

# Palonosetron versus granisetron in combination with aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with gynecologic cancer

Satoe Fujiwara, Yoshito Terai, Satoshi Tsunetoh, Hiroshi Sasaki, Masanori Kanemura, Masahide Ohmichi

Department of Obstetrics and Gynecology, Osaka Medical College, Osaka, Japan

**Objective:** There is no research regarding the appropriate antiemetic agents for female patients, especially those receiving moderately emetogenic chemotherapy (MEC). We evaluated the antiemetic efficacy of a combination of 5-HT<sub>3</sub> receptor with/without aprepitant in patients with gynecological cancer treated with the TC (paclitaxel and carboplatin) regimen of MEC.

**Methods:** We enrolled 38 patients diagnosed with gynecologic cancer and scheduled to receive the TC regimen. The patients were randomly assigned to receive a 5-HT<sub>3</sub> receptor antagonist, either palonosetron in the first cycle followed by granisetron in the second cycle or vice versa. In the third cycle, all patients received a combination of the 5-HT<sub>3</sub> receptor and dexamethasone with/without aprepitant.

**Results:** When three drugs were administered, palonosetron consistently produced an equivalent complete response (CR) rate to granisetron in the acute phase (89.5% vs. 86.8%,  $p=0.87$ ) and delayed phase (60.5% vs. 65.8%,  $p=0.79$ ). With regard to the change in dietary intake, palonosetron exhibited similar efficacy to granisetron in the acute phase (92.1% vs. 89.4%,  $p=0.19$ ) and delayed phase (65.7% vs. 68.4%,  $p=0.14$ ). However, in the delayed phase, the addition of aprepitant therapy with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone produced a higher CR rate than a 5-HT<sub>3</sub> receptor antagonist with dexamethasone (93.3% vs. 47.8%,  $p<0.001$ ) and allowed the patients to maintain a higher level of dietary intake (93.3% vs. 56.5%,  $p<0.001$ ).

**Conclusion:** The addition of aprepitant therapy was more effective than the control therapy of a 5-HT<sub>3</sub> receptor antagonist, and dexamethasone in gynecological cancer patients treated with the TC regimen.

**Keywords:** Antiemetics; Aprepitant; Granisetron; Neoplasms; Palonosetron; Serotonin 5-HT<sub>3</sub> Receptor Antagonist

## INTRODUCTION

Although significant progress has been made in terms of prevention, chemotherapy-induced nausea and vomiting

(CINV) remains a potentially severe and distressing adverse effect of cancer treatment. Uncontrolled CINV may limit the dose intensity of chemotherapy and seriously compromise the patient's quality of life.

The objective of antiemetic therapy is to completely prevent CINV, which is achievable in the majority of patients receiving chemotherapy. Three categories of drugs with the highest therapeutic index for CINV management include: (1) three 5-hydroxytryptamine (5-HT<sub>3</sub>) receptor antagonists (palonosetron and granisetron), (2) neurokinin-1 (NK-1) receptor

Received May 25, 2015, Revised Jun 29, 2015, Accepted Jul 12, 2015

**Correspondence to** Yoshito Terai  
Department of Obstetrics and Gynecology, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan. E-mail: y-terai@poh.osaka-med.ac.jp

Copyright © 2015. Asian Society of Gynecologic Oncology, Korean Society of Gynecologic Oncology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

antagonists (aprepitant), and (3) glucocorticoids (dexamethasone) [1]. The administration of three antiemetic agents is recommended in patients treated with highly emetogenic chemotherapy (HEC) according to the updated antiemetic guidelines of the Multinational Association of Supportive Care in Cancer (MASCC) as well as the American Society of Clinical Oncology (ASCO) [2,3] and guidelines published by the Japan Society of Clinical Oncology (JSCO) in 2010 [4]. However, during treatment with moderately emetogenic chemotherapy (MEC), the administration of two antiemetic drugs, a 5-HT<sub>3</sub> receptor antagonist and dexamethasone, is recommended, with the additional administration of aprepitant as a recommended option [2-4].

The CINV risk also depends on patient characteristics, such as gender, age, and history of alcohol consumption. It has been reported that female patients are at greater risk of CINV [5]. Gynecological oncologists are tasked with treating female patients at greater risk of CINV than males. The most frequently used chemotherapy regimen in patients with gynecological malignancy is the TC regimen (paclitaxel and carboplatin) of MEC [2,3]. In female patients, this regimen is expected to be associated with a greater frequency of CINV, even in those receiving MEC, in comparison with that generally reported in male patients. Although there are some reports of the efficacy of antiemetic agents in patients treated with MEC [6-8], there are no reports assessing female patients at greater risk of emesis. Moreover, in patients receiving HEC, palonosetron has been reported to be more effective than granisetron as a 5-HT<sub>3</sub> receptor antagonist [9,10]. Although various reports exist about HEC, there is currently no research regarding differences in the efficacy of the two 5-HT<sub>3</sub> receptor antagonists palonosetron and granisetron in female patients administered the MEC regimen.

