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ORIGINAL ARTICLE

Efficacy and safety of triple therapy with aprepitant, palonosetron, and dexamethasone for preventing nausea and vomiting induced by cisplatin-based chemotherapy for gynecological cancer: KCOG-G1003 phase II trial

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Abstract
Purpose Prevention of chemotherapy-induced nausea and vomiting (CINV) is crucial for maintaining the quality of life of cancer patients. Female patients have been underrepresented in previous clinical studies of aprepitant or palonosetron. We performed a prospective multicenter study to investigate the efficacy and safety of triple therapy comprising these two agents and dexamethasone in female cancer patients receiving chemotherapy that included cisplatin (≥50 mg/m^2).
Methods Aprepitant was administered at a dose of 125 mg before chemotherapy on day 1 and at 80 mg on days 2 and 3. Palonosetron (0.75 mg) was given before chemotherapy on day 1. Dexamethasone was administered at a dose of 9.9 mg before chemotherapy on day 1 and at 6.6 mg on days 2–4. The

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primary endpoint was the the proportion of patients with a complete response (CR no vomiting and no use of rescue medication) throughout the overall period (0–120 h post-chemotherapy).
Results Ninety-six women (median age 55 years) were enrolled. The overall CR rate was 54.2 %. CR was obtained during the acute phase (0–24 h post-chemotherapy) and the delayed phase (24–120 h post-chemotherapy) in 87.5 and 56.3 % of the patients, respectively. The most common adverse reactions were constipation and fatigue (reported by three patients each).
Conclusions Exhibition of a favorable overall CR rate over existing two-drug combinations suggests that the triple therapy regimen used in the present study is effective and tolerable in patients with gynecological malignancies receiving cisplatin-based chemotherapy. Female patients may have a higher risk of developing CINV.

Keywords Aprepitant · Palonosetron · Nausea · Vomiting · CINV · Cisplatin

Introduction

Chemotherapy-induced nausea and vomiting (CINV) occurs with a high frequency following chemotherapy for cancer and is one of the adverse reactions that causes hardship for patients receiving chemotherapy. Failure to prevent CINV may result in worsening of the physical and mental state of the patient and may even become an obstacle to the continuation of chemotherapy. Thus, prevention or alleviation of CINV is extremely important for maintenance of the quality of life of patients and for continuation of their treatment [1, 2].

Antineoplastic agents cause vomiting via two pathways. In one pathway, enterochromaffin cells of the gastrointestinal mucosa are stimulated by a chemotherapy agent and release 5-hydroxytryptamine (serotonin, 5-HT), a neurotransmitter that activates gastrointestinal 5-hydroxytryptamine type 3 (5-HT_3) receptors and transmits signals to the vomiting center in the lateral reticular formation of the medulla via vagal afferents or via the chemoreceptor trigger zone (CTZ). In the other pathway, a drug directly stimulates the CTZ, and then, signals are transmitted to the vomiting center via dopamine receptors and 5-HT_3 receptors. Furthermore, antineoplastic agents can promote the secretion of substance P in the area postrema and the nucleus solitarius of the medulla oblongata, after which substance P binds to neurokinin-1 (NK-1) receptors and induces vomiting. Attention has recently been paid to this mechanism as a new target for antiemetic therapy [3].

Aprepitant is a selective NK-1 receptor antagonist. Clinical trials of this agent with a new mechanism of action for the prophylaxis for CINV have been undertaken outside Japan, and it has been shown to be effective for both acute CINV and also delayed CINV, which responds poorly to existing medications [4–7]. In Japan, the efficacy of aprepitant was demonstrated in Japanese patients by a phase II trial [8], and authorization for manufacturing/marketing was gained in October 2009.

Palonosetron is a new second-generation 5-HT_3 receptor antagonist that differs from other 5-HT_3 receptor antagonists by showing higher receptor-binding affinity, as well as having an extended half-life of about 40 h (four to five times longer than dolasetron, granisetron, or ondansetron) and an excellent safety profile [9, 10]. In Japan, the efficacy of palonosetron was demonstrated by a randomized, parallel-group, comparative, multicenter study using granisetron hydrochloride as the comparator [11], and manufacturing/marketing authorization was obtained in January 2010.

