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ORIGINAL ARTICLE

A phase III open-label study to assess safety and efficacy of palonosetron for preventing chemotherapy-induced nausea and vomiting (CINV) in repeated cycles of emetogenic chemotherapy

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Abstract
Purpose Prevention of chemotherapy-induced nausea and vomiting (CINV) is of great importance for the completion of multiple cycles of cancer chemotherapy. Palonosetron is a second-generation 5-HT_3 receptor antagonist with proven efficacy for both acute and delayed CINV. This study was designed to assess the safety and efficacy of 0.75 mg palonosetron in repeated cycles of highly emetogenic chemotherapy or anthracycline–cyclophosphamide combination (AC/EC).
Methods We gave 0.75 mg palonosetron to 538 patients 30 min prior to ≥50 mg/m^2 cisplatin or AC/EC on day 1. Prophylactic dexamethasone was administered on days 1–3. The primary endpoint was the incidence rate of adverse events (AEs). The secondary endpoint was complete response rate (CR, defined as no emesis and no rescue medication) throughout the study period.
Results Treatment-related AEs were seen in 44% (237 of 538 patients). Serious AEs were seen in 4% (23 of 538 patients), all considered unrelated or unlikely to be related to palonosetron. Only one patient discontinued the study due to a treatment-related AE. No trend toward worsening of AEs was observed in subsequent cycles of chemotherapy.

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Complete response rates were maintained throughout repeated cycles.
Conclusion The extraordinary safety profile and maintenance of efficacy of 0.75 mg palonosetron combined with dexamethasone were demonstrated throughout repeated chemotherapy cycles.

Keywords Palonosetron · 5-HT_3 receptor antagonist · Antiemetic · Chemotherapy-induced nausea and vomiting · Highly emetogenic chemotherapy

Introduction

Cancer chemotherapy plays a key role in cancer treatment, and it is essential to continue multiple cycles aimed at stabilizing cancer growth and to cure the disease in various clinical settings. Chemotherapy-induced nausea and vomiting (CINV) are among the most problematic adverse events (AEs) in cancer chemotherapy [1–3].

Palonosetron is a second-generation 5-HT_3 receptor antagonist, which has been reported to be effective in the prevention of acute and delayed CINV compared to previous 5-HT_3 receptor antagonists, dolasetron, and ondansetron in moderately emetogenic chemotherapy [4, 5].

Two phase II studies performed in Japan reported a tendency toward better efficacy with the 0.75-mg dose than with 0.25- and 0.075-mg doses of palonosetron, and the excellent safety profile of all these doses suggested that 0.75 mg palonosetron could be the recommended dose for use in a trial [6, 7]. A phase III trial showed non-inferiority of palonosetron to granisetron in the acute phase, superiority of palonosetron to granisetron in the delayed phase in prevention of CINV, and similar safety profiles of palonosetron and granisetron in patients receiving cisplatin or anthracycline–cyclophosphamide combination therapy (AC/EC) [8].

A study has reported the safety and efficacy profile of 0.75 mg palonosetron in repeated cycles of chemotherapy [9].

The goal of this trial was to confirm the safety and efficacy profile of 0.75 mg palonosetron, combined with dexamethasone in patients receiving repeated cycles of highly emetogenic chemotherapy or AC/EC.

Methods

Patients

The patients enrolled in this open-label study on repeated chemotherapy cycles were selected from among patients who had previously completed the randomized phase III trial of palonosetron compared to granisetron [8] and were scheduled to receive the same chemotherapy regimen as in the randomized phase III study (≥50 mg/m^2 cisplatin or AC/EC). All patients provided written informed consent prior to enrollment. Eligible patients were men and women ≥20 years of age with a confirmed diagnosis of malignant disease. Patients were required to have an ECOG performance status of 0–2, adequate bone marrow function (WBC≥3,000/mm^3), hepatic function (AST and ALT <100 U/L or grade ≤3 according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) for patients with liver metastasis), and renal function (creatinine clearance ≥60 mL/min).