Therefore, we examined differences in the efficacy of two 5-HT<sub>3</sub> receptor antagonists, palonosetron and granisetron, in combination with the TC regimen of MEC in patients with gynecological malignancies. In addition, we examined the efficacy of additional treatment with aprepitant in these patients.

## MATERIALS AND METHODS

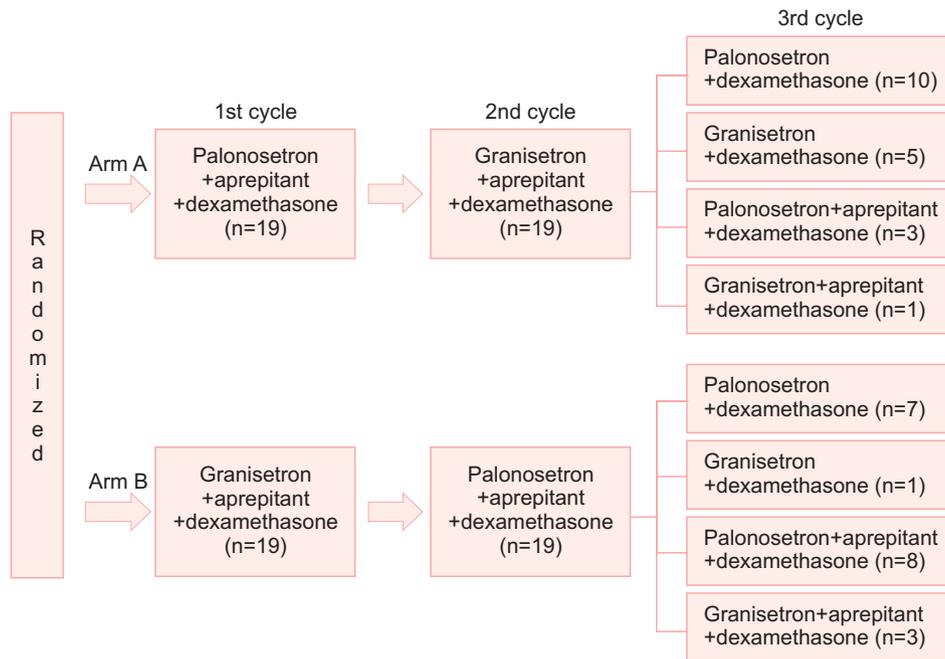
### 1. Study population

Female patients older than 20 years of age with histologically confirmed gynecological cancer (ovarian cancer, peritoneal cancer, endometrial cancer, and cervical cancer) scheduled to receive a TC regimen (with two intravenous cytotoxic antitumor drugs: paclitaxel, 175 mg/m<sup>2</sup> and carboplatin, area

under the curve 5 mg/min/mL, on day 1) were eligible for inclusion in this study. Thirty-eight patients were enrolled in this study between January 2011 and January 2012. The clinical characteristics of the patients are presented in **Table 1**. Eligible patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2 in addition to meeting the following laboratory criteria: aspartate aminotransferase and alanine aminotransferase levels ≤2.5 times the upper limit of the normal range at the facility; a total bilirubin level ≤1.5 times the upper limit of the normal range at the

**Table 1.** Patient demographics and baseline clinical characteristics (n=38)

Variable	No. (%)
Age (yr), median (range)	57.5 (36–76)
≥50	27 (71.1)
Body mass index (kg/m <sup>2</sup> ), median (range)	24.2 (14.8–34.7)
≥25.0	15 (39.5)
Performance status (0/1/2)	36/2/0
Cancer diagnosis	
Endometrial cancer	19 (50.0)
Cervical cancer	7 (18.4)
Ovarian or tubal cancer	10 (26.3)
Double cancer (endometrial and ovarian cancer)	2 (5.3)
Histology	
Serous adenocarcinoma	6 (15.8)
Clear cell adenocarcinoma	5 (13.2)
Endometrioid adenocarcinoma	16 (42.1)
Mucinous adenocarcinoma	2 (5.3)
Squamous cell carcinoma	7 (18.4)
Carcinosarcoma	2 (5.2)
Tumor marker, median (range)	
CA-125 (U/mL)	255.3 (6.9–3,063.6)
Squamous cell carcinoma (ng/mL)	3.2 (0.5–76.7)
Type of surgery	
Type of hysterectomy	
Radical hysterectomy	7 (18.4)
Simple total hysterectomy	31 (81.6)
Type of lymphadenectomy	
Pelvic lymphadenectomy	8 (21.1)
Pelvic and para-aortic lymphadenectomy	30 (78.9)
Bowel resection	1 (2.6)
Interval from surgery to chemotherapy (wk), median (range)	4.8 (3–7)
Previous radiotherapy	0
Previous gastrointestinal surgery	0