Combined administration of NK-1 receptor antagonists, 5-HT_3 receptor antagonists, and steroids is recommended for the prevention of CINV associated with the administration of highly or moderately emetogenic antineoplastic agents in the international guidelines for antiemetic therapy issued by the American Society of Clinical Oncology (ASCO), Multinational Association of Supportive Care in Cancer (MASCC), and National Comprehensive Cancer Network (NCCN) [12–14]. In clinical studies of aprepitant or palonosetron, thus far reported in or outside Japan, there have been relatively few female patients, and the efficacy of these drugs for CINV in patients with gynecological cancer has not yet been established. In addition, no information is available in or outside Japan concerning the clinical efficacy of triple therapy with the

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combination of aprepitant, palonosetron, and dexamethasone in patients with gynecological cancer.

Therefore, we planned the present study to evaluate the efficacy and safety of combined therapy with these three agents for prevention of CINV in patients with gynecological malignancies receiving chemotherapy containing cisplatin, a highly emetogenic antineoplastic agent.

Methods

Patients

Patients aged 20 years or older were enrolled if they were scheduled to receive more than one cycle of highly emetogenic chemotherapy at any of ten facilities related to Kansai Clinical Oncology Group (KCOG) between July 1, 2010 and June 30, 2012. All patients had gynecological cancer and were scheduled to receive cisplatin at a dose of 50 mg/m^2 or more. Patients who fulfilled any of the following criteria were excluded from the study: previous cisplatin use, severe hepatic insufficiency (Child-Pugh score >9), pre-enrollment alanine aminotransferase (glutamic-pyruvic transaminase) or aspartate aminotransferase (glutamic-oxaloacetic transaminase) level >3 times the upper limit of normal, pre-enrollment total bilirubin >2 times the upper limit of normal, and pre-enrollment serum creatinine level >1.5 times the upper limit of normal.

Study treatment

Aprepitant was administered orally, with a dose of 125 mg being given at 60–90 min before chemotherapy on day 1 and 80 mg being administered once daily on days 2 and 3. Palonosetron was administered intravenously with a dose of 0.75 mg at 30–60 min before chemotherapy on day 1. Dexamethasone was administered orally or intravenously, with a dose of 9.9 mg being given at 30–60 min before chemotherapy on day 1 followed by 6.6 mg once daily on days 2–4.

Parameters assessed

The primary endpoint of the study was the proportion of patients with a complete response (CR), which was defined as no episodes of vomiting and no rescue therapy for nausea, throughout the study period from 0 to 120 h after cisplatin administration (overall CR rate). The secondary endpoints were the proportion of patients with CR in the acute phase (0–24 h after cisplatin administration) and in the delayed phase (24–120 h after cisplatin administration) of the study, as well as the proportion of patients with complete protection (CP no vomiting, no rescue therapy, and no significant nausea (visual analog scale score <25 mm)) throughout the study and in the acute and delayed phases. The proportion of patients who gave the response "Little or no effect on activities of daily living" when completing the Functional Living Index-Emesis (FLIE) questionnaire on day 6 was also determined to assess the influence on the quality of life (QOL).

Evaluation of safety

Adverse events and laboratory data were compiled according to the Common Terminology Criteria for Adverse Events (version 4).

Statistical analysis

It was calculated that 81 patients were needed to detect a difference of $P \leq 0.05$ (two-sided) with a 90 % power if the CR rate for antiemetic therapy was assumed to be 70 %. By estimating the rate of exclusion from analysis as about 20 %, the target number of subjects for enrollment was set at 100. In the main analysis, the study therapy would be judged to be effective if the proportion of patients with a CR throughout the study period (0–120 h) exceeded the proportion of patients with a CR with standard therapy (dual therapy with a first-generation 5-HT$_3$ receptor antagonists and dexamethasone) in previous reports.

