Regular Article

Comparison between Antiemetic Effects of Palonosetron and Granisetron on Chemotherapy-Induced Nausea and Vomiting in Japanese Patients Treated with R-CHOP

Mayako Uchida,^{*a,b} Yasuo Mori,^c Tsutomu Nakamura,^b Koji Kato,^c Kenjiro Kamezaki,^c Katsuto Takenaka,^c Motoaki Shiratsuchi,^d Kaori Kadoyama,^b Toshihiro Miyamoto,^c and Koichi Akashi^c

^aDepartment of Pharmacy, Kyushu University Hospital; 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan:

^bEducation and Research Center for Clinical Pharmacy, Osaka University of Pharmaceutical Sciences;

4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan: ^cDepartment of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences; 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan: and

^dDepartment of Medicine and Bioregulatory Science, Kyushu University Graduate School of Medical Sciences; 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

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In the present study, the antiemetic effect of palonosetron, not combined with dexamethasone and aprepitant, on chemotherapy-induced nausea and vomiting was evaluated in patients with malignant lymphoma receiving first-line rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy, and was compared to that of granisetron. A total of 74 patients with non-Hodgkin lymphoma were included in this study (April 2007 to December 2015). Palonosetron (0.75 mg) or granisetron (3 mg) was intravenously administered before R-CHOP therapy. The proportions of patients with complete response (CR) during the overall (0–120 h after the start of R-CHOP therapy), acute (0–24 h) and delayed (24–120 h) phases were evaluated. CR was defined as no vomiting and no use of antiemetic rescue medication. A total of 32 and 42 patients were treated with palonosetron and granisetron, respectively. The CR rate in the palonosetron group was significantly higher than that in the granisetron group during the delayed phase (90.6 and 61.9%, respectively; $p=0.007$). Logistic regression analysis showed that use of palonosetron improved the CR rate during the delayed phase, compared to use of granisetron. Female sex, age less than 60 years, no habitual alcohol intake, and Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 1 were significant risk factors associated with non-CR. The findings of this study suggested the superiority of palonosetron to granisetron, without accompanying dexamethasone and aprepitant, for chemotherapy-induced nausea and vomiting in patients with malignant lymphoma.

Key words palonosetron; granisetron; chemotherapy-induced nausea and vomiting; complete response; delayed phase

Chemotherapy-induced nausea and vomiting (CINV) is a common and one of the most severe problematic adverse events for patients with cancer.¹⁾ Poor control of CINV can lead to physical disorders including dehydration, electrolyte abnormalities, and malnourishment, which could result in discontinuation of chemotherapy and poor QOL.^{2,3)} Therefore, it is very important to prevent CINV to enable patients to complete chemotherapy and maintain QOL.

In the 1990s, serotonin (5-hydroxytryptamine; 5-HT) type 3 (5-HT₃) receptor antagonists were developed as antiemetics for CINV control, and their antiemetic effects were demonstrated to be superior to those of conventional drugs.⁴⁾ By 2005, granisetron and ondansetron had appeared on the market as first-generation 5-HT₃ receptor antagonists. The first-generation 5-HT₃ receptor antagonists show a highly prophylactic effect against acute CINV, which occurs by 24 h after the start of cancer chemotherapy, but demonstrate less effect against delayed CINV. In a previous meta-analysis, additive administration of a first-generation 5-HT₃ receptor antagonist beyond 24 h after chemotherapy was found to be ineffective for delayed CINV.⁵⁾