**Fig. 1.** Study design flowchart. During the first cycle, the patients received palonosetron or granisetron with the other two drugs, aprepitant and dexamethasone. During the next cycle, patients received the other 5-HT<sub>3</sub> antagonist.

facility; and a creatinine level  $\leq 1.5$  times the upper limit of the normal range at the facility. We also excluded patients with a history of a hypersensitivity to 5-HT<sub>3</sub> receptor antagonists or dexamethasone and those with a risk of vomiting for other reasons (symptomatic brain metastasis, active peptic ulcers, gastrointestinal obstruction, and so on). Signed informed consent was obtained from all patients prior to study entry.

## 2. Study design

This investigation was a prospective, stratified randomization, non-blinded, crossover comparative study. This study was conducted at Osaka Medical College between January 2011 and January 2012 after obtaining approval from the Institutional Review Board (IRB No. 0860). **Fig. 1** shows the crossover design of the study. For the first and second cycles of chemotherapy, all patients were administered three antiemetic agents: a 5-HT<sub>3</sub> receptor antagonist (palonosetron or granisetron), a NK-1 receptor antagonist (aprepitant) and dexamethasone. The dose of each drug according to the study group is shown in **Table 2**. The group assignment was performed by simple randomization using a table of random numbers and patients were informed of which group (arm A or B) they were assigned. Both groups of patients received three daily oral doses of aprepitant and dexamethasone. On day 1, the patients in arm A received a single intravenous dose of palonosetron and the patients in arm B received a single dose of granisetron. For the second cycle, as in the first cycle, the patients in both arms received three daily oral

**Table 2.** Doses of the three antiemetic agents

Arm	Medicine (administration route)	Day 1	Day 2	Day 3
Palonosetron	Aprepitant (po)	125	80	80
	Dexamethasone	20 (iv)	4 (po)	4 (po)
	Palonosetron (iv)	0.75	-	-
Granisetron	Aprepitant (po)	125	80	80
	Dexamethasone	20 (iv)	4 (po)	4 (po)
	Palonosetron (iv)	3	-	-

iv, intravenous; po, per os.

doses of aprepitant and dexamethasone. In addition, the patients in arm A received granisetron and the patients in arm B received palonosetron as the 5-HT<sub>3</sub> receptor antagonist. This research involved a crossover study in which two different drugs were administered to the same patient. In the third cycle, the patients were given a 5-HT<sub>3</sub> receptor antagonist and dexamethasone as antiemetic treatment according to the antiemetic guidelines of the Japan Society of Clinical Oncology. However, in the present study, the patients who experienced strong nausea or high levels of anxiety in the previous cycles were given aprepitant with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone in the 3rd cycle. The clinical characteristics of the patients in the third cycle (with or without aprepitant) are presented in **Table 3**.

**Table 3.** Patient demographics and clinical characteristics in the third cycle

Variable	Population in 3rd cycle (n=38)		p-value
	With aprepitant (n=16)	Without aprepitant (n= 22)	
Age (yr)	58.5 (36–76)	56.8 (36–75)	0.09
≥50	14 (87.5)	15 (68.1)	0.22
Interval from surgery (wk)	4.7 (3–7)	4.9 (4–7)	0.19
Cancer diagnosis			
Endometrial cancer	10 (62.5)	9 (40.9)	0.48
Cervical cancer	2 (12.5)	5 (22.7)	0.06
Ovarian or tubal cancer	4 (25.0)	6 (27.3)	0.57
Double cancer endometrial and ovarian cancer	0	2 (9.1)	
Type of surgery			
Type of hysterectomy			
Radical hysterectomy	2 (12.5)	5 (22.7)	0.11
Simple total hysterectomy	14 (87.5)	17 (77.3)	0.14
Type of lymphadnectomy			
Pelvic lymphadnectomy	3 (18.7)	5 (22.7)	0.09
Pelvic and para-aortic lymphadnectomy	13 (81.3)	17 (77.3)	0.07
Bowel resection	0	1 (4.5)	
Previous radiotherapy	0	0	
Previous gastrointestinal surgery	0	0	

Values are presented as median (range) or number (%).