The exclusion criteria included severe, uncontrolled, concurrent illness other than neoplasia; asymptomatic metastases to the brain; seizure disorders requiring anticonvulsants, unless clinically stable; gastric outlet or intestinal obstruction; any vomiting, retching, or grade ≥2 nausea according to CTCAE v3.0; a known hypersensitivity to palonosetron or other 5-HT_3 receptor antagonists or dexamethasone ingredients; participation in another drug study or receipt of any investigational agents other than palonosetron within a month of enrollment in the study; pregnant or breast-feeding women; and all subjects (men or women) who planned conception during the study period.

Study design

This phase III, multicenter, open-label trial was conducted between July 2006 and August 2007 in Japan. Eligible patients received 0.75 mg palonosetron 30 min before cisplatin or AC/EC initiation on day 1 in each cycle. Administration of 16 mg prophylactic dexamethasone i.v. within 45 min before palonosetron on day 1 was also required. Additionally, 8 mg dexamethasone i.v. for patients receiving cisplatin or 4 mg p.o. for patients receiving AC/EC was administered on day 2 (24–26 h after chemotherapy) and day 3 (48–50 h after chemotherapy). For patients receiving irinotecan on day 8 or after, palonosetron was administered 30 min before the administration of irinotecan (e.g., day 8 and day 15 in combination chemotherapy of cisplatin and irinotecan for lung cancer). The interval between administrations of palonosetron had to be 7 days or more. Administration of dexamethasone was permitted before irinotecan at the discretion of each investigator. More than one factor influenced the choice of dexamethasone dose and schedule in this trial, including international antiemetic guidelines [10–12], the results of Japanese clinical studies on antiemetic agents [13, 14], and the findings of a survey on antiemetic treatments conducted in the trial sites. Patients repeatedly received up to four cycles of the study treatment, including treatment received during the first cycle, described as the treatment administered in the previous randomized phase III trial in which the patients participated before entering this

trial. Patients were confirmed for eligibility to continue study treatment before the start of each cycle according to the following discontinuation criteria: not meeting the eligibility criteria; receiving an antiemetic drug within 24 h before the start of a cycle; or vomiting, retching, or grade 2 or higher nausea within 24 h before the start of a cycle.

Efficacy was assessed every 24 h for 5 days, only after administration of cisplatin or AC/EC. The safety profile of palonosetron was assessed from its first administration, until 8 days after its last administration.

The study was conducted according to the Declaration of Helsinki, and written approval was obtained from the Institutional Review Boards at each site before study commencement.

Study visits and assessment procedures

The 12 lead-ECG and laboratory assessments were conducted within 8 days before the beginning of the first cycle, and once each during days 2–4 and 8–10 of each cycle. In patients receiving irinotecan, these assessments were also carried out 7–9 days after every administration of palonosetron. AEs and concomitant medications were recorded.

The investigators judged the causal relationship between AE and palonosetron according to five categories (none, unlikely, possible, probable, and definite). Any AE judged by the investigator to be possibly, probably, or definitely related to palonosetron was regarded as a treatment-related AE.

Study endpoints

The primary endpoint was the rate of AEs in the study. The secondary endpoints were the type, severity, and causal relationship of the AEs, the proportion of patients with a complete response (CR; defined as no emetic episodes and no rescue medication use), and severity of nausea. Severity of nausea was indicated as none, mild, moderate, or severe, according to a Likert scale, based on subjective evaluation by each patient. Patient diaries were used for recording of emetic episodes, nausea, or rescue anti-emetics at daily (24-h) intervals.

Statistical analysis

The safety analysis cohort included all patients who received the study drug. This safety analysis cohort was divided into three subset cohorts: patients receiving irinotecan combined with cisplatin (irinotecan cohort), patients receiving cisplatin combined with other treatment excluding irinotecan (cisplatin cohort), and patients receiving AC/EC (AC/EC cohort). The modified intent-to-treat (ITT) cohort included all patients who received the study drug and chemotherapy (cisplatin or AC/EC). This modified ITT cohort was used for efficacy analysis.

The data for the patients who received palonosetron in the randomized phase III trial [8] have been considered as both "first cycle" efficacy and safety data; thereafter, the first cycle of this open-label study was counted as the second cycle of chemotherapy.

