

RESEARCH ARTICLE

Efficacy of Aprepitant for Nausea in Patients with Head and Neck Cancer Receiving Daily Cisplatin Therapy

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Abstract

Background: Although efficacy of aprepitant for suppressing emesis associated with single-dose cisplatin has been demonstrated, there are limited data on the antiemetic effect of this oral neurokinin-1 receptor antagonist during daily administration of cisplatin. Accordingly, we investigated the efficacy and safety of aprepitant in patients with head and neck cancer (HNC) receiving combination therapy with cisplatin and 5-FU (FP therapy). **Materials and Methods:** Twenty patients with HNC were prospectively studied who received a triple antiemetic regimen comprising granisetron (40 μ g/kg on Days 1-4), dexamethasone (8 mg on Days 1-4), and aprepitant (125 mg on day 1 and 80mg on days 2-5) with FP therapy (cisplatin 20 mg/m² on days 1-4; 5-FU 400 mg/m² on days 1-5) (aprepitant group). We also retrospectively studied another 20 HNC patients who received the same regimen except for aprepitant (control group). **Results:** For efficacy endpoints based on nausea, the aprepitant group showed significantly better results, including a higher rate of complete response (no vomiting and no salvage therapy) for the acute phase ($p=0.0342$), although there was no marked difference between the two groups with regard to percentage of patients in whom vomiting was suppressed. There were no clinically relevant adverse reactions to aprepitant. **Conclusions:** This study suggested that a triple antiemetic regimen containing aprepitant is safe and effective for HNC patients receiving daily cisplatin therapy.

Keywords: aprepitant - cisplatin - antiemetic - head and neck cancer - CINV

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Introduction

In patients receiving anticancer chemotherapy, one of the most troublesome side effects is chemotherapy-induced nausea and vomiting (CINV). Persistent CINV can lead to dehydration, electrolyte abnormalities, and undernutrition, along with deterioration of the patient's physical and mental state, and it often becomes difficult to continue chemotherapy. Thus, preventing or alleviating the symptoms of CINV is important both to maintain the quality of life and to allow continuation of chemotherapy in cancer patients.

The oral neurokinin-1 receptor antagonist aprepitant is an antiemetic drug with a new mechanism of action that not only shows efficacy for acute CINV (within 24 hours of starting chemotherapy) but also for delayed CINV (24 hours or more after starting chemotherapy), which is poorly controlled by current therapies, and the efficacy of aprepitant against the emetic effect of single-dose cisplatin has been demonstrated (Roila et al., 2010; Basch et al., 2011).

We employ a daily cisplatin regimen (FP therapy with daily administration of cisplatin at 20mg/m² from Day 1 to Day 4 and 5-fluorouracil (5-FU) at 400 mg/m² from Day 1 to Day 5) (Brizel et al., 1998) to treat patients with head

and neck cancer (HNC), but there have been few studies on the efficacy of aprepitant during daily administration of cisplatin and no specific antiemetic regimen for daily cisplatin therapy has been established (Roila et al., 2010; Basch et al., 2011; Einhorn et al., 2011). When FP therapy is performed at our department, severe nausea tends to occur on or after the last day of cisplatin administration and it has a strong impact on quality of life (Sun et al., 2005). There have been several other reports that CINV is most severe on Day 4 or Day 5 during daily administration of cisplatin (Einhorn et al., 2007; Jordan et al., 2009; Roila et al., 2010; Einhorn et al., 2011), suggesting that a new regimen for use of aprepitant during daily cisplatin administration should be established (Ellebaek and Herrstedt, 2008; Roila et al., 2010).

When cisplatin is administered for 4 days, the incidence of CINV is expected to peak around Day 4 or later. Although aprepitant is usually administered for 3 days, this would not adequately control CINV associated with 4 days of cisplatin therapy that occurs on Day 5 or later. Therefore, aprepitant was administered for 5 days in the present prospective investigation into the effects of aprepitant in HNC patients receiving cisplatin therapy, with a focus on nausea. The results of this study were expected to provide useful data about the influence of

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aprepitant on the side effects of chemotherapy with highly emetic anticancer drugs.

Materials and Methods

Patients

Patients were eligible for this study if they had HNC and were scheduled to start their first course of FP therapy (cisplatin at 20mg/m² from Day 1 to Day 4 and 5-FU at 400mg/m² from Day 1 to Day 5), if they had not previously received moderately or severely emetic chemotherapy, and if their Eastern Cooperative Oncology Group performance status was 0-2.

Exclusion criteria were as follows: (1) serious hepatic or renal disease, (2) nausea or vomiting within 24 hours before the start of chemotherapy, (3) use of antiemetic drugs within 48 hours before the start of chemotherapy, (4) any factor that could cause nausea or vomiting other than chemotherapy (e.g., brain tumor/metastasis, intestinal obstruction, or active peptic ulcer), (5) scheduled abdominal irradiation, and (6) any other reason that led the attending doctor to conclude that the patient was not eligible.