### 3. Study objectives

The first objective of this study was to demonstrate non-inferiority between the two 5-HT<sub>3</sub> receptor antagonists, granisetron and palonosetron, in combination with three antiemetic agents in the acute and delayed phases in terms of a complete response (CR; no emesis or need for rescue medications). The second objective was to show non-inferiority between the two 5-HT<sub>3</sub> receptor antagonists in terms of changes in the level of dietary intake. Finally, in the sub-analysis conducted during the third cycle, we sought to evaluate the efficacy of an additional dose of aprepitant in terms of the rate of CR and changes in dietary intake.

### 4. Efficacy parameters

Efficacy was monitored via clinical evaluations and patient diaries regarding emesis from the first to the third cycles. From the start of chemotherapy (day 1) and for seven days, the patients' diaries were used to document the date of emetic episodes, use of rescue medications and changes in dietary intake, as well as daily nausea ratings (based on grading according to the National Cancer Institute Common Terminology Criteria for Adverse Events, CTCAE). The patients were allowed to take rescue therapy for nausea or vomiting as needed throughout the study period.

All efficacy analyses started with the TC regimen (day 1) and continued through the subsequent seven days. The primary endpoint was the CR rate during the acute (day 1, 0–24 hours) and delayed periods (day 2–7). The secondary endpoint was the change in dietary intake in both the acute and delayed periods.

### 5. Statistical analysis

All of the statistical analyses were performed using the JMP Pro 11 (SAS Institute Inc., Cary, NC, USA). Fisher exact test was used for comparisons of the CR rate between groups, and the chi-square test was used to assess the changes in level of dietary intake. Differences in efficacy parameters were determined to be significant at p-values of 0.05 using two-sided tests.

## RESULTS

A total of 38 female patients with gynecological cancer receiving the TC regimen (paclitaxel and carboplatin) were enrolled. The intent-to-treat population included 19 patients who received palonosetron on day 1 (Arm A) and 19 patients who received granisetron on day 1 (Arm B).

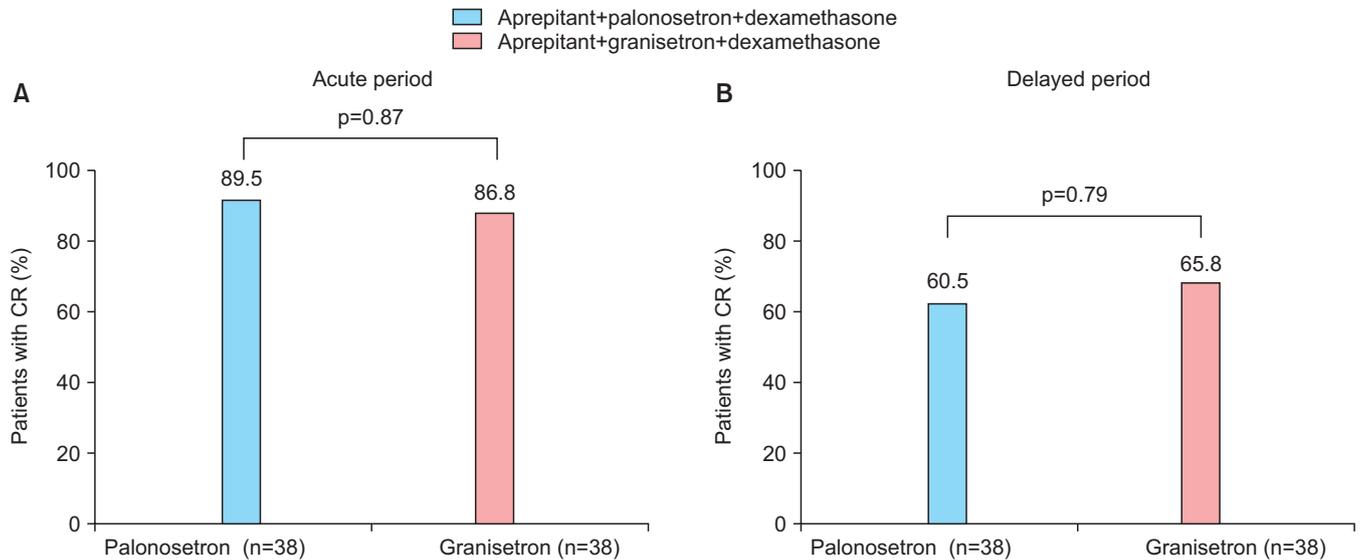
**1. Complete response**

In the first and second cycles, during the acute phase, the CR rate was 89.5% among the patients who received palonosetron and 86.8% among the patients who received granisetron, with a non-significant difference between the two groups ( $p=0.87$ ). During the delayed phase, the CR rate was 60.5% among the patients who received palonosetron