Ethical considerations

The present study was conducted in accordance with ethical principles based on the Declaration of Helsinki and the "Ethical Guidelines for Clinical Studies." It was approved by an appropriate institutional review board and ethics committee at each participating center after assessment of the protocol and written information provided for the patients. All patients gave written informed consent prior to inclusion in the study. This study was registered with the University Hospital Medical Information Network (UMIN) clinical trial registry (no. UMIN000003820).

Results

Patient characteristics

A total of 96 patients were enrolled, and their characteristics are summarized in Table 1. All patients were female and their median age was 55 years (range 32–75 years). They were treated for the following gynecological malignancies: endometrial cancer in 61 patients (63.5 %), cervical cancer in 14 patients (14.6 %), and ovarian cancer in 19 patients (19.8 %). Among them, 49 patients (51.0 %) had a history of morning

Table 1 Patient characteristics

		Number	Percent
Total		96	100.0
Age (years)			
	Median	55	
	Range	32–75	
Performance status			
	0	91	94.8
	1	5	5.2
Gynecological malignancy			
	Endometrial cancer	61	63.5
	Ovarian cancer	19	19.8
	Cervical cancer	14	14.6
	Others	2	2.1
Cisplatin dose			
	≥50 and <60	57	59.4
	≥60 and <70	31	32.3
	≥70	8	8.3
	Mean	56.0	
Chemotherapy regimen			
	Cisplatin/Adriamycin	46	47.9
	Cisplatin/Irinotecan	26	27.1
	Cisplatin/Docetaxel	12	12.5
	Cisplatin/Taxol	7	7.3
	Cisplatin alone	2	2.1
	Cisplatin/5-fluorouracil	2	2.1
	Cisplatin/Doxorubicin	1	1.0
Prior chemotherapy			
	Vomiting—Yes	19	19.8
	Vomiting—No	15	15.6
No prior chemotherapy		62	64.6
Drinking alcohol			
	Yes	17	17.7
	No	79	82.3
Motion sickness			
	Yes	30	31.3
	No	66	68.8
morning sickness			
	Yes	49	51.0
	No	47	49.0

sickness during pregnancy, 30 (31.3 %) had a history of motion sickness, and 17 (17.7 %) drank alcohol. Furthermore, 34 patients (35 %) had received prior anticancer chemotherapy, and 19 patients (19.8 %) had experienced nausea. The mean dosage of cisplatin was 56 mg/cm^2, and the other drug used in combination with cisplatin was adriamycin in 46 patients (47.9 %), irinotecan in 26 patients (27.1 %), and docetaxel in 12 patients (12.5 %).

Table 2 Efficacy data

	Study phase	Percent	95 % confidence interval
CR	Acute	87.5	(79.2–93.4)
	Delayed	56.3	(45.7–66.4)
	Overall	54.2	(43.7–64.4)
CP	Acute	82.3	(73.2–89.3)
	Delayed	45.8	(35.6–56.3)
	Overall	44.8	(34.6–55.3)
No emesis	Acute	90.6	(82.9–95.6)
	Delayed	71.9	(61.8–80.6)
	Overall	71.9	(61.8–80.6)
No rescue therapy	Acute	95.8	(89.7–98.9)
	Delayed	65.6	(55.2–75.0)
	Overall	62.5	(52.0–72.2)
No nausea	Acute	74.0	(64.0–82.4)
	Delayed	33.3	(24.3–44.1)
	Overall	30.2	(21.5–40.8)
No significant nausea	Acute	89.6	(81.7–94.9)
	Delayed	62.5	(52.6–72.8)
	Overall	62.5	(52.6–72.8)

The results for patients with no nausea and with no significant nausea are based on data for 95 patients because there was one omission

