RESEARCH ARTICLE

Efficacy and Safety of an Increased-dose of Dexamethasone in Patients Receiving Fosaprepitant Chemotherapy in Japan

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Abstract

Background: Antiemetic triplet therapy including dexamethasone (DEX) is widely used for patients receiving highly emetogenic chemotherapy (HEC). In Japan, the appropriate dose of DEX has not been established for this combination. Materials and Methods: To assess the efficacy and safety of increased-dose DEX, we retrospectively examined patients receiving HEC with antiemetic triplet therapy. Results: Twenty-four patients (fosaprepitant group) were given an increased-dose of DEX (average total dose: 45.8mg), fosaprepitant, and 5-HT3 antagonist. A lower-dose of DEX (33.6mg), oral aprepitant, and 5-HT3 antagonist were administered to the other 48 patients (aprepitant group). The vomiting control rates in the fosaprepitant and aprepitant groups were 100% and 85.4% in the acute phase, and were 75.0% and 64.6% in the delayed phase. The incidences of toxicity were similar comparing the two groups. Conclusions: Triplet therapy using an increased-dose of DEX is suggested to be safe and effective for patients receiving HEC.

Keywords: Highly emetogenic chemotherapy - dexamethasone - fosaprepitant

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a severe adverse event in patients receiving cancer chemotherapy. More than 90% of patients develop nausea and vomiting during highly emetogenic chemotherapy (HEC), which includes cisplatin. Therefore, efficient antiemetic therapy is required in order to assure ongoing delivery of HEC and to improve patient quality of life.

Guidelines for the management of CINV recommend administration of antiemetic prophylaxis, consisting of a 5-HT3 antagonist, dexamethasone (DEX), and a NK1 receptor inhibitor, for patients receiving HEC. NK1 receptor inhibitors include the oral agent aprepitant and the intravenous agent fosaprepitant (Roila et al., 2010). Fosaprepitant is a water-soluble phosphoryl pro-drug of aprepitant (Hale et al., 2000). Conversion of fosaprepitant to aprepitant in the human serum occurs immediately after injection. In a phase III clinical study, the antiemetic efficiency of an intravenous single dose fosaprepitant (150 mg IV on day 1) was equivalent that of a 3-day course of oral aprepitant (125 mg on day 1, 80 mg on days 2-3) for patients receiving HEC (Grunberg et al., 2011). In a Japanese phase III study, antiemetic triplet combination therapy including fosaprepitant was superior to doublet therapy with a 5-HT3 antagonist and DEX for patients receiving HEC (Saito et al., 2013).

Because the NK1 receptor inhibitor can suppress metabolism of DEX, doses of DEX should be reduced at the first and second days when used in combination with NK1 receptor inhibitor. While doses of DEX given in a previous international phase III study were 12 mg on day 1, 8 mg on day 2 and 16 mg on days 3-4, doses of DEX employed in the Japanese study were 10 mg on day 1, 4 mg on day 2 and 8 mg on day 3. The antiemetic efficacy of the triplet therapy in the acute and delayed phases were 94% and 65%, respectively, in the Japanese study and were 89% and 74.8%, respectively, in the international study. Appropriate doses of delayed phase DEX when used as a component of the triplet combination have not yet been clarified.

After fosaprepitant was released in Japan in 2011, we administered the same doses of DEX as the international phase III study in combination with fosaprepitant for patients receiving HEC. The present study was a retrospective analysis of the efficacy and safety of the triplet therapy consisting of fosaprepitant, a5-HT3 antagonist and DEX for HEC in Japan.

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Materials and Methods

Purpose and study design

The present study was conducted in order to assess the antiemetic efficacy and safety of triplet therapy consisting of fosaprepitant, high-dose DEX and a 5-HT3 antagonist for patients with advanced cancer receiving HEC in Japan. This study was a retrospective observational study that was conducted in a single institution.