Palonosetron, which is a second-generation 5-HT₃ receptor antagonist, has a higher binding affinity for the 5-HT₃ recep-

tor and a 4- to 10-fold longer half-life, compared to those of the first-generation 5-HT₃ receptor antagonists.⁶⁾ It has been reported that the antiemetic effects of palonosetron were superior to those of the first-generation 5-HT₃ receptor antagonists ondansetron^{7,8)} and dolasetron⁹⁾ during the overall, acute, and delayed phases, although the patients in these studies had diverse backgrounds in relation to ethnicity, cancer type, chemotherapy regimen, and history of chemotherapy. Saito *et al.* conducted a phase III trial in Japanese patients receiving highly emetogenic chemotherapy (HEC), and demonstrated that the antiemetic efficacy of palonosetron against CINV was non-inferior to that of granisetron in the acute phase but superior to that of granisetron in the delayed phase.¹⁰⁾ Furthermore, the superior efficacy of palonosetron compared to that of first-generation 5-HT₃ receptor antagonists has been reported in a previous systemic review and meta-analysis.^{11,12)} Palonosetron is listed as a recommended medication for HEC by the Multinational Association of Supportive Care in Cancer¹³⁾ and for moderately emetogenic chemotherapy (MEC) by the National Comprehensive Cancer Network¹³⁾ and the American Society of Clinical Oncology.¹⁴⁾ In a study limited to hematological malignancy, the antiemetic effects of palonosetron have been assessed in patients with Hodgkin lymphoma¹⁵⁾ and

*To whom correspondence should be addressed. e-mail: mayaco@gly.oups.ac.jp

non-Hodgkin lymphoma,^{16–18)} although it is unclear whether palonosetron has antiemetic effects superior to those of the first-generation 5-HT₃ receptor antagonists in these patients.

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy is a representative standard therapy for low- and intermediate-grade non-Hodgkin lymphomas. According to some antiemetic guidelines,^{13,14,19)} combination anthracycline/cyclophosphamide chemotherapy, including R-CHOP, is classified as HEC, and the use of a 5-HT₃ antagonist in combination with dexamethasone and aprepitant is recommended for antiemetic management of CINV with HECs. Meanwhile, most patients receiving R-CHOP therapy are in a state of immunosuppression,^{20,21)} and therefore it is considered that administration of glucocorticoids such as dexamethasone and prednisone for the prevention of CINV can lead to excess immunosuppression. Aprepitant has the potential to inhibit CYP 3A4,²²⁾ and it may influence the pharmacokinetics of R-CHOP therapy drugs including cyclophosphamide and prednisone, both of which are metabolized by CYP 3A4. The use of dexamethasone and aprepitant requires considerable attention from the viewpoint of drug interactions during R-CHOP therapy.^{23,24)}

We conducted a prospective study to assess the efficacy and safety of palonosetron, without the addition of dexamethasone and aprepitant, in comparison to granisetron in patients with non-Hodgkin lymphoma receiving R-CHOP therapy, which is used as a single-dose treatment for malignant lymphoma, among the hematological malignancies.

PATIENTS AND METHODS

Patients In the present study, eligible participants were patients 20 years of age and older who received R-CHOP chemotherapy as the first treatment for non-Hodgkin lymphomas in the Department of Hematology, Kyushu University Hospital (April 2007 to December 2015). We excluded patients with hyponatremia, hypercalcemia, adrenal metastasis, an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of more than 2 or nausea and/or vomiting at the start of R-CHOP therapy. And, the patients did not take laxative agents and antiemetic drugs including olanzapine and lorazepam at the start of R-CHOP therapy.

R-CHOP Therapy The R-CHOP therapy regimen is shown in Table 1. Rituximab (375 mg/m²) was administered on day 0 or 1. Cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and vincristine (1.4 mg/m² up to 2.0 mg/m²) were administered on day 1, and prednisolone (100 mg/body) was administered on days 1 to 5. Twenty-one days were defined as one course. Intravenous palonosetron (0.75 mg/body) or

granisetron (3 mg/body) were administered 30 min before the initiation of R-CHOP therapy. Metoclopramide, prochlorperazine, haloperidol, and/or hydroxyzine were used as rescue medications.

Data Collection and Assessment All data were collected from the electronic medical record system. We excluded data after the second course in order to remove confounding factors such as predictive nausea and vomiting. We assessed the occurrence of nausea, vomiting, or use of rescue medication during the overall (0 to 120 h after the start of R-CHOP therapy), acute (0 to 24 h), and delayed (24 to 120 h) phases. Adverse drug events (ADEs), including nausea and vomiting, were monitored during the overall study period and described in the electronic medical record system twice a day (morning and evening) by doctors, nurses, and pharmacists, according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.