Safety data were listed and summarized descriptively (data on file). Toxicity grades were generated for hematology and blood chemistry parameters, according to CTCAE v.3.0 adapted toxicity grades, and treatment-related AE were tabulated. New adverse events (NAE) and worsened adverse events (WAE) were listed to identify the safety profile of palonosetron on repeated administration. An NAE was defined as an AE not observed in the first cycle and observed only in the second or subsequent cycles. A WAE was defined as an AE that could be seen in the first cycle but worsened in grade only from the second cycle or later compared to the grade observed in the first cycle.

To evaluate the influence of palonosetron on cardiovascular abnormality, the proportion of patients with QTc prolonged to more than 60 ms from baseline or more than 500 ms was examined in the safety analysis cohort by chemotherapy (cisplatin or AC/EC).

A sample size of 300 patients was needed to find AEs observed in 1% or more of patients after repeating the administration of palonosetron two or more times, including the safety data of palonosetron in the randomized phase III study.

The proportions of patients with CR or no nausea were assessed during the acute phase (0–24 h post-chemotherapy), the delayed phase (24–120 h post-chemotherapy), and the overall phase (0–120 h post-chemotherapy) in each cycle.

All statistical analyses were performed using SAS software (version 8.2; SAS Institute, Cary, NC, USA).

Results

We enrolled 546 patients to receive a single i.v. dose of palonosetron, but eight of these patients did not receive the study treatment since three patients met discontinuation criteria for this study and five patients were withdrawn from this study at the discretion of the investigators. Therefore, 538 patients were evaluated for safety. These 538 patients were also included in the modified intention-to-treat (ITT) cohort for efficacy analysis.

Demographic data for the safety analysis cohort are presented in Table 1. Of the 538 patients in the safety analysis cohort, 304 (57%) women and 358 (67%) patients overall were aged ≥55 years. The most common types of malignant disease were non-small cell lung carcinoma (249 patients [46%]) and breast carcinoma (224 patients [42%]).

Table 1 Patient demographics and baseline characteristics

		N=538	
		N	%
Age categories (years)	Mean, SD	57.8, 10.4	
	≥55	358	66.5
	<55	180	33.5
Height (cm)	Mean, SD	160.00, 8.25	
Weight (kg)	Mean, SD	57.89, 10.07	
Sex	Women	304	56.5
	Men	234	43.5
PS	0	388	72.1
	1	147	27.3
	2	3	0.6
Previous surgery	No	257	47.8
	Yes	281	52.2
Previous radiation	No	486	90.3
	Yes	52	9.7
Alcohol consumption within 180 days of enrollment	No	236	43.9
	Rarely	72	13.4
	Sometimes	60	11.2
	Everyday	170	31.6
Tumor type	Non-small cell lung carcinoma	249	46.3
	Small cell lung carcinoma	45	8.4
	Breast carcinoma	224	41.6
	Others	20	3.7
Chemotherapy	Cisplatin with treatment excluding irinotecan	277	51.5
	Cisplatin with irinotecan	37	6.9
	AC/EC	224	41.6

Regarding chemotherapy regimen, 277 of 538 patients (51%) were given cisplatin combined with other treatment excluding irinotecan, 224 of 538 patients (42%) received AC/EC, and 37 of 538 patients (7%) were given irinotecan. Furthermore, vinorelbine (95 of 277 patients [34%]) and gemcitabine (89 of 277 patients [32%]) were agents commonly combined with cisplatin; fluorouracil (92 of 224 patients [41%]) was associated with AC/EC.

The numbers of patients receiving palonosetron in each cycle are shown in Table 2. Over 50% of the patients received palonosetron through cycle 3. The minimum, median, and maximum numbers of administrations of palonosetron throughout the study period were 1, 3, and 10, respectively.

Of the 538 patients in the safety analysis cohort, 536 patients (99.6%) experienced at least one AE. In the subcohort of the safety analysis, patients reported to have at least one AE, 99% (275 of 277) of patients were in the cisplatin cohort, 100% (224 of 224) in the AC/EC cohort, and 100% (37 of 37) in the irinotecan cohort. Treatment-related AEs judged by the investigators to be possibly, probably, or definitely related to palonosetron were reported in a total of 44% (237 of 538) of the safety analysis cohort, including 35% (97 of 277) of the cisplatin cohort, 55% (123 of 224) of the AC/EC cohort, and 46% (17 of 37) of the irinotecan cohort.

