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\textsubscript{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 (≥50 mg/m\textsuperscript{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. 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.

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\textsubscript{3} = serotonin, CC = complete control, CI = confidence interval, CINV = chemotherapy-induced nausea and vomiting, CR = complete response, DEX = dexamethasone, HEC = highly emetogenic chemotherapy, NK\textsubscript{1} = neurokinin type-1, PS = performance status, ULN = upper limit of the normal.

Keywords: cisplatin, dexamethasone, fosaprepitant, high emetic chemotherapy

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Compliance with ethical standards.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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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-HT3) antagonist, dexamethasone (DEX), and a neurokinin type-1 (NK1) receptor antagonist,[3] 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-HT3 antagonist and DEX in patients receiving HEC.[3] Because NK1 receptor antagonists suppress DEX metabolism, the concentration of DEX reaches high plasma levels when used in combination with NK1 receptor antagonists.[3] 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 days 2 and 16 mg on days 3 and 4,[3] 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-HT3 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 study 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-HT3 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 (≥50 mg/m2) were eligible. The main eligibility criteria included histologically or cytologically confirmed solid cancer, age ≥20 years, Eastern Cooperative Oncology Group performance status (PS) of 2 or less, neutrophil count ≥1000/mm3, platelet count ≥75,000/mm3, hemoglobin ≥8.0 g/dL, aspartate transaminase and alanine transaminase <2.0 × the upper limit of the normal (ULN) range in the institution, total bilirubin ≤2.0 × ULN, and creatinine clearance estimated by the Cockcroft-Gault equation ≥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 nausea/vomiting, and nausea ratings at about noon on days 2–6 were 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 preset 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 (≥50 mg/m²) 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 a history of prior chemotherapy before this study, of which 34 patients (84.1%) received cisplatin-based combination chemotherapy. Thirty-seven patients (84.1%) received cisplatin (≥50 mg/m²), with a mean dose of 67.7 mg/m² (standard deviation; 9.24 mg/m²) and a median dose of 70.5 mg/m² (range, 48–80 mg/m²) (Table 2). The antiemetic prophylaxis regimen is shown in Table 2. 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 cancer received chemoradiotherapy combined with S-1 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 (≥50 mg/m²), with a mean dose of 67.7 mg/m² (standard deviation; 9.24 mg/m²) and a median dose of 70.0 mg/m² (range, 50–80 mg/m²; Table 2). The antiemetic prophylaxis regimen is shown in Table 2. All of the patients received the prescribed triplet antiemetic therapy.

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

| Characteristics          | Number (n=44) | %  |
|--------------------------|--------------|----|
| Age                      | Median (range) | 65 (30–75) | 77.3 |
| 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. | %  |
|----------------------------------------|----|
| Regimen of chemotherapy                |    |
| Cisplatin plus S-1†                     | 43 |
| Cisplatin plus 5-FU‡                    | 21 |
| Cisplatin /5-FU /Docetaxel              | 16 |
| Cisplatin plus etoposide                | 7  |
| Cisplatin plus other drug               | 14 |
| Doses of cisplatin, mg/m²               |    |
| 50–60                                   | 2  |
| 60–69                                   | 19 | 43 |
| 70–79                                   | 11 | 25 |
| 80 g                                    | 12 | 27 |
| Mean±SD†                                | 70 (46–80) |
| Day 1: Cisplatin plus etoposide         |    |
| Dexamethasone, 12 mg, drip infusion     |    |
| Day 2: Cisplatin plus S-1               |    |
| Dexamethasone, 8 mg, drip infusion      |    |
| Days 3, 4: Cisplatin plus S-1           |    |
| Dexamethasone, 16 mg, drip infusion     |    |
| †: 5-FU, 5-fluorouracil                 |    |

3.3. Efficacy

The percentage of patients who achieved a CR in the treatment phase was 70% (95% confidence interval [CI]: 53%–93%). 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 of 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
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

### Table 3

| 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                 | 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                 |
| Hiccups               | 10                  | 23                 | 0                  | 0                 |
| Appetite loss         | 29                  | 66                 | 3                  | 7                 |
| Vasculitis            | 3                   | 7                  | 0                  | 0                 |
| Increased serum AST\(^{[2]}\)/ALT\(^{[2]}\) | 12                  | 27                 | 0                  | 0                 |
| Increased serum creatinine | 8                  | 18                 | 0                  | 0                 |
| Hyperglycemia         | 13                  | 30                 | 1                  | 2                 |
| Insomnia              | 2                   | 5                  | 0                  | 0                 |

\(^{[2]}\) AST, aspartate aminotransferase.  
\(^{[2]}\) ALT, alanine aminotransferase.
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 10mg on day 1, 4mg on day 2, and 8mg on day 3.\[3]\] Whereas, in the latest Japanese phase 3 (TRIPLE) trial of the antiemetic effects are correlated with the daily total dose of DEX.

The present observation that the CR rate in the delayed phase was comparable to that in the EASE trial 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 20mg.\[6] Recent guidelines for the management of CINV recommend that the maximum total dose of DEX is 20mg per day.\[3]\] However, it is still unclear if the antiemetic effects are correlated with the daily total dose of DEX equal to or less than 20mg, 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.

### Table 4

| 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 | 0.067   |
| Triplet chemotherapy        | 6.41       | 0.88–77.58 | 0.036   |
| Upper gastrointestinal cancer | 2.86     | 0.28–147.53| 0.647   |
| Performance status ≥ 2      | 0.45       | 0.01–52.21 | 0.647   |
| Not confirmed alcohol intake | 1.84     | 0.44–7.95  | 0.356   |
| Multivariate analysis       |            |            |         |
| Female sex                  | 6.05       | 1.22–30.00 | 0.028   |
| Triplet chemotherapy        | 9.89       | 1.47–60.70 | 0.019   |

*CI, confidence interval.*

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