The prospective study on palonosetron was conducted in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Ethics Committee of Kyushu University Graduate School and Faculty of Medicine (approval No. 24-359 of the institutional review board). For the control group, the data on granisetron were gathered from the results of our retrospective study, which was conducted in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Ethics Committee of Kyushu University Graduate School and Faculty of Medicine (approval No. 24-928027 of the institutional review board).

The endpoint of this study was the proportion of patients with complete response (CR) or complete control (CC) during the overall, acute, and delayed phases. CR was defined as no vomiting and no use of antiemetic rescue medication. CC was defined as CR and no more than mild nausea (grade 0 or 1). In the present study, all patients with CR achieved CC.

Statistical Analysis Fisher's exact test was used to examine differences in frequencies of categorical data between the palonosetron and granisetron groups. The statistical significance of the difference between the median values of age was calculated with the Mann–Whitney *U*-test. The factors with *p* values <0.25 in univariate analyses were included in a stepwise multivariate logistic regression analysis with backward selection. Data were analyzed using SPSS Statistics 22 (IBM Corp., Tokyo, Japan, and a *p* value <0.05 was considered statistically significant.

RESULTS

Patient Baseline Clinical Characteristics A total of 74 patients with non-Hodgkin lymphoma were included in this

Table 1. R-CHOP Therapy Regimen

Drugs ^{a,b,c)}	Daily dosage	Route of administration	Timing of administration
Rituximab	375 mg/m ²	i.v. infusion (50 mg/h after the first 30 min, it can be escalated in 50 mg/h increments every 30 min, to a maximum 400 mg/h)	once daily on day 0 or 1
Cyclophosphamide	750 mg/m ²	2-h i.v. infusion	once daily on day 1
Doxorubicin	50 mg/m ²	bolus injection (2–3 min)	once daily on day 1
Vincristine ^{d)}	1.4 mg/m ²	bolus injection (2–3 min)	once daily on day 1
Prednisolone	100 mg/body	p.o.	once daily for 5 d

i.v.=intravenously; p.o.: per oral. a) Patients did not receive dexamethasone and aprepitant. b) Palonosetron (0.75 mg/body) was i.v. administered on day 1. c) Granisetron (3 mg/body) was i.v. administered on day 1. d) Maximum daily dose was 2 mg.

Table 2. Patient Characteristics

Variable	Palonosetron	Granisetron	<i>p</i> Value
Number of patients	32	42	
Sex			
Male	13	20	0.639
Female	19	22	
Age			
Median, year (range)	60.5 (23–78)	63.0 (23–76)	0.866
ECOG-PS ^{a)} score			
0	26	29	0.289
1	6	13	
Diagnosis			
Diffuse large B-cell lymphoma	22	23	0.334
Follicular lymphoma	5	13	
Other	5	6	
Alcohol intake			
Habitual	8	11	1.000
Non-habitual	7	8	
No	17	23	

a) ECOG-PS, Eastern Cooperative Oncology Group performance status.

study. The patients' baseline clinical characteristics are shown in Table 2. There were no significant differences in the variables between the granisetron and palonosetron groups.

Antiemetic Effects The proportions of patients with or without vomiting and rescue medications in the palonosetron and granisetron groups were significantly different during the overall and delayed phases ($p=0.006$ and 0.014 , respectively) (Fig. 1A). The CR rates during the overall study period were 71.9 and 54.8% in the palonosetron and granisetron groups, respectively. The proportions of patients without vomiting during the overall phase were 87.5 and 64.3% in the palonosetron and granisetron groups, respectively. During the overall phase, 2 of the 4 patients in the palonosetron group with vomiting required rescue medications, whereas all 15 patients in the granisetron group with vomiting required these medications. During the acute phase, there were no statistically significant differences in the proportions of patients with or without vomiting and rescue medications between the palonosetron and granisetron groups ($p=0.135$) (Fig. 1B). The CR rate achieved during the delayed phase in the palonosetron group was 90.6%, higher than the value of 61.9% achieved in the granisetron group (Fig. 1C).