Table 3 shows the main treatment-related AEs that occurred in at least 2% of patients in the safety analysis

Table 2 Number of patients in each cycle in the safety analysis cohort

N = total number of patients in a cohort

n = number of patients for each cycle

Cohort	N	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
		n	%	n	%	n	%	n	%
Cisplatin	277	277	100.0	230	83.0	153	55.2	66	23.8
Irinotecan	37	37	100.0	36	97.3	25	67.6	7	18.9
AC/EC	224	224	100.0	220	98.2	211	94.2	98	43.8

Table 3 Treatment-related adverse events

Cohort	Cisplatin (*N*=277)			AC/EC (*N*=224)			Irinotecan (*N*=37)			Total (*N*=538)		
	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)
Constipation	31 (11.2)	12 (4.3)	1 (0.4)	57 (25.4)	19 (8.5)	2 (0.9)	5 (13.5)	2 (5.4)	0 (0.0)	93 (17.3)	33 (6.1)	3 (0.6)
Electrocardiogram QTc prolonged	6 (2.2)	2 (0.7)	1 (0.4)	14 (6.3)	16 (7.1)	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	20 (3.7)	20 (3.7)	1 (0.2)
Angiopathy	19 (6.9)	1 (0.4)	0 (0.0)	16 (7.1)	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	0 (0.0)	37 (6.9)	1 (0.2)	0 (0.0)
Alanine aminotransferase increased	12 (4.3)	6 (2.2)	3 (1.1)	4 (1.8)	2 (0.9)	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.7)	16 (3.0)	9 (1.7)	4 (0.7)
Aspartate aminotransferase increased	11 (4.0)	5 (1.8)	4 (1.4)	2 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	13 (2.4)	9 (1.7)	4 (0.7)
Headache	9 (3.2)	0 (0.0)	0 (0.0)	12 (5.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (3.9)	1 (0.2)	0 (0.0)
Gamma-glutamyl-transferase increased	5 (1.8)	2 (0.7)	1 (0.4)	2 (0.9)	0 (0.0)	1 (0.4)	1 (2.7)	0 (0.0)	1 (2.7)	8 (1.5)	2 (0.4)	3 (0.6)

Possibly, probably, or definitely related to study product and over 2% incidence of patients in the safety analysis cohort

N = total number of patients in a cohort

G1, G2, G3 = Grade of adverse event as per CTCAE v.3

n = number of patients with at least one treatment-related AE

cohort. The incidences of constipation and electrocardiographic QTc variation were higher in patients receiving AC/EC than in those receiving cisplatin.

The proportions of patients who experienced an increase in QTc value more than 60 ms (QT1) from baseline or more than 500 ms (QT2) are summarized in Table 4. There was no clinically significant difference in the proportion of patients who experienced increase in QTc value between the patients receiving cisplatin and those receiving AC/EC, and the proportion was low (less than 3%) in both treatments, with no QTc variation reported to be symptomatic.

The incidence of NAE, defined as AEs observed only from the second cycle, was very low (less than 1%). In addition, the incidence of WAE, defined as AEs worsened by grade, starting from the second cycle compared to their grade in the first cycle, was very low (less than 0.5%). Among NAEs and WAEs, only one case of angiopathy was judged to be definitely related to palonosetron. This patient recovered within a day without treatment.

Serious AEs were reported in 4% of patients (23 of 538). All of these events were judged to be unrelated or unlikely to be related to palonosetron by the investigators.

Three patients withdrew from the study. Only one withdrawal, due to atrial fibrillation, was judged to be possibly related to palonosetron. The atrial fibrillation was not serious and resolved in 8 days with medical treatment. Two other patients withdrew from the study due to AEs judged to be related to chemotherapy or treatment for concomitant disease.