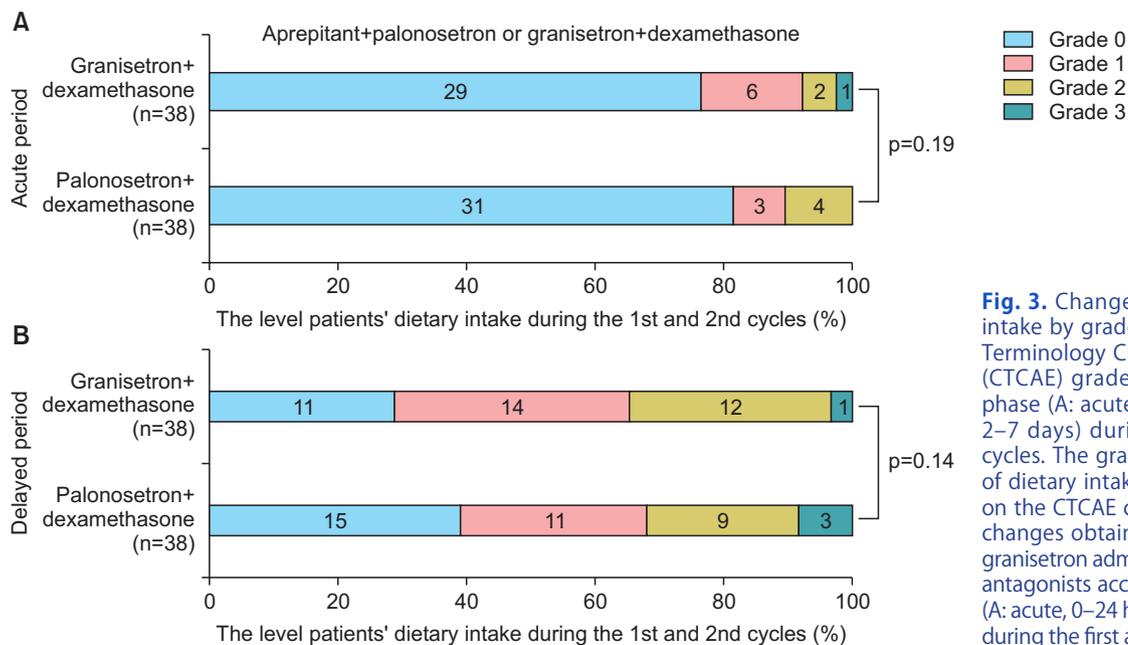
and 65.8% among the patients who received granisetron, with no significant differences ( $p=0.79$ ) (Fig. 2).

**2. Changes in the level of dietary intake**

Fig. 3 shows the percentage of patients classified according to the grade (based on the CTCAE grading) of changes in the level of dietary intake. We compared the percentage of



**Fig. 2.** Proportion of patients achieving a complete response (CR; no emetic episodes or use of rescue therapy) according to the study phase (A: acute, 0–24 hours; B: delayed, 2–7 days) during the first and second cycles. We compared the CR rates achieved with palonosetron and granisetron administered as 5-HT<sub>3</sub> receptor antagonists according to the study phase (A: acute, 0–24 hours; B: delayed, 2–7 days) during the first and second cycles.



**Fig. 3.** Changes in the level of dietary intake by grade based on the Common Terminology Criteria for Adverse Events (CTCAE) grade according to the study phase (A: acute, 0–24 hours; B: delayed, 2–7 days) during the first and second cycles. The grade of change in the level of dietary intake was determined based on the CTCAE criteria. We compared the changes obtained with palonosetron or granisetron administered as 5-HT<sub>3</sub> receptor antagonists according to the study phase (A: acute, 0–24 hours; B: delayed, 2–7 days) during the first and second cycles.

patients with grade 0 or 1 and found the reduction in the level of dietary intake to be lower. During the acute phase, the percentage of patients with grade 0 or 1 was 92.1% among those who received palonosetron and 89.4% among those who received granisetron, with a non-significant difference between the two groups ( $p=0.19$ ). During the delayed phase, the percentage of patients with grade 0 or 1 was 63.5% of the subjects who received palonosetron and 65.7% of those who received granisetron, with no significant differences ( $p=0.14$ ). With respect to the combination of the addition of aprepitant therapy with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone, there were no clinically relevant differences between the patients who received palonosetron and granisetron.

### 3. Efficacy of an additional dose of aprepitant

In this study, during the third cycle of TC administration, the antiemetic regimen consisted of a combination of two antiemetic drugs, a 5-HT<sub>3</sub> receptor antagonist and dexamethasone, without aprepitant, according to the guidelines [2-4]. However, aprepitant was also given during this cycle to patients exhibiting a remarkable loss of dietary intake during the first two cycles and those with strong anxiety regarding the potential for nausea and vomiting in the next cycle.