Adverse Drug Events (ADEs) The numbers of patients experiencing ADEs in the palonosetron and granisetron groups are shown in Table 3. The most frequent ADE was constipation in both the palonosetron and granisetron groups (96.9 and 69.0%, respectively), and there was a statistically significant difference in the frequency of occurrence between the two groups ($p=0.002$). Over half of the patients in both groups experienced anorexia, neutropenia, and leucopenia. Abdominal distension, hypertension, stomatitis, and headache were also observed, although their frequencies were less than 10% in both the palonosetron and granisetron groups. There were no statistically significant differences in the frequencies of ADEs other than constipation between the two groups (Table 3).

Factors Influencing CINV Control The nausea and vomiting in 46 out of 74 (62.2%) patients receiving R-CHOP therapy were completely controlled by treatment with palonosetron or granisetron during the overall study period, although

Fig. 1. The Proportions of Patients with or without Vomiting and Rescue Medications during Overall (A), Acute (B), and Delayed (C) Phases in Palonosetron and Granisetron Groups

The cumulative proportion of each stacked column totals 100%, and columns represent the following: no vomiting and no use of rescue medications (opened); no vomiting and use of rescue medications (dotted); vomiting and no use of rescue medications (gray); and vomiting and use of rescue medications (shaded).

Table 3. Number of Patients Experiencing ADEs in Palonosetron and Granisetron Groups

ADEs ^{a)}	Palonosetron (<i>n</i> =32)	Granisetron (<i>n</i> =42)	<i>p</i> Value ^{b)}
Constipation	31 (96.9%)	29 (69.0%)	0.002
Leucopenia	25 (78.1%)	25 (59.5%)	0.132
Neutropenia	25 (78.1%)	24 (57.1%)	0.083
Anorexia	18 (56.3%)	22 (52.4%)	0.816
Malaise	10 (31.3%)	19 (45.2%)	0.241
Fever	6 (18.8%)	9 (21.4%)	0.992
Hepatic function abnormal	4 (12.5%)	5 (11.9%)	0.841
Stomach discomfort	4 (12.5%)	2 (4.8%)	0.218
Peripheral neuropathy	2 (6.3%)	7 (16.7%)	0.125
Abdominal distension	2 (6.3%)	3 (7.1%)	0.371
Hypertension	2 (6.3%)	1 (2.4%)	0.077
Stomatitis	2 (6.3%)	1 (2.4%)	0.077
Headache	1 (3.1%)	3 (7.1%)	0.212

a) Adverse drug events (ADEs) with frequencies of more than 5% in either group are listed. b) A significant difference is in italics.

the nausea and vomiting in 28 patients were not. To detect factors influencing CINV control, univariate and multivariate analyses were performed (Table 4). In the univariate analy-

Table 4. Factors Influencing Chemotherapy-Induced Nausea and Vomiting Control

Variables	Overall phase						Acute phase						Delayed phase					
	Univariate			Multivariate			Univariate			Multivariate			Univariate			Multivariate		
	CR ^(a)	Non-CR	p Value	OR	95% CI	p Value	CR ^(a)	Non-CR	p Value	OR	95% CI	p Value	CR ^(a)	Non-CR	p Value	OR	95% CI	p Value
5-HT ₃ receptor antagonist																		
Palonosetron	23	9	0.153	1			25	7	0.310	—			29	3	0.007	1		
Granisetron	23	19		3.0	0.8–10.9	0.098	28	14		—			26	16		7.8	1.8–33.6	0.006
Sex																		
Male	25	8	0.053	1			29	4	0.009	1			26	7	0.593	—		
Female	21	20		6.0	1.5–23.7	0.011	24	17		17.2	2.6–115.2	0.003	29	12		—		
Age (years)																		
60 and above	32	7	<0.001	1			34	5	0.002	1			34	5	0.015	1		
less than 60	14	21		20.0	4.3–93.1	<0.001	19	16		27.1	4.0–184.2	0.001	21	14		6.3	1.7–23.2	0.006
ECOG-PS score																		
0	37	18	0.171	1			43	12	0.043	1			41	14	1.000	—		
1	9	10		6.5	1.4–30.7	0.017	10	9		24.5	3.2–185.8	0.002	14	5		—		
Type of lymphoma																		
Diffuse large B-cell lymphoma	30	15	0.620	—			34	11	0.615	—			33	12	0.411	—		
Follicular lymphoma	10	8		—			12	6		—			12	6		—		
Other	6	5		—			7	4		—			10	1		—		
Alcohol intake																		
Habitual or moderate	40	19	0.073	1			46	13	0.025	1			46	13	0.190	1		
No	6	9		6.9	1.2–39.4	0.031	7	8		9.0	1.3–60.0	0.024	9	6		3.9	0.9–17.4	0.074