Patient selection

Patients who received cancer chemotherapy including cisplatin (≥ 50 mg/m^2) during the period from December 2009 to January 2013 in the Department of Hematology and Oncology of Kyushu University Hospital were examined in this study. All patients were given a 3-day course of oral aprepitant or a single dose of intravenous fosaprepitant (150 mg) on day 1. Patients who received prior administration of aprepitant or fosaprepitant were excluded.

Evaluation

The efficacy of antiemetic therapy was continuously evaluated by patients' self-assessment in overall phase, which was the period from the start of HEC to day 5. The acute phase was first day after the initiation of chemotherapy and the delayed phase was the period from day 2 to day 5. Complete response (CR) was defined as no episodes of vomiting or rescue therapy (defined as treatment with drug therapy to treat nausea or vomiting), and total control (TC) was defined as no episodes of nausea and vomiting or rescue therapy. Time to treatment failure was the period from the start of antiemetic therapy to the first episode of vomiting or rescue therapy. The primary endpoint of this study was the CR rate at the overall phase, and secondary endpoints were the CR rates at the acute and delayed phases, TC rates at the overall, acute and delayed phases, duration of effective therapy, and incidences of adverse events. Adverse events over 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 (NCI CTCAE) ver. 4.0.

Treatment administration

Patients who received aprepitant were given 125 mg orally before chemotherapy on day 1 and then given 80 mg orally once daily on days 2 and 3. A 5-HT3 antagonist was administered before chemotherapy on day 1. DEX was administered for at least 1 day via the oral or intravenous route. In other patients treated with fosaprepitant, 150 mg of the drug was given intravenously on day 1 before chemotherapy. A 5-HT3 antagonist, granisetron (3 mg), was administered intravenously before chemotherapy. For DEX, 9.9 mg was given intravenously on day 1, 6.6 mg was given intravenously on day 2, and 6.6-13.2 mg was given intravenously on days 3-4.

Statistical analysis

Statistical analysis of data in both antiemetic treatment groups was performed using the Mann Whitney U-test for patient backgrounds and using the chi-square test for patient number of chemotherapy regimens and doses of DEX. Fisher's exact test was used for the analysis of the CR rate, TC rate, adverse events, and univariate analyses of risk factors for nausea and vomiting. The statistical significance level was set at $p<0.05$.

Results

Patients

Forty-eight patients who were given a 3-day course of oral aprepitant, and 24 patients who were given a single dose of intravenous fosaprepitant were retrospectively analyzed. All patients had advanced cancer and were treated with a HEC regimen that included more than 50 mg/m^2 of cisplatin. Patient characteristics are shown in Table 1. Median age was 63 years in both groups. Males comprised 75% of the aprepitant group and 79% of the fosaprepitant group. Patients with performance status 0 and 1 comprised 87.5% of the aprepitant group and 79% of the fosaprepitant group (no statistically significant difference). Possible factors that might influence the emetic events during chemotherapy, such as previous history of emetic events, alcohol intake, and history of radiotherapy, were present in equal proportions when comparing the two groups. Most patients examined in this study had upper gastrointestinal cancers, while others had advanced solid tumors, including carcinoma of undefined origin, osteosarcoma, extrapulmonary small cell carcinoma, and peritoneal cancer (Table 1).

Treatments

Approximately 85.4% of patients in the aprepitant group and 95.8% of patients in the fosaprepitant group were treated with cisplatin-based combination chemotherapy, mostly associated with fluoropyrimidines, including S-1 (tegafur, gimeracil, oteracil potassium), capecitabine and 5-FU. While granisetron was employed in all patients in the fosaprepitant group, 77.1% of patients