The proportion of patients with complete response to each of the four chemotherapy cycles considered in this study ranged from 72% to 77% in the acute phase, from 56% to 63% in the delayed phase, and from 52% to 56% in the overall phase (Fig. 1a). Similarly, the proportion of patients with no nausea in each cycle ranged from 55% to 61% in the acute phase, from 35% to 41% in the delayed phase, and from 33% to 39% in the overall phase (Fig. 1b). There were no major differences in the efficacy parameters

Table 4 Number of patients (percent) with QTc variations in cisplatin and AC/EC cohort in each cycle

Chemotherapy		Cycle 1		Cycle 2		Cycle 3		Cycle 4	
			%		%		%		%
Cisplatin	Evaluable patients (*N*)	314		266		178		73	
	QT1 (*n*)	3	1.0	5	1.9	1	0.6	2	2.7
	QT2 (*n*)	1	0.3	2	0.8	0	0.0	0	0.0
AC/EC	Evaluable patients (*N*)	223		220		211		98	
	QT1 (*n*)	4	1.8	3	1.4	4	1.9	1	1.0
	QT2 (*n*)	0	0.0	1	0.5	0	0.0	0	0.0

QT1 more than 60 ms from baseline, *QT2* more than 500 ms (absolute QTc value)

N = total number of evaluable patients in a cohort for each cycle

n = number of patients with QT1 or QT2 for each cycle

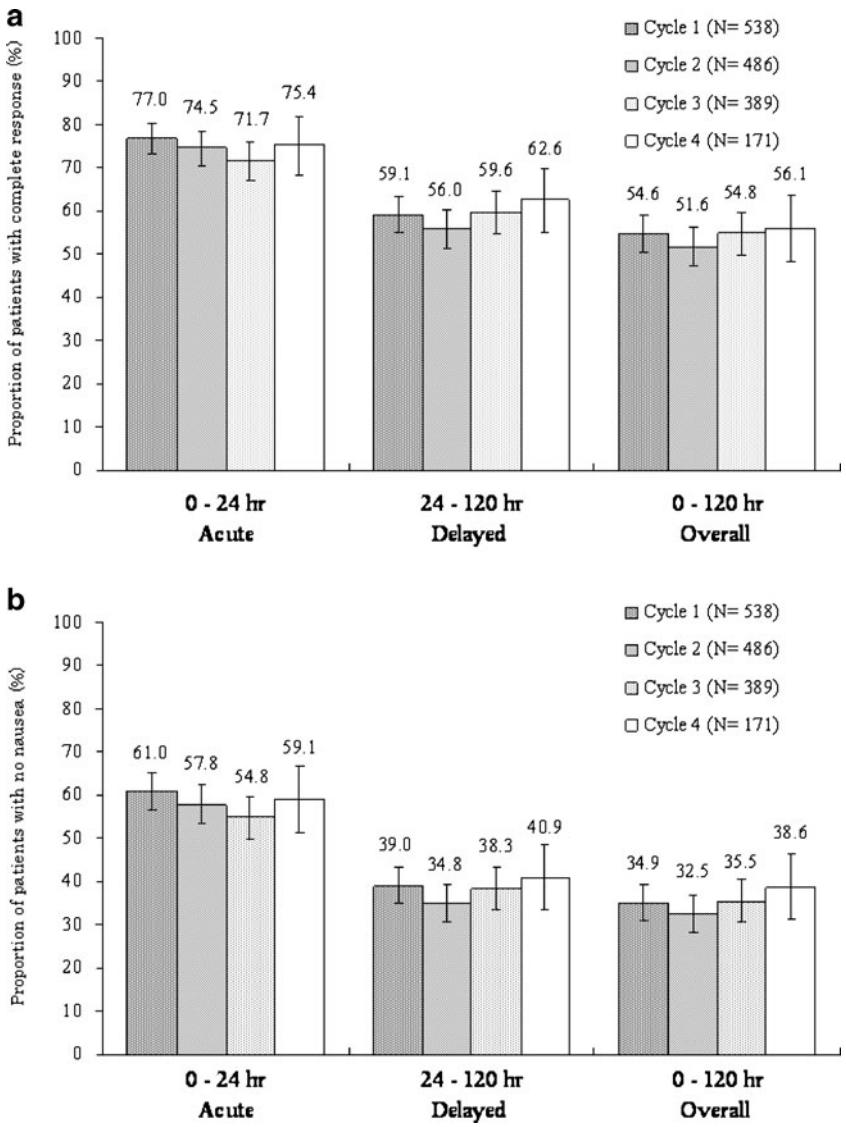

Fig. 1 **a** Proportion of patients with complete response for each study cycle. **b** Proportion of patients with no nausea for each study cycle. *Error bars* indicate 95% confidence intervals

among cycles within the acute (0–24 h), delayed (24–120 h), or overall (0–120 h) phases.