CR complete response, *CP* complete protection

Antiemetic effect

The antiemetic effect of study therapy is summarized in Table 2. The overall CR rate, which was the primary endpoint, was 54.2 %, while the acute CR rate and delayed CR rate were 87.5 and 56.3 %, respectively. The proportion of patients with no emesis was 90.6, 71.9, and 71.9 % in the acute phase, delayed phase, and overall, respectively, while the corresponding CP rates were 82.3, 45.8, and 44.8 %. The proportion of patients with no nausea was 74.0, 33.3, and 30.2 % in the acute phase, delayed phase, and overall, respectively. The proportion of patients with no nausea on a daily basis for 5 days after administration of chemotherapy is shown in Fig. 1. Control of CINV was poorest at 4 days after the administration of chemotherapy. The proportion of patients who did not need rescue therapy was 95.8, 65.6, and 62.5 % in the acute phase, delayed phase, and overall, respectively. The proportion of patients who gave the response "Little or no effect on activities of daily living" when completing the FLIE questionnaire on day 6 was determined to assess QOL. It was 82.3 % for the vomiting domain, 43.8 % for the nausea domain, and 59.4 % for the combined nausea/vomiting domain. With regard to the nine items in the nausea domain of the FLIE questionnaire, the impact of nausea on daily activities was greatest for "Ability to enjoy a meal" (Fig. 2).

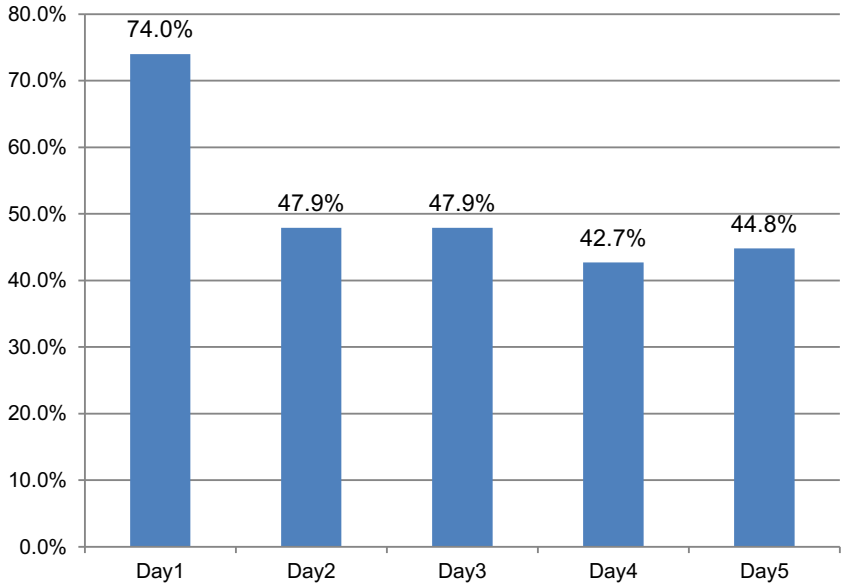

Fig. 1 Proportion of patients with no nausea

Safety

Triple therapy with aprepitant, palonosetron, and dexamethasone showed good tolerability throughout the study period. The most frequently reported adverse reactions were constipation and fatigue, each of which was noted by three patients (3 %).

Discussion

The present multicenter clinical study aimed to evaluate the effect of triple therapy with aprepitant (an NK-1 receptor antagonist), palonosetron (a second-generation 5-HT_3 receptor antagonist), and dexamethasone on CINV in patients with female malignancies who received cisplatin-based chemotherapy. Female sex is known as a risk factor for CINV. In addition, cisplatin is an antineoplastic agent that frequently causes CINV. Accordingly, the subjects of the present study may represent a population of patients in whom CINV would be difficult to control. Cisplatin-containing regimens are classified as highly emetogenic chemotherapy in the guidelines for antiemetic therapy issued by the ASCO [12], MASCC [13], NCCN [14], and Japan Society of Clinical Oncology [15].