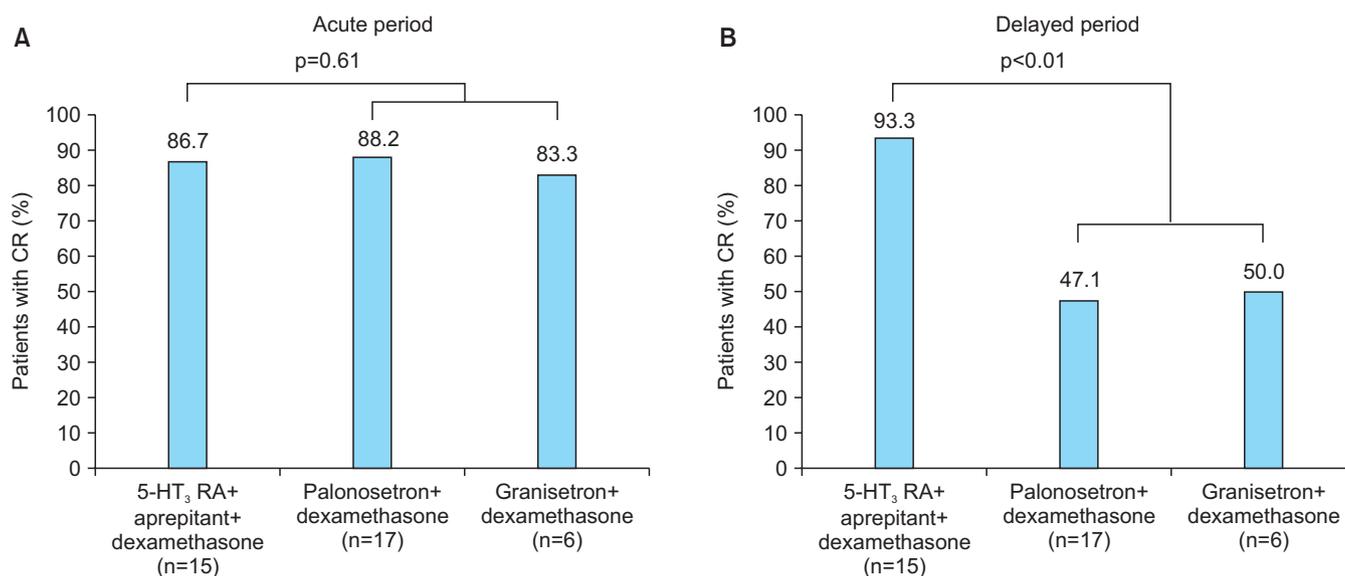
The results of the comparison of the groups who received a combination of the addition of aprepitant therapy with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone ( $n=23$ ; three drugs group) or a 5-HT<sub>3</sub> receptor antagonist with dexametha-

sone ( $n=15$ ; two drugs group) as chemotherapy in the third cycle are shown in Figs. 4, 5. There were no significant differences in the CR rate between the three drugs group and the two drugs group in the acute phase (86.7% to 82.6%,  $p=0.61$ ). However, in the delayed phase, when aprepitant was added, the CR rate rose in comparison with that observed in the two drugs group (93.3% to 47.8%,  $p<0.001$ ). Similarly, there were no significant differences in the effect in suppressing nausea between the 5-HT<sub>3</sub> receptor antagonists (palonosetron or granisetron) when administered in the two drugs group. Moreover, there were no significant differences in the level of dietary intake between the subjects who received palonosetron and granisetron in either the acute or delayed period.