Table 1. Patient Characteristics

Characteristics	Aprepitant Group N=48	Fosaprepitant Group N=24	p value
Age, median (range)	63 (26-77)	63 (43-75)	0.65*[1]
Sex (male:female)	36:12	19:5	0.78
PS (0/1:2)	42:06	23:1	0.41
History of chemotherapy Induced nausea and vomiting	4 (8.3%)	4 (16.7%)	0.43
Confirmed alcohol intake	25 (52.1%)	8 (33.3%)	0.21
Simultaneous irradiation	5 (10.4%)	4 (16.7%)	0.47
Type of malignancy			0.797 *[2]
Gastric cancer	19	11	
Esophageal cancer	16	9	
Cancer of unknown origin	7	3	
Others	6	1	
Regimen of chemotherapy			0.187*[1]
CDDP / S-1	24	11	
CDDP / Capecitabine	1	3	
CDDP / 5FU	16	9	
CDDP / VP-16	3	0	
CDDP / other drug	4	1	

p value:calculated by*[1]; Mann-Whitney U-test,*[2]; χ^2-test, Fisher's exact test

were treated with granisetron, 6.3% of patients were treated with ramosetron, and 16.7% of patients were treated with palonosetron in the aprepitant group (Table 2). Total administration doses of DEX during the period from the initiation of the chemotherapy to day 5 were lower in the aprepitant group (mean±standard deviation [SD]; 33.6±9.56 mg) than in the fosaprepitant group (45.8±13.34 mg). Although doses of DEX on day 1 were similar when comparing the two groups (aprepitant vs. fosaprepitant: 12.46±3.12 mg vs. 12.0±0.0 mg), doses given on days 2-4 were significantly higher in the fosaprepitant group (36±9.14 mg) than in the aprepitant group (21.1±8.18 mg) (Table 2).

Efficacy

CR rates during the overall phase were 64.6% in the aprepitant group and 75.0% in the fosaprepitant group (p=0.431). CR rates in the acute phase were 85.4% and 100% in the aprepitant group and in the fosaprepitant group, respectively (p=0.087). CR rates in the delayed phase were 64.6% and 75.0%, in the aprepitant group and in the fosaprepitant group, respectively (p=0.431) (Figure 1). The TC rate during the overall, acute and delayed phase in aprepitant group and fosaprepitant group were 50.0% and 66.7% (p=0.215), 83.3% and 95.8% (p=0.256) and 50.0% and 66.7% (p=0.215), respectively. There was no statistically significant difference in the TC rates when comparing the two groups (Figure 1). In terms of time to treatment failure, the CR rate was 100% from day 1 to day

Table 2. Prophylactic Antiemetic Therapy

Drug	Aprepitant Group N=48	Fosaprepitant Group N=24	p value
NK1 receptor inhibitor	Aprepitant Day 1: 125mg orally Day 2: 80mg orally Day 3: 80mg orally	Fosaprepitant Day 1: 150mg intravenously	
Type of 5-HT3 antagonist	No (%)	No (%)	0.039*[1]
Granisetron	37 (77.1)	24 (100)	
Ramosetron	3 (6.3)	0 (0)	
Palonosetron	8 (16.7)	0 (0)	
Mean dose of Dexamethasone (mg) (Standard deviation)			
Overall period	33.6 9.56	45.8 (13.34)	<0.0003*[2]
Day 1	12.46 3.12	12.0 (0.0)	0.476*[2]
Days 2-4	21.1 8.18	36.0 (9.14)	<0.0001*[2]

p value: calculated by *[1]:χ^2-test, *[2]; t-test

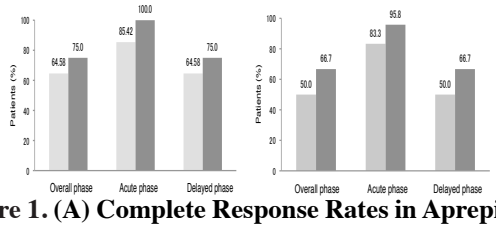

Figure 1. (A) Complete Response Rates in Aprepitant Group and Fosaprepitant Group During the Overall, acute, delayed phases following chemotherapy. There were no statistically significant differences between both groups. (B) Total control rates in aprepitant group and fosaprepitant group during the overall, acute, delayed phase. No statistically significant differences between two groups were found in respective phases. Aprepitant group: light-colored column, Fosaprepitant group: dark-colored column