Discussion

In this phase III trial for patients receiving cisplatin or AC/EC in repeated chemotherapy cycles, an excellent palonosetron safety profile was observed.

Many women were enrolled in this trial because AC/EC was the treatment for breast cancer. Although the population of this study consisted of patients receiving highly emetogenic chemotherapy or AC/EC, they did not receive three-drug antiemetic regimens including a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant. This is because aprepitant was not available in Japan at the time when this study was conducted. The dose of palonosetron, approved by the Ministry of Health, Labor and Welfare (MHLW) in Japan, was higher than that recommended by the international guidelines [12]. Both 0.75- and 0.25-mg doses of palonosetron exhibited superiority to ondansetron or dolasetron in the delayed phase in two comparative phase III studies for moderately emetogenic chemotherapy [4, 5]. Additionally, 0.75 mg palonosetron was superior to granisetron in the delayed phase in a phase III study for highly emetogenic chemotherapy [8]. The 0.75-mg i.v. dose of palonosetron is the dose approved in Japan by the MHLW, driven by results of the phase III comparative study [8] and two phase II dose-ranging studies for use in combination with dexamethasone [6, 7]. These dose-ranging phase II and comparative phase III studies showed no difference in safety between the two doses of 0.75 and 0.25 mg palonosetron.

The safety profile of this study showed that AEs related to palonosetron were similar to those identified in the safety profile described in a single chemotherapy cycle studies,

with a single administration of palonosetron [8]. Also, in a small population treated with palonosetron in each irinotecan cycle, almost weekly, the safety profile was similar to that described in single palonosetron dose studies.

NAE and WAE were reported in a very small number of patients and were mainly judged not to be related to palonosetron but to antineoplastic treatment or to the primary disease. No worsening trend in AEs was observed in the subsequent cycles of chemotherapy. Therefore, the results of this study did not arouse any special concern related to the administration of palonosetron in repeated cycles of chemotherapy.

Interactions of some 5-HT_3 receptor antagonists with human cardiac ion channels are known and have been reported [15], and recently, the effect of palonosetron on QTc prolongation has been studied in an European double-blind, randomized, placebo-controlled trial, which showed no significant effect on any ECG interval, including QTc duration, with intravenous palonosetron administered up to 2.25 mg, three times the study dose [16]. In the double-blind, randomized phase III study, the incidences of QTc prolongation in the palonosetron group and in the granisetron group were comparable [8]. In the present study, we carefully evaluated ECG because the effect of palonosetron on ECG interval was not known at the start of this study. The incidence of QTc prolongation was higher in those patients receiving AC/EC than in those receiving cisplatin; however, the proportion of patients with an increase in QTc (more than 500 ms as an absolute value or more than 60 ms difference from the baseline value) was very low, both in the patients receiving cisplatin and those receiving AC/EC. Therefore, the influence of palonosetron on QTc interval was not found to be clinically significant, as reported in previous studies [8, 16].

Maintenance of the efficacy of palonosetron was also shown during its administration throughout repeated chemotherapy cycles. De Wit et al. [17] reported that the antiemetic effect of granisetron plus dexamethasone was not maintained over multiple cycles of highly emetogenic chemotherapy because failure in its protection against delayed emesis negatively influenced the antiemetic effect against acute emesis in the subsequent cycles. We considered that efficacy of palonosetron in the delayed phase might contribute to the maintenance of antiemetic effect throughout repeated chemotherapy cycles. It is of great importance to assure maintenance of efficacy, as well as to provide a very good safety profile to assure patient compliance with chemotherapy, especially when administered in multiple cycle regimens.

In conclusion, in this multiple cycle study conducted with palonosetron, the analysis of AEs did not raise any safety concerns; the type and intensity of treatment-related AEs were consistent with previous reports for palonosetron and for 5-HT_3 receptor antagonists; they did not change after repeated administration of the study drug. Both the excellent safety profile and the sustained efficacy of 0.75 mg palonosetron were shown throughout repeated chemotherapy cycles in this study, and also even when it was administered more frequently (at least 7-day intervals) in patients receiving irinotecan-containing regimens.

Further research is warranted to assess this maintenance of efficacy and the excellent safety profile of palonosetron in multiple cycles of emetogenic chemotherapy as well as in combination with other antiemetic class agents.

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