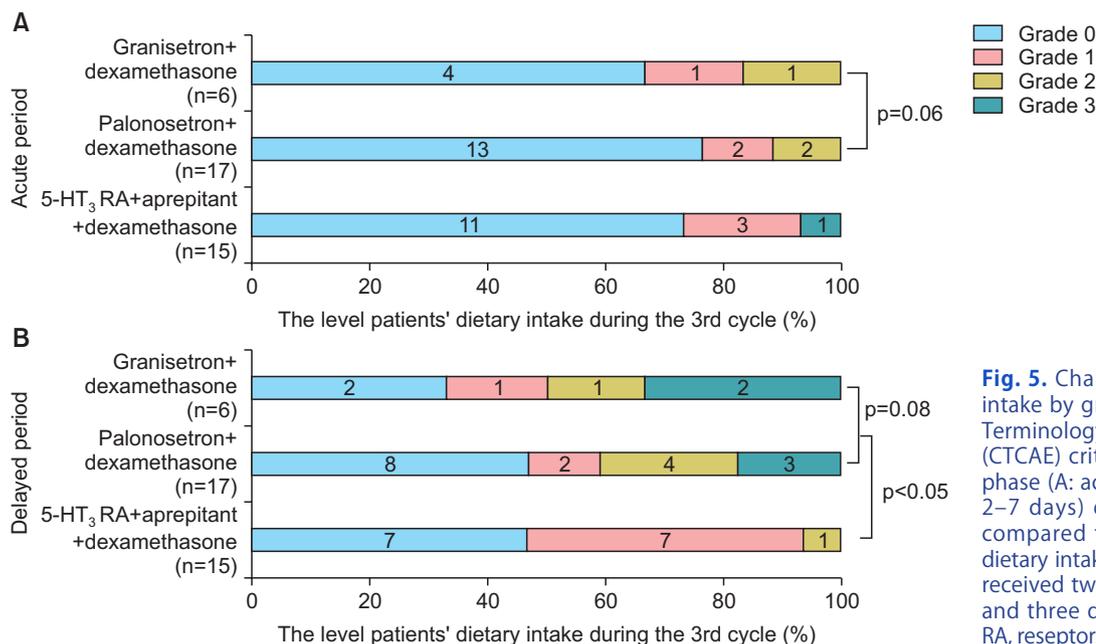
Moreover, the level of dietary intake in the delayed phase was significantly better in the group treated with the addition of aprepitant therapy with a 5-HT<sub>3</sub> receptor antagonist (palonosetron or granisetron) and dexamethasone than those treated with the combination of a 5-HT<sub>3</sub> receptor antagonist with dexamethasone (93.3% to 56.5%,  $p<0.001$ ).

## DISCUSSION

CINV is a complex phenomenon consisting of both acute (0–24 hours) and delayed (24–120 hours) components that may have different physiological mechanisms [1]. Effective antiemetic regimens for highly and MEC have historically been



**Fig. 4.** Proportion of patients achieving a complete response (CR; no emetic episodes or use of rescue therapy) according to the study phase (A: acute, 0–24 hours; B: delayed, 2–7 days) during the third cycle. Comparison of the three drugs group (addition of aprepitant) and two drugs group. We compared the CR rates between the two groups according to the study phase (A: acute, 0–24 hours; B: delayed, 2–7 days) during the third cycle. RA, receptor antagonist.



**Fig. 5.** Changes in the level of dietary intake by grade based on the Common Terminology Criteria for Adverse Events (CTCAE) criteria according to the study phase (A: acute, 0–24 hours; B: delayed, 2–7 days) during the third cycle. We compared the changes in the level of dietary intake between the patients who received two drugs (without aprepitant) and three drugs during the third cycle. RA, receptor antagonist.

based on the combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone. This combination is highly effective for controlling acute emesis, but less so for delayed emesis, and the contribution of a first-generation 5-HT<sub>3</sub> receptor antagonist to the management of delayed emesis has been questioned. The properties of palonosetron, a second-generation 5-HT<sub>3</sub> receptor antagonist, include a prolonged half-life of approximately 40 hours and effects on receptor internalization. These properties underlie the effectiveness of this drug in the management of delayed nausea and vomiting. In a recently reported double-blind randomized phase III trial of patients undergoing HEC, a 3-day treatment regimen consisting of palonosetron on day 1 and dexamethasone on days 1–3 provided complete protection against delayed CINV, the effects of which were superior to those of a single dose of granisetron on day 1 plus dexamethasone on days 1–3 [10]. In the present study, we used different 5-HT<sub>3</sub> receptor antagonists in the first and second cycles because we wanted to confirm the different effects of palonosetron and granisetron in the same individuals. The number of CR rates during the acute and delayed phase who received palonosetron in TC regimen was not significantly different compared with the patients received granisetron in this study. Ohzawa et al. [11] also reported that there were no significant differences in the incidence of CINV in breast cancer patients who received palonosetron and granisetron. It might be that the treatment with the 5-HT<sub>3</sub> receptor antagonists and dexamethasone cannot prevent CINV in female patients who undergo MEC regimens such as the TC regimen.

With respect to MEC regimens, recent guidelines, such as the MASCC antiemesis tool (MAT), ASCO guidelines for antiemesis and JSCO guidelines for antiemesis, generally recommend the use of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone with or without the neurokinin-1 receptor antagonist aprepitant [2–4]. Aprepitant enhances the ability to prevent CINV in patients receiving HEC, such as that involving cisplatin. According to the National Comprehensive Cancer Network (NCCN) guidelines, the use of aprepitant is recommended only in select patients receiving MEC, although the characteristics of these select patients are unclear. However, no clinical study has evaluated whether palonosetron or aprepitant is the best antiemetic therapy for MEC.

