Duodenum	2	4.5
	Rectum	1	2.3
	Lung	1	2.3
	Head and neck	1	2.3
	Prostate gland	1	2.3
	Unknown primary origin	1	2.3

Table 2

Chemotherapy and antiemetic prophylaxis.

Chemotherapy	Number (n = 44)	%
Regimen of chemotherapy		
Cisplatin plus S-1[*]	19	43
Cisplatin plus 5-FU[†]	9	21
Cisplatin /5-FU/Docetaxel	7	16
Cisplatin plus etoposide	3	7
Cisplatin plus other drug	6	14
Doses of cisplatin, mg/m^2		
50–59	2	5
60–69	19	43
70–79	11	25
80$\leqq$	12	27
Mean $\pm$ SD[‡]	67.7 $\pm$ 9.24	
Median (range)	70 (48–80)	
The schedule of antiemetic prophylaxis regimen		
Day 1:	Fosaprepitant, 150 mg; Granisetron, 1 or 3 mg; Dexamethasone, 12 mg, drip infusions	
Day 2:	Dexamethasone, 8 mg, drip infusion	
Days 3, 4:	Dexamethasone, 16 mg, drip infusion	

[*] S-1, tegafur/gimeracil/oteracil

[†] 5-FU, 5-fluorouracil

[‡] SD, standard deviation

cancer received chemoradiotherapy combined with 5-FU and cisplatin. Three patients with neuroendocrine cancer received combined therapy of etoposide and cisplatin. All of the patients were treated with a high dose of cisplatin ($\geq$50 mg/m^2), with a mean dose of 67.7 mg/m^2 (standard deviation; 9.24 mg/m^2) and a median dose of 70.0 mg/m^2 (range, 50–80 mg/m^2; Table 2). The antiemetic prophylaxis regimen is shown in Table 2. All of the patients received the prescribed triplet antiemetic therapy.

3.3. Efficacy

The percentage of patients who achieved a CR in the treatment phase was 70% (95% confidence interval [CI]: 55%–83%). The CR rates in the acute and delayed phases were 91% (95% CI: 78%–97%) and 70% (95% CI: 55%–83%), respectively (Fig. 1A). Since the CR rate in the treatment phase exceeded the preset value 67%, our results appeared to be statistically noninferior to the CR rate calculated in the EASE trial. The percentages of patients with CC in the overall, acute, and delayed phases were 66% (95% CI: 50%–80%), 91% (95% CI: 78%–97%), and 66% (95% CI: 50%–80%), respectively (Fig. 1B). With regard to time-to-treatment failure, the CR rate was 90.9% on day 1, 86.4% on day 2, 84.1% on day 3, 81.8% on day 4, and 70.5% on day 5 (Fig. 2).

3.4. Tolerability

All of the patients who received fosaprepitant were included in the safety analysis. Table 3 summarizes the adverse events reported within 14 days from the administration of cisplatin. Common adverse events of Grade 3 or 4 other than nausea and vomiting were leukopenia, neutropenia, anorexia, fatigue, and hyponatremia. No significant increases were found in the incidence of chemotherapy-related adverse events compared with past clinical trials. A total of 9 of 44 patients (20%) suffered from infusion-related adverse events including pain, erythema and swelling surrounding the infusion site. No severe infusion-related adverse events were observed. There was no increase in
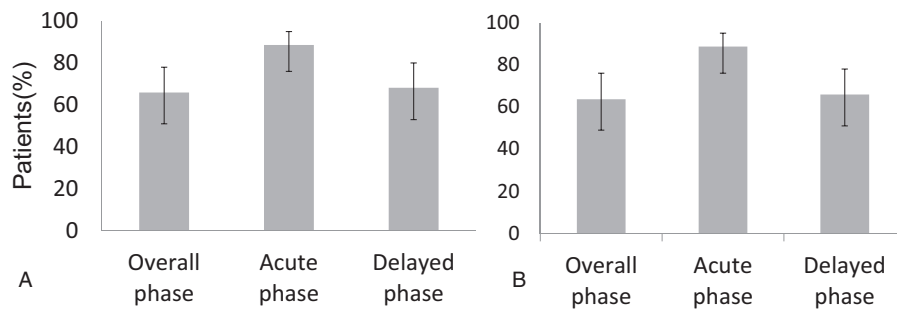
Figure 1. Rates of complete response (CR; A) and complete control (CC; B) of emesis in each phase. The column shows the rates of CR and CC and the error bar indicates the 95% confidence intervals. CC = complete control, CR = complete response.

the incidence of severe adverse events possibly related to the administration of high-dose DEX including hyperglycemia, severe infections, sleeplessness, and mental translation. One patient with type 2 diabetes mellitus showed Grade 3 hyperglycemia on days 5 and 14, and another patient had Grade 3 hypokalemia that was probably related to the high dose of DEX. No grade 5 adverse events and serious adverse events required an emergency hospitalization were reported in the study.