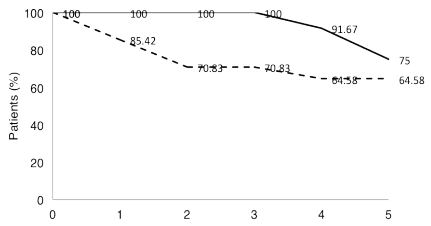

Figure 2. Time to Treatment Failure (first vomit or rescue use). CR rates from day1 to day 5 following chemotherapy in aprepitant group and fosaprepitant group. Aprepitant group: dotted-line, Fosaprepitant group: solid line

Table 3. Adverse Events

	Aprepitant group (N=48) No (%)	Fosaprepitant group (N=24) No (%)	p value
All grade			
Constipation	23 (47.9)	14 (58.3)	0.46
Fatigue	25 (61.0)	4 (80.0)	0.64
Diarrhea	13 (27.1)	8 (33.3)	0.59
Hiccup	19 (39.6)	12 (50.0)	0.45
Appetite loss	19 (39.6)	15 (62.5)	0.08
Vascular pain	4 (8.3)	5 (20.8)	0.15
Vasculitis	0 (0.0)	4 (16.7)	0.0103*
AST/ALT	20 (41.7)	3 (12.5)	0.0156*
Increased serum creatinine	16 (33.3)	7 (29.2)	0.79
Hyperglycemia	22 (45.8)	4 (25.0)	0.12
Delirium	1 (2.0)	2 (8.3)	0.26
Insomnia	13 (27.1)	8 (33.3)	0.59
Grade 3/4			
Fatigue	4 (8.3)	3 (12.5)	0.68
Diarrhea	1 (2.1)	2 (8.3)	0.26
Hiccup	1 (2.1)	0 (0.0)	1
Appetite loss	4 (8.3)	4 (16.7)	0.43
AST/ALT	1 (2.1)	1 (4.2)	1
Increased serum creatinine	2 (4.2)	0 (0.0)	0.55
Neutropenia	6 (12.5)	1 (4.2)	0.41
Anemia	1 (2.1)	4 (16.7)	0.0395*
Delirium	0 (0.0)	1 (4.2)	0.33
Hyperglycemia	4 (8.3)	2 (8.3)	1
FN/severe infection	4 (8.3)	3 (12.5)	0.68

*; Statistically significant, p values were calculated by Fisher' exact test.

Table 4. Factors Predicting Anti-emetic Effects - Univariate Analysis

Factor	Odds ratio	95% confidence interval	p value
Age<50	1.26	0.33-4.84	0.736
Female	2.37	0.77-7.28	0.146
PS≥2	1.75	0.19-13.91	0.597
History of prior chemotherapy	1.21	0.42-3.46	0.789
Confirmed alcohol intake	1.45	0.54-3.93	0.613
Use of fosaprepitant	0.61	0.20-1.82	0.431
Substandard doses of DXM	0.71	0.25-1.99	0.61
Use of Palonosetron	1.08	0.24-4.74	1

p value: calculated by Fisher's exact test

3, 91.7% on day 4, and 75.0% on day 5 in fosaprepitant group. In aprepitant group, the CR rate was 85.4% on day 1, 70.8% on days 2 and 3, and 64.6% on days 4 and 5 (Figure 2).