In general, as to the risk profile for CINV, age, gender and the medication history of past chemotherapy regimens have been mentioned [12]. The rate of a CR in patients treated with a combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone without aprepitant, in the delayed period after MEC has been reported to be approximately 80% [13]. However, in the present study, the administration of the TC regimen in patients with gynecological malignancies receiving a combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone resulted in a lower antiemetic response in the delayed period, with a CR rate of approximately 48% and a decrease in the level of dietary intake of approximately 50%. Molassiotis et al. [14] reported that gender in particular is an important risk factor for CINV. Nearly half of the female patients <70 years who mainly received a carboplatin-based

MEC experienced vomiting or used a rescue medication after the administration of MEC despite receiving granisetron and dexamethasone treatment [15]. These results suggest that female patients are at greater risk of CINV. In this study, the efficacy of an additional dose of aprepitant for MEC was confirmed; an antiemetic response of approximately 90% was observed following the additional administration of aprepitant with the TC regimen among the patients with gynecological malignancies. These results suggest that positive supportive care is required for antiemesis when administering chemotherapy in female patients, who are higher risk of CINV, even when receiving MEC. The major limitation associated with the present study is the small sample size. Large-scale randomized crossover clinical trials are necessary to evaluate the efficacy of the addition of aprepitant therapy with a 5-HT<sub>3</sub> receptor antagonist (palonosetron or granisetron) and dexamethasone in comparison to treatment with a 5-HT<sub>3</sub> receptor antagonist (palonosetron or granisetron) and dexamethasone without the addition of aprepitant during the first and second cycles of a MEC such as the TC regimen.

In conclusion, using a combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone with aprepitant, the CR rate and level of dietary intake in both the acute and delayed phases were more effective compared with that achieved with a combination of a 5-HT<sub>3</sub> receptor antagonist with dexamethasone. Therefore, in order to maintain the patient's quality of life, we suggest that, when providing the TC regimen to patients with gynecological malignant cancer, it is necessary to take into consideration the addition of aprepitant therapy with a 5-HT<sub>3</sub> receptor antagonist (palonosetron or granisetron) and dexamethasone.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGMENTS

This work was supported by a JSPS KAKENHI Grant, Number 25462621 (to Y. Terai).

## REFERENCES

1. Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med* 2008;358:2482-94.

2. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, et al. 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* 2010;21 Suppl 5:v232-43.
3. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2011;29:4189-98.
4. Japan Society of Clinical Oncology. Japan Society of Clinical Oncology guideline for antiemetic, ver. 1. Tokyo: Japan Society of Clinical Oncology; 2010.
5. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials: a review. *Ann Oncol* 1991;2:107-14.
6. Kaizer L, Warr D, Hoskins P, Latreille J, Lofters W, Yau J, et al. Effect of schedule and maintenance on the antiemetic efficacy of ondansetron combined with dexamethasone in acute and delayed nausea and emesis in patients receiving moderately emetogenic chemotherapy: a phase III trial by the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1994;12:1050-7.
7. The Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. *N Engl J Med* 2000;342:1554-9.
8. Pater JL, Lofters WS, Zee B, Dempsey E, Walde D, Moquin JP, et al. The role of the 5-HT<sub>3</sub> antagonists ondansetron and dolasetron in the control of delayed onset nausea and vomiting in patients receiving moderately emetogenic chemotherapy. *Ann Oncol* 1997;8:181-5.
9. Tian W, Wang Z, Zhou J, Zhang S, Wang J, Chen Q, et al. Randomized, double-blind, crossover study of palonosetron compared with granisetron for the prevention of chemotherapy-induced nausea and vomiting in a Chinese population. *Med Oncol* 2011;28:71-8.
10. Saito M, Aogi K, Sekine I, Yoshizawa H, Yanagita Y, Sakai H, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. *Lancet Oncol* 2009;10:115-24.
11. Ohzawa H, Miki A, Hozumi Y, Miyazaki C, Sagara Y, Tanaka Y, et al. Comparison between the antiemetic effects of palonosetron and granisetron in breast cancer patients treated with anthracycline-based regimens. *Oncol Lett* 2015;9:119-24.
12. Sekine I, Segawa Y, Kubota K, Saeki T. Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. *Cancer Sci* 2013;104:711-7.
13. Grote T, Hajdenberg J, Cartmell A, Ferguson S, Ginkel A, Charu V. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. *J Support Oncol* 2006;4:403-8.
14. Molassiotis A, Stamataki Z, Kontopantelis E. Development and preliminary validation of a risk prediction model for chemotherapy-related nausea and vomiting. *Support Care Cancer* 2013;21:2759-

- 67.
15. Tanioka M, Kitao A, Matsumoto K, Shibata N, Yamaguchi S, Fujiwara K, et al. A randomised, placebo-controlled, double-blind study of aprepitant in nondrinking women younger than 70 years receiving moderately emetogenic chemotherapy. *Br J Cancer* 2013;109:859-65.