In the aprepitant group, 20 patients were studied prospectively from May 2010 to June 2012. In the control group, 20 other patients treated from May 2009 to April 2010 were studied retrospectively. All of the patients started their first course of a regimen involving daily administration of cisplatin at 20 mg/m².

Study treatment

Patients in the aprepitant group were administered the drug once a day at a dose of 125mg on Day 1 and 80mg on Days 2 to 5. They also received granisetron (a 5-HT₃ receptor antagonist) intravenously at 40µg/kg once a day on Days 1 to 4 and dexamethasone intravenously at 8 mg once a day on Days 1 to 4 (Table 1). In the control group, granisetron and dexamethasone were administered by the same regimens as mentioned above (Table 1).

Evaluation of efficacy

Evaluation of efficacy was performed over an 8-day period from the first day of cisplatin therapy to 4 days after completing cisplatin administration. Within that period, vomiting on Days 1 to 4 was defined as acute and vomiting on Days 5 to 8 was defined as delayed. Patients in the aprepitant group received a diary to record CINV and salvage therapy for the 8-day study period with each course of chemotherapy. In the control group, information about CINV and salvage therapy was collected retrospectively from the medical records of 20 other patients.

The primary endpoint of this study was the percentage

of patients (courses) with a complete response (CR, defined as no vomiting and no salvage therapy) in the entire 8-day period, the acute phase (Days 1-4), and the delayed phase (Days 5-8). Secondary endpoints were as follows: i) the percentage of patients (courses) with only mild nausea (no vomiting, no salvage therapy, and no moderate/severe nausea) during the overall 8-day period, the acute phase, and the delayed phase; ii) the percentage of patients (courses) with total control of nausea (no vomiting, no salvage therapy, and no nausea) during the overall period, the acute phase, and the delayed phase; iii) the percentage of patients (courses) without nausea during the overall period, the acute phase, and the delayed phase; and iv) the percentage of patients (courses) without vomiting during the overall period, the acute phase, and the delayed phase.

Each patient in the prospective study evaluated the severity of nausea once a day by classifying it into the following 4 categories: no nausea, mild nausea (eating and drinking were possible despite nausea), moderate nausea (drinking fluids was possible, but not eating), and severe nausea (neither eating nor drinking was possible). The subjects recorded these evaluations in their patient diaries. The patients in the prospective study also recorded the time of each episode of vomiting in the diary. If consecutive vomiting episodes occurred within 1 minute, these were classified as a single event.

The attending doctor and the patient recorded the details of salvage therapy in the medical record and the patient diary, respectively. Salvage therapy was only provided to alleviate nausea and/or vomiting at the request of the patient and was not provided prophylactically.

Statistical analysis

The efficacy evaluations for each course were combined and comparison was performed between the two groups by using the chi-square test. The level of significance was set at $p=0.05$.

Ethical considerations

This study was approved by the Ethics Committee of Nagasaki University Hospital and was performed in accordance with the standards laid down in the 1964 Declaration of Helsinki. All of the subjects gave written informed consent to participation in the study.

Results

Clinical characteristics of the subjects are shown in Table 2. There were no marked differences of these characteristics between the aprepitant group and the control group. The CR rate for the overall study period (Days 1 to 8), which was the primary endpoint, is shown

Table 1. Antiemetic Medications

	Drug	Day 1	Day 2	Day 3	Day 4	Day 5
Aprepitant group	Aprepitant (p.o.)	125 mg	80 mg	80 mg	80 mg	80 mg
	Dexamethasone (i.v.)	8 mg	8 mg	8 mg	8 mg	Not administered
	Granisetron (i.v.)	40 mg/kg	40 mg/kg	40 mg/kg	40 mg/kg	Not administered
Control group	Dexamethasone (i.v.)	8 mg	8 mg	8 mg	8 mg	Not administered
	Granisetron (i.v.)	40 mg/kg	40 mg/kg	40 mg/kg	40 mg/kg	Not administered

in Figure 1, as well as the CR rate and the percentage of patients (courses) without vomiting during the acute phase (Days 1 to 4) and the delayed phase (Days 5 to 8) (secondary endpoints). There was no significant difference between the groups with respect to the CR rate for the overall period and the delayed phase, but the CR rate during the acute phase was significantly higher in the aprepitant group ($p=0.0342$). The percentage of patients (courses) with complete protection, total control, no nausea, and no vomiting (secondary endpoints) is shown in Figure 2a-d, respectively.