3.5. Factors predicting antiemetic effects

Univariate and multivariate analyses were performed to assess correlations between the incidence of CINV and patient factors. In the overall phase, cisplatin-based triplet chemotherapy and female gender were thought to be risk factors for CINV with an odds ratio of 14.80 (95% CI: 1.52–144.00, $P = .020$) and 6.61 (95% CI: 1.13–38.50, $P = .036$), respectively. Other established risk factors, age younger than 50 years, poor PS, and alcohol intake were not significant risk factors in the present study (Table 4).

4. Discussion

In this single-arm phase 2 study, we explored the efficacy and safety of antiemetic triplet therapy consisting of fosaprepitant, a 5-HT$_3$ antagonist, and sufficient doses of DEX in Japanese

patients receiving HEC regimens. The CR rates were 70% in the overall phase, 91% in the acute phase, and 70% in the delayed phase, which were one of the most favorable responses in the previous clinical studies in Japan. In the EASE trial performed in the Western countries, which evaluated the efficacy of fosaprepitant in combination with ondansetron and DEX, the CR rates in the overall, acute, and delayed phases were 71.9%, 89%, 74.3%, respectively.[2] In this study, the CR rates in the overall and acute phase were equivalent to those in the EASE trial. In the previous Japanese phase 3 trial, which evaluated the efficacy of fosaprepitant, the CR rates in the overall, acute, and delayed phases were 64.2%, 93.6%, 64.7%, respectively.[3] Because we considered that the 10% lower CR rate in the delayed phase of the Japanese phase 3 trial compared to the EASE trial was due to insufficient doses of DEX, we used the same doses of DEX in this study as those used in the EASE trial. In our phase 2 study, sufficient doses of DEX improved the antiemetic effects compared with those of the Japanese phase 3 trial, and the CR rates in our study were similar to those in the EASE trial, suggesting that sufficient doses of DEX might have the potential to favorably control acute emesis.

Antiemetic effects in the delayed phase might be due to factors other than DEX doses such as the patient's background and racial differences. For example, patients with gastrointestinal tumors
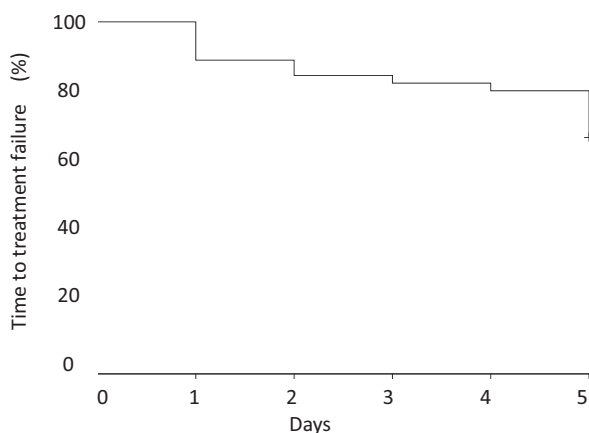

Figure 2. Kaplan–Meier curves of time to treatment failure of antiemetic prophylaxis in all patients (n = 44).

Table 3
Adverse events.

Adverse events (n = 44)	All grade number	%	Grade 3/4 number	%
Hematological toxicity				
Leukopenia	17	39	9	20
Neutropenia	17	39	11	25
Anemia	16	36	2	5
Thrombocytopenia	19	43	0	0
Febrile neutropenia	–	–	5	11
Nonhematological toxicity				
Constipation	19	43	0	0
Fatigue	25	57	2	5
Diarrhea	7	16	1	2
Hiccup	10	23	0	0
Appetite loss	29	66	3	7
Vasculitis	3	7	0	0
Increased serum AST[*]/ALT[†]	12	27	0	0
Increased serum creatinine	8	18	0	0
Hyperglycemia	13	30	1	2
Insomnia	2	5	0	0

[*] AST, aspartate aminotransferase.
[†] ALT, alanine aminotransferase.

Table 4

Factors predicting anti-emetic effects.

Risk factor	Odds ratio	95% CI[*]	P value
Univariate analysis			
Age < 50	1.32	0.10–13.13	1
Female sex	4.01	0.75–24.31	.067
Triplet chemotherapy	6.41	0.88–77.58	.036
Upper gastrointestinal cancer	2.86	0.28–147.53	.647
Performance status ≧ 2	0.45	0.01–5.21	.647
Not confirmed alcohol intake	1.84	0.44–7.95	.357
Multivariate analysis			
Female sex	6.05	1.22–30.00	.028
Triplet chemotherapy	9.89	1.47–66.70	.019

[*] CI, confidence interval.

tend to be susceptible to nausea and vomiting because of gastrointestinal obstruction. In the EASE trial, patients with lung cancer accounted for one-half of the enrollment and the number of patients with gastrointestinal cancer was small. On the other hand, 90% of patients had upper digestive cancer in this study. Additionally, there were seven patients (16%) treated with the triplet chemotherapy in our study. By subgroup analysis of our study, patients with triplet chemotherapy had a significantly higher risk of CINV in the overall phase. Although the present study mostly consisted of patients who had gastrointestinal cancer and included patients with high emetogenic triplet chemotherapy, satisfactory antiemetic effects were observed. Thus, the use of sufficient doses of DEX was assumed to be important in such patients with unfavorable conditions.