In the present study, a CR rate of 54.2 % was achieved by triple therapy with aprepitant, palonosetron, and dexamethasone. This study demonstrated that the triple-agent strategy is

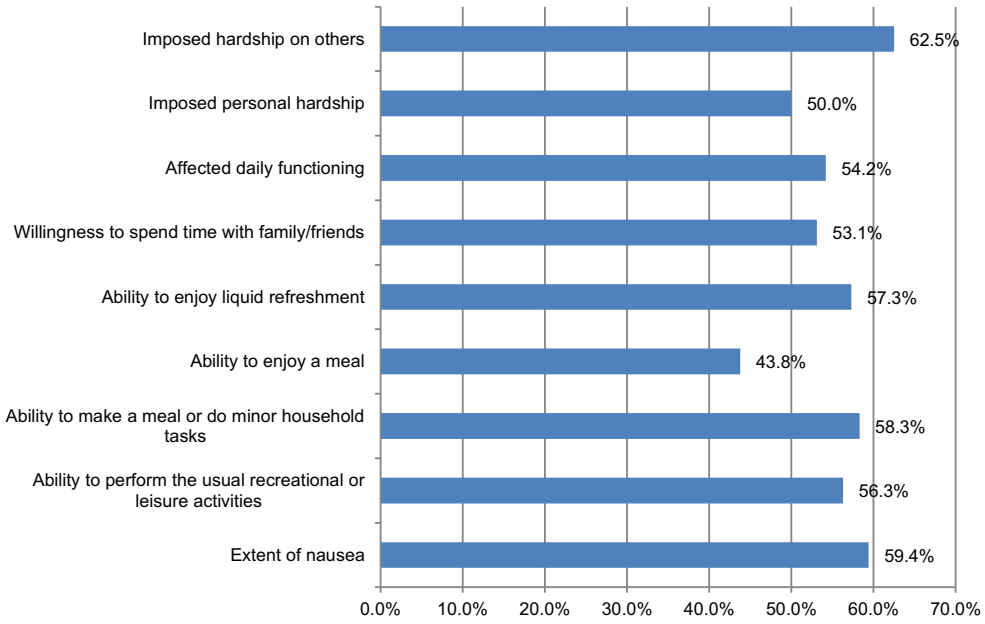

Fig. 2 Nine items in the nausea domain of the Functional Living Index-Emesis questionnaire

Table 3 Comparison of triple therapy regimens

	No. of patients	Percentage of female patients	Cisplatin ≥70 mg/m^2	CR	No emesis	No nausea	No significant nausea	5-HT$_3$ receptor antagonist
Hesketh et al. (2003)	260	48	70 %	73 %	78 %	48 %	73 %	Ondansetron
Poli-Bigelli et al. (2003)	261	37	82 %	63 %	66 %	49 %	71 %	Ondansetron
Schmoll et al. (2006)	243	39	75 %	72 %	77 %	–	73 %	Ondansetron
Takahashi et al. (2011)	149	24	100 %	71 %	77 %	34 %	69 %	Granisetron
Present study	96	100	9 %	54 %	72 %	30 %	63 %	Palonosetron

CR complete response

useful, because it achieved similar CR rates to standard therapy (with a first-generation 5-HT$_3$ receptor antagonist plus dexamethasone) that was used as the comparator in previous clinical trials of aprepitant or palonosetron: Hesketh et al. [4] and Poli-Bigelli et al. [5], respectively, reported a CR rate of 52.3 and 43.3 % with the standard ondansetron-dexamethasone combination. In addition, a CR rate of 40.3 % was reported with the combination of palonosetron and dexamethasone [11]. However, the triple therapy used in the present study achieved a lower CR rate than other triplet regimens, since the CR rate was 72.7, 62.7, and 72.0 % with triple therapy using ondansetron (a first-generation 5-HT$_3$ receptor antagonist) as reported by Hesketh et al. in 2003 [4], Poli-Bigelli et al. in 2003 [5], and Schmoll et al. in 2006 [16], respectively. In addition, a CR rate of 70.5 % for a triplet regimen using granisetron (another first-generation 5-HT$_3$ receptor antagonist) was reported by Takahashi et al. in 2011 (Table 3) [8]. One reason for this difference from other studies may be that our subjects were all female patients. Women are known to be susceptible to CINV, and stratified analysis has shown that dual therapy with a first-generation 5-HT$_3$ receptor antagonist and dexamethasone achieves a lower CR rate in women than in men [17]. In other clinical studies with a lower proportion of women than the present study, the CR rate for triple therapy that included palonosetron as the first-generation 5-HT$_3$ receptor antagonist was reported to be 70.3 % (percentage of women in the study population 23.4 %) by Longo et al. [18] and 81.0 % (percentage of women 23 %) by Miura et al. [19]. Since patients with previous chemotherapy were also enrolled in the present study, an analysis was conducted to compare the subgroups with and without prior chemotherapy, but similar results were obtained (Table 4). Accordingly, although the fact that the subjects of the present study were all women should have an influence, the possibility of other factors cannot be ruled out because it has been reported that the addition of aprepitant to dual therapy with a first-generation 5-HT$_3$ receptor antagonist and dexamethasone can overcome the increased risk of CINV associated with the female gender [17].