The two groups showed no significant differences with regard to the percentage of patients (courses) without

Table 2. Patient Characteristics

	Aprepitant group	Control group	P value
Number	20	20	
Total no. of courses	50	50	
Men:Women	17.03	17.03	1.0000 ^a
Mean age	59.9±7.22	65.7±6.94	0.0135 ^b
Stage			
I	0	1	0.5153 ^c
II	4	1	
III	3	1	
IV	13	15	
Performance status			
0	18	15	0.4075 ^a
1	2	5	

^aFisher's exact test; ^bt-test; ^cchi-square test

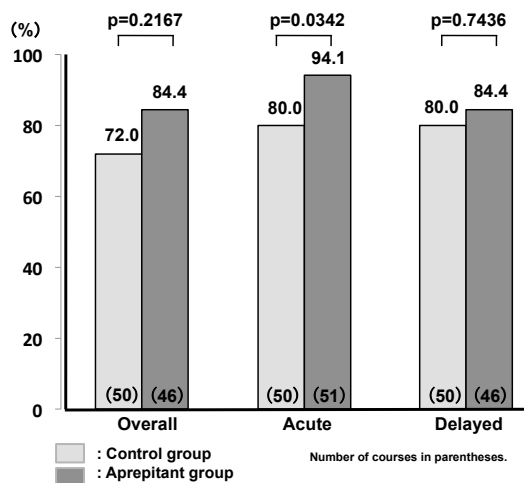


Figure 1. CR Rate There was no Significant Difference between the Two Groups with Respect to the CR Rate for the Overall Study Period (Days 1 to 8) and the Delayed Phase (Days 5 to 8), but the CR Rate During the Acute Phase (Days 1 to 4) was Significantly Higher in the Aprepitant Group

vomiting in any of the 3 evaluation periods. However, fewer patients in the aprepitant group had vomiting during the overall period and acute phase when compared with the control group. Regarding patients with complete protection, total control, and no nausea, results were significantly better in the aprepitant group for the overall study period, acute phase, and delayed phase. Regarding safety, no clinically important side effects occurred in the aprepitant group during the observation period.

Discussion

In this study, administration of aprepitant led to marked suppression of nausea induced by daily administration of cisplatin. In many previous studies on the daily administration of cisplatin, steroids were administered until around Day 8 (Ellebaek and Herrstedt, 2008; Jordan et al., 2009; Albany et al., 2012). However, we administered aprepitant from Day 1 to Day 5 as antiemetic therapy together with a 5-HT₃ receptor antagonist and a steroid from Day 1 to Day 4. With a single dose of cisplatin, the day of administration (Day 1) is defined as the acute phase, and Days 2 onward are defined as the delayed phase. However, daily administration of cisplatin (a highly emetic drug) causes overlapping nausea and/or vomiting in the acute and delayed phases (Ellebaek and Herrstedt, 2008; Jordan et al., 2009). In the present study, we defined the period from Day 1 to Day 4 (duration of cisplatin administration) as the acute phase and the period from Day 5 to Day 8 as the delayed phase.

Aprepitant showed efficacy against nausea in the overall study period as well as the acute phase and the delayed phase. However, the possibility that the overall efficacy was due to the carry-over effect of aprepitant (its antiemetic effect may be carried over to subsequent courses) cannot be ruled out. In this study, there was no significant difference of the CR rate and vomiting in the overall study period and the delayed phase, which was because there were also patients with vomiting in the control group. Further improvement in the control of CINV is needed. Possible measures include prolonging the administration period of aprepitant (Jordan et al., 2009), prolonging administration of steroids (Jordan et al., 2009), combined use of palonosetron (Einhorn et al., 2007), and administration of aprepitant on Day 3 and later days (Albany et al., 2012). Xiao et al. (2014) also suggested recently that CINV after highly emetogenic chemotherapy may be prevented by the use of an electronic anti-nausea instrument with hydrochloride palonosetron

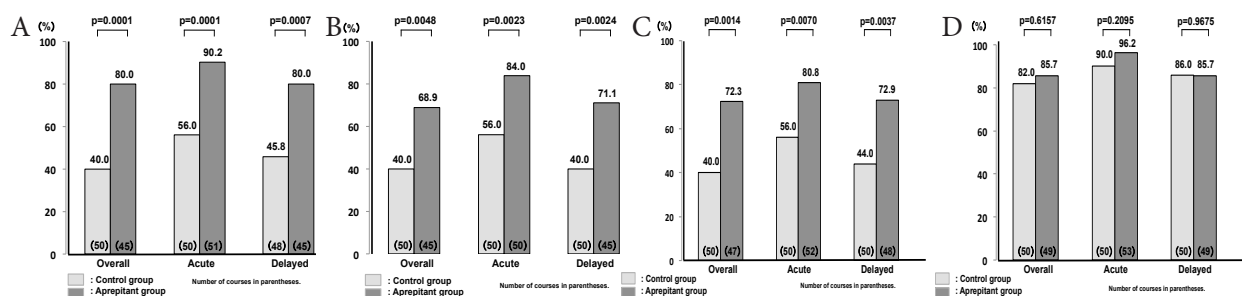


Figure 2. (A) Complete Protection, (B) Total Control, (C) No Nausea, and (D) No Vomiting