To discuss the efficacy of antiemetic therapy avoiding racial differences, 2 phase 3 trials that evaluated the efficacy of triplet antiemetic therapy in Japanese cancer patients were informative. The CR rates in the delayed phase was 64.7% in a Japanese phase 3 trial that evaluated the efficacy of fosaprepitant and employed DEX doses of 10 mg on day1, 4 mg on day 2, and 8 mg on day 3.[3] Whereas, in the latest Japanese phase 3 (TRIPLE) trial of the triplet antiemetic therapy consisting of aprepitant, palonosetron and DEX, doses of DEX were 12 mg on day 1, 8 mg on days 2–4, and the CR rate in the delayed phase was 67.2%.[5] The results in both studies were slightly inferior to the results of the EASE trial. These observations suggest that Japanese cancer patients might be vulnerable to the development of CINV in the delayed phase regardless of doses of DEX. The present observation that the CR rate in the delayed phase was comparable to that in the EASE trial might have clinical significance.

Although some studies have suggested the antiemetic effects of DEX in patients receiving anticancer chemotherapy, the results of the meta-analysis suggested that antiemetic effects in the acute and delayed phases did not improve despite the increased dose of DEX by more than 20 mg.[6] Recent guidelines for the management of CINV recommend that the maximum total dose of DEX is 20 mg per day.[1] However, it is still unclear if the antiemetic effects are correlated with the daily total dose of DEX equal to or less than 20 mg, so adequate doses of DEX in the delayed phase remain inconclusive. Additionally, metabolism and onset of DEX potentially vary according to each individual or race. We need to assess the correlation between plasma DEX concentration and antiemetic effectiveness in individual patients because of lack of supportive data in the past.

Regarding the safety of the triplet antiemetic therapy in the present study, Grade 3 hyperglycemia and hypokalemia developed in a few cases. The former had a complication of type 2

diabetes mellitus. Additionally, the increase of the adverse events associated with the high doses of DEX, such as severe infection or psychiatric symptoms, did not increase compared with the results of previous clinical trials. Although the safety profiles in the present study could encourage the administration of sufficient doses of DEX in patients, late-onset adverse events of antiemetic therapy were not detected as a limitation of the study.

Although the present prospective phase 2 study assessed a small number of patients, these results suggest that sufficient doses of DEX (the same as those used in the EASE study) in combination with fosaprepitant and granisetron may be a promising option for improving the antiemetic effects in Japanese cancer patients receiving HEC regimens.

Author contributions

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References

[1] Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. J Clin Oncol 2015;34:381–6.
[2] Grunberg 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;29:1495–501.
[3] 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;24:1067–73.
[4] McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 2003;74:17–24.
[5] Suzuki K, Yamanaka T, Hashimoto H, et al. Randomized, double-blind, phase III trial of palonosetron versus granisetron in the triplet regimen for preventing chemotherapy-induced nausea and vomiting after highly emetogenic chemotherapy: TRIPLE study. Ann Oncol 2016;27:1601–6.
[6] Italian Group for Antiemetic ResearchDouble-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. Italian Group for Antiemetic Research. J Clin Oncol 1998;16:2937–42.
[7] Ioannidis JP, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. J Clin Oncol 2000;18:3409–22.

[8] Hale JJ, Mills SG, MacCoss M, et al. Phosphorylated morpholine acetal human neurokinin-1 receptor antagonists as water-soluble prodrugs. J Med Chem 2000;43:1234–41.

[9] Navari RM, Reinhardt RR, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 Antiemetic Trials Group. N Engl J Med 1999;340:190–5.

[10] Goedhals L, Heron JF, Kleisbauer JP, et al. Control of delayed nausea and vomiting with granisetron plus dexamethasone or dexamethasone alone in patients receiving highly emetogenic chemotherapy: a double-blind, placebo-controlled, comparative study. Ann Oncol 1998;9:661–6.

[11] Kris MG, Gralla RJ, Tyson LB, et al. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. J Clin Oncol 1989;7:108–14.

[12] Hesketh PJ, Grunberg SM, Gralla RJ, et al. 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-the Aprepitant Protocol 052 Study Group. J Clin Oncol 2003;21:4112–9.

[13] Hesketh PJ, Aapro M, Street JC, et al. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. Support Care Cancer 2010;18:1171–7.