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Investigation of a new antiemetic regimen in patients receiving highly emetogenic chemotherapy

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It has been suggested that three-drug combination therapy employing aprepitant, palonosetron, and dexamethasone is useful for treating nausea and vomiting associated with cancer chemotherapy (chemotherapy-induced nausea and vomiting, CINV). However, whether this three-drug regimen is superior to other antiemetic agents available before the release of aprepitant and palonosetron has been unclear. This study compared the efficacy of the three-drug regimen with that of conventional antiemetic therapy in 132 patients who received cisplatin at a dose of 50 mg/m^2 or higher during the period from January 2009 to December 2012. The percentage of patients without vomiting or salvage treatment (*i.e.*, those with a complete response) showed a significant difference between combination therapy including aprepitant and antiemetic therapy without aprepitant. There was no significant difference between the groups with regard to the percentage of patients without nausea during the acute phase within 24 hours, but a significant difference was observed during the delayed phase from 24 hours to 72 hours. There was also a significant difference in the percentage of patients without vomiting throughout the study period when the three-drug combination therapy group was compared with the granisetron group and the granisetron plus aprepitant group. When used in combination with aprepitant, superiority of palonosetron over granisetron has not been reported in Japan, but the present results suggested such superiority. The three-drug regimen may be useful for preventing CINV in patients receiving highly emetogenic chemotherapy.

Key Words: Aprepitant, Palonosetron, Highly emetogenic chemotherapy, CINV, Antiemetic therapy

Introduction

Problematic side effects of chemotherapy for cancer include nausea and vomiting. Chemotherapy-induced nausea and vomiting (CINV) often causes marked impairment of the quality of life in cancer patients. CINV results in electrolyte abnormalities and dehydration, as well as reducing dietary intake, which leads to nutritional disorders and weight loss. CINV also causes deterioration of the mental state and physical condition, and often prevents completion of chemotherapy according to schedule[1,2]. In Japan, standard antiemetic therapy since the 1990s has been the two-drug combination of dexamethasone and a 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist (RA).

Aprepitant is a selective neurokinin-1 (NK-1) RA and is an antiemetic drug that suppresses nausea and vomiting by preventing substance P from binding to NK-1 receptors in the central nervous system, since substance P levels are increased by anticancer drugs[3–5]. Aprepitant was developed by Merck & Co., Inc., Kenilworth, N.J.,

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U.S.A, and was released in Japan in 2009, while fosaprepitant (an injectable product) was released in 2011. Palonosetron, a second-generation 5-HT_3 RA, was developed by Helsinn in Switzerland and was marketed in Japan in 2010. The plasma elimination half-life of palonosetron is longer than that of conventional 5-HT_3 RAs about 40 hours versus approximately 3–5 hours and this drug exerts a long-lasting antiemetic effect by continuous inhibition of serotonin binding[6]. These two drugs are not only promising for the management of acute nausea and vomiting, but also delayed nausea and vomiting that cannot be adequately controlled by standard therapy.

In the principal guidelines on antiemetic treatment from overseas (American Society of Clinical Oncology, Multinational Association of Supportive Care in Cancer, and National Comprehensive Cancer Network) and the "Guidelines on the correct use of antiemetics" issued by the Japan Society of Clinical Oncology in May 2010[7], three-drug combination therapy with aprepitant, a 5-HT_3 RA, and dexamethasone is recommended for patients receiving highly emetogenic chemotherapy (HEC). Our previous study showed that this three-drug regimen was useful for preventing CINV in patients receiving HEC[8]. There have been several other studies that suggested the efficacy of this three-drug combination therapy[9, 10]. However, there have not been any studies that compared the three-drug regimen with antiemetic treatment available before the release of aprepitant and palonosetron, and the superiority of three-drug combination therapy has not been demonstrated. Therefore, we performed this study to compare three-drug combination therapy (aprepitant, palonosetron, and dexamethasone) with conventional therapy available before introduction of these newer agents in patients receiving HEC.