Tolerability

Five of 24 patients in the fosaprepitant group suffered from vascular pain, and four patients had vasculitis (Table 3). In all of these patients, chemotherapy was administered via peripheral forearm veins. One of 5 patients with grade 1 vascular pain had onset of pain during intravenous

infusion of fosaprepitant. Vascular pain and vasculitis in the others cases appeared during intravenous infusion of anti-cancer agents. Grade 1/2 elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed more frequently in the aprepitant group than in the fosaprepitant group, but no differences were noted between the two groups in terms of grade 3/4 elevations in AST/ALT. Appetite loss and fatigue of grade 3 and higher were frequently observed in both groups. Although grade 3/4 anemia was more common in the fosaprepitant group than in the aprepitant group, the incidence of other adverse events was almost equal when comparing the two groups. No statistical significant differences were found in the incidence of hyperglycemia, severe infections, sleeplessness, and delirium (i.e., adverse effects possibly related to high-dose administration of DEX) when comparing the two groups.

Factors predicting an antiemetic effect

Although previous reports have suggested that CINV is associated with various factors, including younger age (less than 50 years), female sex, a previous history of CINV, and alcohol intake, univariate analysis in the present study failed to identify any factors predicting emesis (Table 4).

Discussion

The present study retrospectively examined the efficacy and safety of antiemetic triplet combination therapy with fosaprepitant and increased doses of DEX for patients with advanced solid tumors. The antiemetic CR rates of triplet therapy consisting of a 5-HT3 antagonist, fosaprepitant and DEX in the acute and delayed phases were 100% and 75.0%, respectively. Grunberg and his colleagues (Grunberg et al., 2011) reported that the CR rates of antiemetic triplet therapy with fosaprepitant in the acute and delayed phases were 89.0% and 74.3%, respectively, which is similar to findings seen in the present study. In addition, the antiemetic CR of triplet therapy consisting of a 5-HT3 antagonist, fosaprepitant and increased doses of DEX had better efficacy when compared to decreased DEX regimen employed in a Japanese phase III trial, especially in the delayed phase (Saito et al., 2013).

In our study, the CR rates in the delayed phase were 64.6% in the aprepitant group and 75.0% in the fosaprepitant group, and the TC rates were 50.0% and 66.7%, respectively. These data suggest that the antiemetic effects of fosaprepitant group were superior in the delayed phase when compared with aprepitant group. However, this study was limited by its retrospective nature and the fact that the patient backgrounds, including the component of antiemetic therapy, were different when comparing the two study groups.

The median age of the patients in the fosaprepitant group was 63 years, and the proportion of patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and 1 was 95.8%. Most patients had advanced gastrointestinal cancers and sarcomas. Patients with advanced gastrointestinal cancers who are undergoing chemotherapy might have worsening gastrointestinal symptoms, because of the remaining primary tumor and the influence of surgical treatments. Therefore, factors that predict good control of emesis in this study were not identified.

One of the possible reasons for the enhanced antiemetic in the delayed-phase CR/TC in the fosaprepitant group was the increased dose of DEX. Total doses of DEX (mean±SD) were 33.60±9.56 mg in the aprepitant group and 45.80±13.34 mg in the fosaprepitant group. In a clinical study using DEX and 5-HT3 antagonist, 20 mg of DEX on day 1 produced a more effective antiemetic effect in patients receiving HEC when compared with 4-8 mg of DEX given on day 1 (Italian Group for Antiemetic Research, 1998). Indeed, 45 to 54.5% of the CR rates for HEC were achieved in response to 8 mg of DEX on days 2-3 and by 4-8 mg of DEX on days 4-5 (Kris et al., 1989; Goedhals et al., 1998). Meta-analysis of 5,613 patients among 32 trials suggested that DEX exerted efficient antiemetic effects during the acute and delayed phases after HEC and moderately emetogenic chemotherapy (MEC) (John et al., 2000). Therefore, the planned doses of DEX in the phase III trial (20 mg on day 1 and 8 mg on days 2-4) were likely adequate.