In the present study, only 30 % of patients had no nausea throughout the observation period, and adequate control of nausea was not achieved. Rescue medication was administered at the discretion of the attending physician at each participating center because the present study was a multicenter investigation. Accordingly, one reason for the low CR rate may be that rescue therapy was provided without careful consideration of patient's complaints about nausea at some centers. Therefore, different measures should be taken for the control of nausea in future studies.

In another study of patients undergoing highly emetogenic chemotherapy (TRIPLE), comparison was performed between granisetron (a first-generation 5-HT$_3$ receptor antagonist) and palonosetron (a second-generation 5-HT$_3$ receptor antagonist) with basal antiemetic therapy using aprepitant and dexamethasone [20]. The overall CR rate was the primary endpoint, and this showed no statistically significant difference between the two groups. Palonosetron group was significantly superior to the granisetron group with regard to the nausea domain rates for complete control and total control. In view of our present finding that the control of nausea was even poor with

Table 4 Results for patients with and without prior chemotherapy

	No. of patients	Percentage of female patients	Cisplatin ≥70 mg/m^2	CR	No emesis	No nausea	No significant nausea	Prior chemotherapy
Longo et al. (2010)	222	23	98 %	70 %	93 %	60 %	91 %	Chemo-naïve
Miura et al. (2013)	64	23	95 %	81 %	–	54 %	67 %	Chemo-naïve
Present study	96	100	9 %	54 %	72 %	30 %	63 %	Cisplatin-naïve
	62*	100	8 %	55 %	68 %	31 %	63 %	Chemo-naïve

CR complete response

palonosetron, the influence of female gender is considered to be strong.

Recently, the efficacy of olanzapine for controlling nausea has been reported. This agent is one of the multi-acting receptor antipsychotics (MARTA) used for the treatment of schizophrenia, which can block dopamine receptors, serotonin receptors, histamine receptors, adrenergic receptors, and other receptors associated with CINV. Olanzapine was recently reported to be effective for preventing CINV based on its mechanism of action [21]. Therefore, concomitant use of olanzapine is another option that is available.

In order to achieve further improvement of the control of CINV, several additional treatments are likely to be introduced. Since nausea often reaches a peak at 4 days after the administration of anticancer agents (Fig. 2), treatment with aprepitant for 5 days is also likely to be a useful option. Furthermore, administration of dexamethasone for a period of up to 5 days is recommended by guidelines established in Japan, and this regimen is also available.

The present study was the first to investigate the usefulness of triple therapy with aprepitant, palonosetron, and dexamethasone for prevention of CINV in Japanese patients with gynecological cancer receiving cisplatin-containing chemotherapy. This triple therapy was ascertained to be effective compared with the current standard therapy using first-generation 5-HT_3 receptor antagonists and dexamethasone. Nevertheless, the preventive effect of triple therapy tended to be weaker in the present study than that reported previously. All of the subjects were female and therefore may have been predisposed to develop CINV, but the reason is unclear. Control of delayed nausea is an important measure against CINV in the gynecology field. Thus, it may be necessary for medical and co-medical staff, including pharmacists and nurses, to conduct further follow-up of patients.

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Conflict of interest The authors have no conflicts of interest to declare.

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