CR = complete response; OR = odds ratio; 95% CI = 95% confidence interval; ECOG-PS = Eastern Cooperative Oncology Group performance status. ^{a)} All patients with CR achieved complete control (CC).

sis, use of palonosetron, age, sex, ECOG-PS, diagnosis, and alcohol intake were chosen as variables. The variables with p values of less than 0.25 were included in the subsequent multivariate logistic regression analysis. Age less than 60 years was a factor reducing the CR rate during the overall, acute, and delayed phases. Female sex, ECOG-PS score of 1, and no alcohol intake were factors that also lowered the CR rate during the overall and acute phases, whereas use of palonosetron was able to improve the CR rate during the delayed phase, compared to the use of granisetron. Type of lymphoma was not identified as a significant influencing factor during any of the phases.

DISCUSSION

The efficacy of 5-HT₃ receptor antagonists for the prevention of CINV has been demonstrated in many studies for patients with diverse backgrounds in relation to ethnicity, type of cancer, chemotherapy regimen, and history of chemotherapy,⁷⁻⁹ although the data regarding the antiemetic effects of these medications are not entirely sufficient for patients with hematological malignancies. To date, it has been reported that antiemetic regimens including the first-generation 5-HT₃ receptor antagonists ondansetron and granisetron were more effective for CINV control in patients with Hodgkin and non-Hodgkin lymphomas receiving MEC, compared to metoclopramide-based antiemetic regimens.^{25,26} In addition, two single-arm studies conducted in Italy and Japan showed that a single dose of palonosetron was effective for achieving CR during overall, acute, and delayed CINV in more than 70% of patients with non-Hodgkin lymphoma.^{16,18} In the present study, we compared antiemetic effects between palonosetron and granisetron, and found that the rate of CINV management with the use of palonosetron reached at least 70% during the overall study period and was non-inferior during the overall and acute phases and superior during the delayed phase, compared to granisetron use (Table 4). The superiority of palonosetron to the first generation 5-HT₃ receptor antagonists has been also reported from the viewpoint of antiemetic prophylaxis for delayed CINV, as well as overall and acute CINV, in populations of patients of whom most had solid cancer.^{7,8,10,27,28} However, regardless of adherence to the antiemetic guidelines, the incidence of delayed nausea remains high in patients receiving HEC or MEC,²⁹ and the efficacy of 5-HT₃ receptor antagonists for treatment of delayed emesis remains controversial.³⁰ The use of dexamethasone and aprepitant also requires considerable attention because drug interactions may occur during R-CHOP therapy.^{23,24} In the present study, the administration of palonosetron, not combined with dexamethasone and aprepitant, achieved a CR rate of over 90% during the delayed phase (Fig. 1), and the multivariate logistic regression analysis showed that palonosetron use was an independent significant factor improving the CR rate during the delayed phase, compared to granisetron use (Table 4). However, it remains unclear whether the antiemetic effect of palonosetron alone is superior to that of three-antiemetic regimen consisting of palonosetron, aprepitant, and dexamethasone for CINV. Regarding treatment-related adverse events, the frequency of constipation in the palonosetron group was significantly higher than that in the granisetron group in the present study (Table 3). Constipation is a general cause of