Methods

1. Patients and treatment

This study was conducted in 132 patients who received inpatient chemotherapy with cisplatin at a dose of 50 mg/m^2 or higher (administration time: 2 hours) and received one of the following antiemetic regimens in Kawaguchi Municipal Medical Center from January 2009 to December 2012: (1) granisetron (3 mg on the day of chemotherapy) and dexamethasone (9.9 mg i.v. on the day of chemotherapy and 6.6 mg i.v. or 8 mg p.o. on the following two days) in 26 patients (Group G); (2) granisetron (3 mg, one or two doses on the day of chemotherapy), dexamethasone (9.9 mg i.v. on the day of chemotherapy and 6.6 mg i.v. or 8 mg p.o. on the following two days), and aprepitant (125 mg on the day of chemotherapy and 80 mg on the following two days) in 42 patients (Group A); and (3) palonosetron (0.75 mg), dexamethasone (9.9 mg i.v. on the day of chemotherapy and 6.6 mg i.v. or 8 mg p.o. on the following two days), and aprepitant (125 mg on the day of chemotherapy and 80 mg on the following two days) in 64 patients (Group P). No anticonvulsant drugs were used concomitantly, and radiotherapy was not performed in any patient. It should be noted that dexamethasone was administered for three days at our Center, although the "Guidelines on the correct use of antiemetics" issued by the Japan Society of Clinical Oncology stipulate administration for five days. The difference of such dosing period is due to the fact that chemotherapy regimen was not prepared in our hospital as of 2012. Now, we have chemotherapy regimen which is in accordance with the Antiemetic Guideline.

2. Data collection

The gender, age, details of cisplatin therapy, type of cancer, number of vomiting episodes and severity of nausea during five days from the initiation of chemotherapy, use of salvage treatment, and details of salvage treatment were retrospectively extracted from the electronic medical records of the patients.

3. Evaluation

Symptoms that occurred within 24 hours of the administration of anticancer drugs were classified as acute symptoms, while symptoms that occurred from 24 hours onward were classified as delayed symptoms. The percentage

of patients without vomiting or salvage treatment (*i.e.*, those with a complete response) during the whole study period (five days after administration of cisplatin) was calculated in each group. Both acute and delayed nausea/vomiting were also evaluated. Acute and delayed nausea/vomiting were graded according to the Common Toxicity Criteria for Adverse Events version 4.0 (Japanese version, translated by the Japan Clinical Oncology Group).

4. Statistical analysis

Statistical evaluation was performed by using the chi-square test and Fisher's exact test with SPSS version 18.0 software. If the probability (2-sided) was <0.05, the difference was considered significant.

5. Ethical considerations

This study was approved by the Institutional Review Board of Kawaguchi Municipal Medical Center prior to commencement.

Results

The mean age of the patients was 61.2 ± 10.5 years, and there were 84 men and 48 women. Only 5 patients had received chemotherapy containing cisplatin prior to this study. The most common malignancy was lung cancer, followed by gynecologic cancer and gastrointestinal cancer (Table 1). There were significant inter-group differences of sex, age, and cisplatin dose (Table 1).

There was a significant difference in the percentage of patients without vomiting or salvage treatment (*i.e.*, CR) during the whole study period between Group G and Group A, as well as between Group G and Group P, with the percentages being higher in Groups A and P than in Group G (Fig. 1). There was difference in the percentage of patients without acute nausea among the three groups, but there was a significant difference of the percentage with delayed nausea between Groups G and A or between Groups G and P, with the percentages being larger in Groups A and P than in Group G (Fig. 2). The percentage of patients without vomiting during the whole study period showed a significant difference between Groups G and P or between Groups A and P, with the percentage being higher in Group P than in Group G or Group A. In Group P, 100% of the patients were without vomiting (Fig. 3). Residual analysis performed for any two groups between which a significant difference was confirmed showed significant differences of all pairs. Salvage treatment was used for 14 of 26 patients in Group G, 11 of 42 patients in Group A, and 15 of 64 patients in Group P, with metoclopramide being the main salvage agent. The percentage of patients on salvage therapy differed significantly between the groups, with Group P containing the

Table 1: Characteristics of the groups

	Group G	Group A	Group P	P value
Gender (male / female)	23 / 3	14 / 28	49 / 15	0.000*
Age (years)	65.3±5.3	55.9±12.3	63.0±9.4	0.02*
Cisplatin dose (mg/m^2)	72.9±2.7	68.4±5.2	71.6±4.8	0.000*
Prior cisplatin (Yes / No)	1 / 25	0 / 42	4 / 60	0.651
Malignancy				
Lung cancer (non-small cell / small cell)	26 (19 / 7)	16 (15 / 1)	56 (43 / 13)	
Gynecologic cancer	0	22	0	
Gastrointestinal cancer	0	4	8	

Group G: granisetron + dexamethasone; Group A: granisetron + aprepitant + dexamethasone; Group P: palonosetron + aprepitant + decadron

*: Kruskal-Wallis test, p<0.05.