DEX is metabolized by CYP3A4, and therefore, serum DEX levels can increase in response to CYP3A4 inhibitors, such as aprepitant. Therefore, a lower dose of DEX should be used when administered in combination with aprepitant (McCrea et al., 2003). Heskesh et al. reported that 12 mg of DEX in the acute phase and 8 mg of DEX in the delayed phase in association with a 3-day course of oral aprepitant effectively controlled emesis in both phases (Hesketh et al., 2003). Since fosaprepitant is a water-soluble phosphoryl pro-drug for aprepitant and was administered intravenously on day 1, serum aprepitant concentrations gradually decrease after injection, resulting in decrement in the AUC of DEX on days 3-4. After equalizing the AUC of DEX in the aprepitant arm and the fosaprepitant arm in the international phase III clinical study, doses of DEX were set as 12 mg on day 1, 8 mg on day 2, and 16 mg on days 3-4 in the fosaprepitant arm (Grunberg et al., 2011). Therefore, the appropriate administration of DEX might provide efficient antiemetic effects in both the acute and delayed phases of HEC.

Next, we compared the safety profile of fosaprepitant group to aprepitant group. There is no difference in adverse events associated with chemotherapy and DEX between two groups and the incidence of adverse events in this study was similar to that seen in previous phase 3 trials. Therefore, the use of high dose DEX did not appear to result in increased toxicity. However, the antiemetic effects and adverse events were measured only in a single course of chemotherapy in this study, and these results do not exclude the possibility of adverse events caused by long-term administration of DEX. Therefore, further follow up is necessary to assess the long-term tolerability of antiemetic combination therapy including high dose DEX for patients with gastrointestinal cancers or breast cancer, in which longer courses of treatment are necessary.

Granisetron was employed in all patients in the fosaprepitant group. Since a previous report suggested

that the antiemetic effect of ondansetron and granisetron are equivalent (del Giglio et al., 2000), the specific 5-HT3 antagonist utilized might not have a significant influence on the differences of antiemetic effects between the two regimens used in the present study. However, the 5-HT3 antagonist palonosetron might have improved antiemetic effect, even in the late period, when compared with other 5-HT3 antagonists (Aapro et al., 2006). Palonosetron was thus recommended as a standard antiemetic therapy for HEC and MEC in guidelines published in Europe and the US. Higher doses of DEX in combinations with NK1 receptor inhibitors and palonosetron might improve the CR rates and TC rates in delayed phase than commonly used antiemetic triplet therapy in Japan.

The use of various chemotherapies, including HEC, continues to increase, and antiemetic therapy using an appropriate and safe dose of DEX is necessary. A prospective clinical study to evaluate the antiemetic efficacy and safety of combination therapy using DEX in association with NK1 inhibitor is needed. Therefore, we plan to conduct a phase II clinical trial examining this issue, including pharmacokinetics/pharmacodynamics analysis of DEX in Japanese patients.

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References

Aapro MS, Grunberg SM, Manikhas GM, et al (2006). A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Ann Oncol*, **17**, 1441-9.

del Giglio A, Soares HP, Caparroz C, Castro PC (2000). Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting-Results of a meta-analysis of randomized controlled trials. *Cancer*, **89**, 2301-8.

F. Roila, J. Herrstedt, M. Aapro, 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**, 232-43.

Goedhals L, Heron JF, Kleisbauer JP, Pagani O, Sessa C (1998). 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*, **9**, 661-6.

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**, 1495-501.

Hale JJ, Mills SG, MacCoss M, et al (2000). Phosphorylated morpholine acetal human neurokinin-1 receptor antagonists as water-soluble prodrugs. *J Med Chem*, **43**, 1234-41.

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 The Aprepitant Protocol 052 Study Group. *J Clin Oncol*, **21**, 4112-9.

Italian Group for Antiemetic Research (1998). Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. *J Clin Oncol*, **16**, 2937-42.

John PA. Ioannidis, Paul JH, Joseph L (2000). Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: A meta-analysis of randomized evidence. *J Clin Oncol*, **18**, 3409-22.

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

McCrea JB, Majumdar AK, Goldberg MR, et al (2003). Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther*, **74**, 17-24.

Saito H, Yoshizawa H, Yoshimori K, et al (2013). 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**, 1067-73.