nausea and vomiting,³¹ and it might weaken the antiemetic effect of palonosetron. Saito *et al.* reported that no significant difference in the frequency of constipation was observed between the palonosetron and granisetron groups in a phase III study, when dexamethasone was concomitantly used before chemotherapy,¹⁰ although it was unclear whether co-treatment of dexamethasone and aprepitant was associated with a lower frequency of constipation induced by palonosetron. Considering these findings together, palonosetron would be the most effective medication for CINV control in patients with hematological malignancy receiving R-CHOP therapy, for whom dexamethasone and aprepitant are preferably avoided, although with careful attention to constipation.

Patient sex, age, and drinking history are significant factors influencing CINV control. Thus far, it has been reported that female sex, younger age, and/or no alcohol intake were risk factors reducing the degree of response to antiemetic therapy including metoclopramide and methylprednisolone,^{32,33} and that including ondansetron, dexamethasone, and aprepitant^{34,35} during cancer chemotherapy. These findings were almost consistent with our present findings showing that female sex, age less than 60 years, and no alcohol intake were significant factors associated with nausea and vomiting during the overall and acute phases (Table 4). Additionally, in the present study, ECOG-PS score of 1 was identified as a risk factor inducing incomplete control of overall and acute CINV in patients with malignant lymphomas (Table 4). According to the NCCN antiemetic guidelines, nausea and vomiting can result in decline of a patient's performance status, but it is unclear whether the performance status influences the antiemetic management of CINV by use of palonosetron. More recently, in the report by Miyata *et al.*, ECOG-PS was not identified as a significant factor influencing the antiemetic effect of palonosetron against overall and delayed CINV in patients with non-Hodgkin lymphoma undergoing CHOP regimen administration.¹⁸ It was not clear whether the difference from our present result was due to the difference in chemotherapy regimens.

Concerning the mechanisms of CINV, it has been considered that a chemotherapeutic agent stimulates the release of 5-HT from enterochromaffin cells in the intestine, leading to activation of 5-HT₃ receptors located on vagal afferent nerves, which convey signals to the chemoreceptor trigger zone (CTZ), initiating the vomiting reflex.^{36,37} Darmani *et al.* conducted the shrew studies, showing that the neurokinin-1 (NK₁) receptor, which is a target for the neurotransmitter substance P, is expressed in the CTZ and intestine, similarly to the 5-HT₃ receptor, and changes in NK₁ receptor expression appear to be associated with cisplatin- and cyclophosphamide-induced emesis.^{38,39} An *in vitro* study using cells transfected with 5-HT₃ receptor demonstrated that exposure to palonosetron inhibited the 5-HT₃-induced activation of the response to substance P, and palonosetron triggered long-term 5-HT₃ receptor internalization.⁴⁰ Granisetron and ondansetron were unlikely to have these effects.⁴⁰ The plasma elimination half-life of palonosetron after a single intravenous dose was over 40 h in patients with cancer,^{6,41} which is longer than that of granisetron.^{42,43} These characteristics of palonosetron could explain its superiority to the first-generation 5-HT₃ receptor antagonists for delayed CINV and possibly acute CINV as well in clinical settings, although it remains unclear why female sex, younger age, non-habitual alcohol intake, and higher

ECOG-PS were risk factors for incomplete control of CINV.

In conclusion, our present results demonstrated the ability of palonosetron compared to granisetron to appropriately suppress delayed CINV in patients receiving R-CHOP therapy, even without co-administration of dexamethasone and aprepitant. These findings suggest the superiority of palonosetron to granisetron for delayed CINV in patients with malignant lymphoma, for whom immunosuppressive medications and/or CYP3A4 inducers/inhibitors are preferably avoided. Younger age and no habitual alcohol intake were independent risk factors influencing CINV management during the delayed phase after the start of R-CHOP therapy, although further studies are needed to clarify the underlying mechanism.

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Conflict of Interest The authors declare no conflict of interest.

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