In the present study, the percentage of patients without nausea in the aprepitant group during the overall study period, acute phase, and delayed phase was 72.3%, 80.8%, and 72.9%, respectively. In a study conducted by Jordan et al., aprepitant was administered from Day 1 until 2 days after completing administration of highly emetic anticancer drugs (an average of 5.5 days and maximum of 7 days) and dexamethasone (8mg/day) was administered during chemotherapy and for 2 days afterward, and the percentage of patients without nausea during the overall study period, acute phase, and delayed phase was 76.3%, 78.9%, and 78.9%, respectively (Jordan et al., 2009). In that study, the chemotherapy administration period was longer and the mean age of the patients was younger than in our study (the mean age was 43 years versus 59.9 years). Accordingly, prolonged administration of aprepitant and steroids could be expected to achieve further improvement of nausea (Jordan et al., 2009). Einhorn et al. administered palonosetron (Days 1, 3, and 5) and dexamethasone (20 mg on Days 1-2, 8mg on Days 6-7, and 4mg on Day 8) during daily cisplatin therapy for 5 days, and reported good control of nausea (Einhorn et al., 2007). Albany et al. conducted a phase III clinical trial in patients receiving daily cisplatin for 5 days to treat germ cell tumors that compared a group with oral aprepitant from Day 3 to Day 7 and a group with oral placebo from Day 3 to Day 7 (dexamethasone was administered at 20mg on Days 1 and 2 in both groups, and then at 8 mg in the aprepitant group and at 8 mg in the placebo group from Day 6 to Day 8). The nausea rate (evaluated on a visual analog scale) was lower in the aprepitant group, but there was no significant difference between the two groups (Albany et al., 2012). Compared with these studies, we administered a lower steroid dose for a shorter period in our study. Thus, altering the dosage of steroids and use of palonosetron may further improve CINV.

The present study has several limitations. The first limitation relates to the comparison between two arms whose data were collected in different fashion, with one in a prospective setting and the other had data collected retrospectively. Hence, caution is needed in interpreting the findings. Although we utilized patient diaries to ensure that minor CINV episodes (easily missed in routine assessment) were recorded, it was impossible to fully exclude the possibility of overestimating the efficacy of aprepitant. There may also be between-group differences in terms of patient education about prophylactic therapy. This is relevant because nausea has been regarded as a “neuropsychic” experience, and the manner in which patients are informed could influence outcomes, independent of drug action. Second, the sample size of the present study was not large enough to draw a definitive conclusion. Further research with larger prospective cohorts is warranted.

Nevertheless, this study suggested the usefulness of aprepitant for suppressing CINV during daily administration of cisplatin, a highly emetic anticancer agent.

References

- Albany C, Brames MJ, Fausel C, et al (2012). Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study. *J Clin Oncol*, **30**, 3998-4003.
- Basch E, Prestrud AA, Hesketh PJ, et al (2011). Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*, **29**, 4189-98.
- Brizel DM, Albers ME, Fisher SR, et al (1998). Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med*, **338**, 1798-804.
- Einhorn LH, Brames MJ, Dreicer R, et al (2007). Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer*, **15**, 1293-300.
- Einhorn LH, Grunberg SM, Rapoport B, Rittenberg C, Feyer P (2011). Antiemetic therapy for multiple-day chemotherapy and additional topics consisting of rescue antiemetics and high-dose chemotherapy with stem cell transplant: review and consensus statement. *Support Care Cancer*, **1**, 1-4.
- Ellebaek E, Herrstedt J (2008). Optimizing antiemetic therapy in multiple-day and multiple cycles of chemotherapy. *Curr Opin Support Palliat Care*, **2**, 28-34.
- Jordan K, Kinitz I, Voigt W, et al (2009). Safety and efficacy of a triple antiemetic combination with the NK-1 antagonist aprepitant in highly and moderately emetogenic multiple-day chemotherapy. *Eur J Cancer*, **45**, 1184-7.
- 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*, **5**, 232-43.
- Sun CC, Bodurka DC, Weaver CB, et al (2005). Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. *Support Care Cancer*, **13**, 219-27.
- Xiao Y, Liu J, Liu YC, et al. (2014). Phase II study on EANI combined with hydrochloride palonosetron for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Asian Pac J Cancer Prev*, **15**, 3951-4.