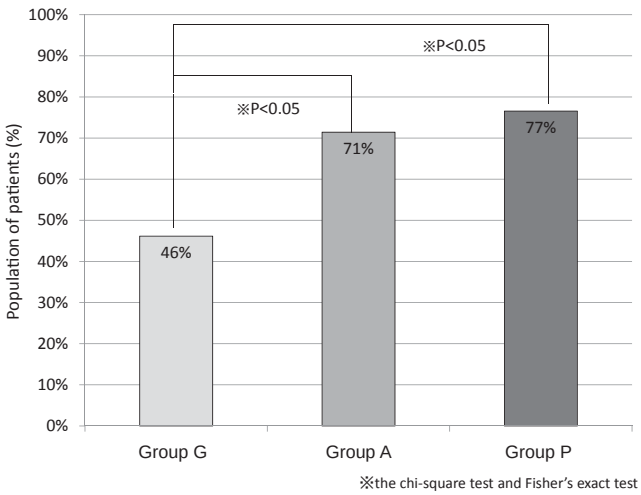

Fig. 1: Overall complete response

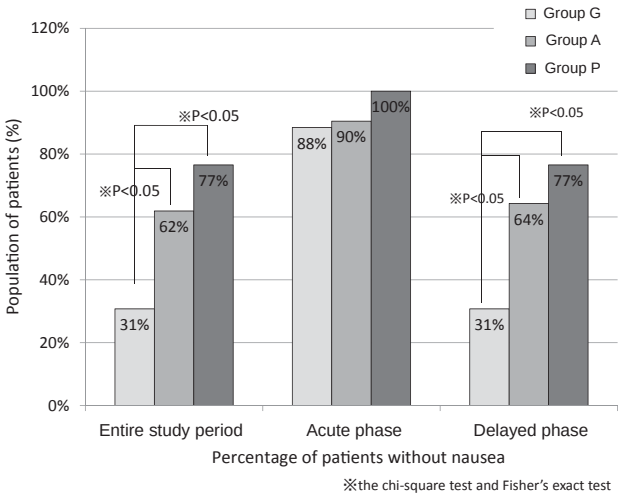

Fig. 2: Overall complete response

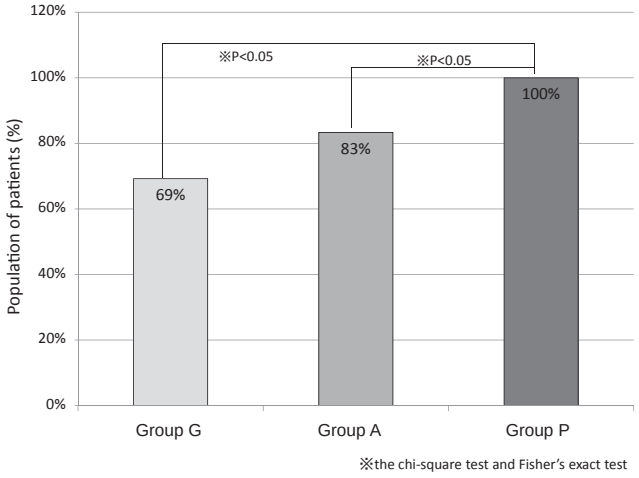

Fig. 3: Percentage of patients without vomiting during the whole study period

smallest number of such patients. In Group G, Grade 2 nausea was noted in three patients, while all other nausea was Grade 0 or 1. In Group A, Grade 2 nausea was observed in two patients and all other nausea was Grade 0 or 1. In Group P, all nausea was Grade 0 or 1, and nausea of Grade 2 or more severe was not observed. Only one patient each in Groups G and A vomited five times or more. No vomiting was observed in Group P. CINV was treated with appropriate salvage therapy, and no serious adverse reactions occurred that required cessation of chemotherapy in any group.

Discussion

The main objective when managing CINV is to prevent its onset. It is important to utilize the best preventative measures when a patient is at risk of nausea and vomiting because good control of CINV can increase the completion rate of chemotherapy and improve survival. Neymark et al.11) reported that patients with lung cancer from the EORTC08975 trial who discontinued protocol treatment had worse survival than patients who completed protocol treatment, and that vomiting was an independent risk factor for failing to complete protocol treatment. Therefore, prevention of CINV can be the most important factor in achieving continuation of chemotherapy.

The present study investigated the effect of three-drug combination therapy using aprepitant, palonosetron, and dexamethasone on nausea and vomiting in comparison with prior treatment in patients receiving HEC with cisplatin at doses of 50 mg/m^2 or higher. CINV associated with cisplatin has a biphasic pattern, since acute symptoms occur within 24 hours and delayed symptoms are seen from 24 hours onward, with the peak of delayed nausea and vomiting at 48–72 hours after administration[12, 13]. In the present study, there was no significant difference among the three groups with regard to prevention of acute nausea. Suzuki *et al.* have also reported similar results[14]. This may have been because acute CINV is closely associated with serotonin[15] and 5-HT$_3$ RAs (granisetron and palonosetron) were used as prophylaxis in this study. Thus, it can be concluded that there was no appreciable difference between the present three-drug combination therapy and prior treatment in terms of the effect on acute phase nausea. The CR rate and the prevention rate of delayed nausea were higher in Groups A and P (which received aprepitant) than in Group G (which did not receive aprepitant), and the differences were significant. This suggested that CR and control of delayed nausea were greatly influenced by aprepitant. It has been reported that delayed CINV is not only associated with serotonin but also with substance P[16]. This report was supported by the results of our study. Ichihara *et al.* also reported that aprepitant had a favorable effect on delayed nausea and

vomiting[17]. There were significant differences between Groups P and G or between Groups P and A with regard to the prevention of vomiting during the whole study period. In particular, the significant difference between Groups P and G suggests that the sustained effect of palonosetron, a long-acting 5-HT_3 RA, contributed to the control of vomiting. When an NK-1 RA was not used, superiority of palonosetron over granisetron was suggested in patients receiving moderately emetogenic chemotherapy[18]. However, in combined use with an NK-1 RA, superiority of palonosetron over other 5-HT_3 RAs has not been demonstrated[7, 19]. In the present study, a significant difference in the percentage of patients without vomiting was observed between Group A and Group P. Although the sample size was small, superiority of palonosetron over granisetron was suggested when combined with an NK-1 RA. These results suggested that three-drug combination therapy with aprepitant, palonosetron, and dexamethasone is superior to prior regimens without these agents for prevention of CINV in patients receiving HEC.

Since aprepitant and palonosetron became available in addition to standard antiemetic therapy with granisetron and dexamethasone, the treatment of delayed CINV has changed dramatically and the frequency of performing salvage therapy has decreased. The primary objective of prophylaxis is to prevent the onset of CINV. Inadequate antiemetic prophylaxis at the start of chemotherapy can lead to anticipatory nausea and vomiting when the next dose of chemotherapy is given, and it can be difficult to prevent CINV under such circumstances. Therefore, we believe that the emetogenic nature of chemotherapy should be evaluated thoroughly and appropriate antiemetic treatment should be performed.

This study was a retrospective investigation conducted at a designated cancer care hospital, so comparisons were not done under uniform conditions. In addition, the patient population was small and there were significant differences of characteristics between the groups. Potential biases due to such differences cannot be ruled out. For example, only Group A contained patients with gynecologic cancer and it is believed that female patients are more likely to develop CINV. However, the percentage of patients without delayed-phase nausea was significantly higher in Group A than in Group G.

In conclusion, this study showed that three-drug combination therapy with aprepitant, palonosetron, and dexamethasone is superior to conventional antiemetic therapy available before the release of aprepitant and palonosetron for prevention of nausea and vomiting in patients receiving HEC. To our knowledge, this is the first study performed in Japan to indicate the superiority of palonosetron over granisetron when used concomitantly with aprepitant. Our results may be useful for establishing an appropriate antiemetic regimen to treat patients receiving HEC. We plan to perform further investigations of this issue.

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