original article

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A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy

M. S. Aapro[1], S. M. Grunberg[2], G. M. Manikhas[3], G. Olivares[4], T. Suarez[5], S. A. Tjulandin[6], L. F. Bertoli[7], F. Yunus[8], B. Morrica[9], F. Lordick[10] & A. Macciocchi[11]

[1]IMO, Clinique de Genolier, Genolier, Vaud, Switzerland; [2]University of Vermont, Burlington, Vermont, USA; [3]St. Petersburg Oncology Center, St. Petersburg, Russia; [4]Centro Medico La Raza, IMSS, Mexico City, Mexico; [5]Centro Anticanceroso de Mérida, Merida, Yucatan, Mexico; [6]Russian Oncology Center n.a. Blokhin, Moscow, Russia; [7]Southern Hematology and Oncology, Birmingham, Alabama, USA; [8]The Boston Cancer Center Group, Memphis, Tennessee, USA; [9]Presidio Ospedaliero di Cremona, Cremona, Italy; [10]Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [11]Helsinn Healthcare, SA, Lugano, Switzerland

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Background: This pivotal phase III trial evaluated the efficacy and safety of palonosetron in preventing acute and delayed chemotherapy-induced nausea and vomiting (CINV) following highly emetogenic chemotherapy (HEC).
Patients and methods: Patients were randomized to a single intravenous dose of palonosetron 0.25 mg or 0.75 mg, or ondansetron 32 mg prior to HEC. Dexamethasone pre-treatment (with stratification) was used at investigator discretion. The primary efficacy endpoint was the proportion of patients with complete response (CR) during the first 24 h post-chemotherapy (acute phase).
Results: In the intent-to-treat analysis (n = 667), palonosetron 0.25 mg and 0.75 mg were at least as effective as ondansetron in preventing acute CINV (59.2%, 65.5%, and 57.0% CR rates, respectively); CR rates were slightly higher with palonosetron than ondansetron during the delayed (24–120 h) and overall (0–120 h) phases. Two thirds of patients (n = 447) received concomitant dexamethasone. Patients pre-treated with palonosetron 0.25 mg plus dexamethasone had significantly higher CR rates than those receiving ondansetron plus dexamethasone during the delayed (42.0% versus 28.6%) and overall (40.7% versus 25.2%) phases. Palonosetron and ondansetron were well tolerated.
Conclusions: Single-dose palonosetron was as effective as ondansetron in preventing acute CINV following HEC, and with dexamethasone pre-treatment, its effectiveness was significantly increased over ondansetron throughout the 5-day post-chemotherapy period.
Key words: chemotherapy-induced nausea and vomiting, emesis, 5-HT_3 receptor antagonist, highly emetogenic chemotherapy, palonosetron

introduction

All patients receiving chemotherapy are not at equal risk for developing chemotherapy-induced nausea and vomiting (CINV). Chemotherapeutic and patient characteristics are among the contributing factors, with the specific chemotherapeutic agent and dose administered probably the most significant risk factors [1]. Agents with the highest emetogenic potential result in emesis during the first 24 h post-chemotherapy (acute CINV) in well over 90% of patients without anti-emetic prophylaxis and include cisplatin, high-dose cyclophosphamide, carmustine, dacarbazine, mechlorethamine, and streptozotocin [1–3]. Patient characteristics that increase the risk of CINV include female gender, younger age, previous exposure to chemotherapy, history of alcohol abstention, and presence of nausea and vomiting with prior chemotherapy [4].

Poor control of acute CINV is an established predictor for delayed CINV that typically peaks in severity between day 2 and day 4 post-chemotherapy, depending on the emetogenic profile of the agent(s) used [5–9]. Because 5-HT_3 receptors are important neurotransmitters involved in CINV, drugs that

Correspondence to: Dr A. Macciocchi, c/o Gaia Piraccini, Helsinn Healthcare, SA via Pian Scairolo 9, 6912 Pazzallo (Lugano), Switzerland. Tel: +41-91-985 21 21; Fax: +41-91-993 21 22; E-mail: gpi@helsinn.com

Data from this trial were previously presented in part at the Multinational Association of Supportive Care in Cancer International Symposium 2003, Berlin, Germany: Aapro MS, Bertoli LF, Lordick F, Bogdanova NV, Macciocchi A. Palonosetron is effective in preventing acute and delayed chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy (HEC). Support Care Cancer 2003; 11: 291. Abstract A-17. Additional results were presented at the American Society of Health-System Pharmacists Midyear Clinical Meeting, 2005, Las Vegas, Nevada, USA: Natale JJ and Cartmell AD. Improved efficacy of single-day regimen of palonosetron plus dexamethasone versus ondansetron plus dexamethasone in preventing highly emetogenic chemotherapy-induced nausea and vomiting (CINV) [abstract and poster]. ASHP Midyear Clinical Meeting. 2005; 40: P690E.

inhibit these receptors are commonly used in clinical practice. Among the various types of available anti-emetic agents, 5-HT_3 receptor antagonists have become established as the cornerstone of therapy for prevention of CINV, due to their proven efficacy and low incidence of side effects compared with alternatives [10, 11]. Acute response rates seen with 5-HT_3 antagonist monotherapy following moderately or highly emetogenic chemotherapy [12] are further increased when used in combination with a corticosteroid such as dexamethasone [10, 13]. First-generation 5-HT_3 receptor antagonists (ondansetron [Zofran®], granisetron [Kytril®], dolasetron [Anzemet®], and tropisetron [Navoban®]) possess an equivalent safety and efficacy profile when used at equipotent doses [2, 14–16]. However, despite treatment with these agents, over half of patients continue to experience nausea and/or vomiting following highly emetogenic chemotherapy [17–22].

Palonosetron is a novel, highly potent, and selective second-generation 5-HT_3 receptor antagonist that has a strong receptor binding affinity [23] and a long plasma elimination half-life (∼40 h) [24]. Based on data from three phase III pivotal comparative trials, palonosetron hydrochloride injection 0.25 mg (Aloxi®, Onicit®) is indicated for the prevention of CINV associated with moderately and highly emetogenic chemotherapy [25]. Two of the three phase III trials have been published in recent years investigating the effect of palonosetron in patients receiving moderately emetogenic chemotherapy [26, 27]. These trials demonstrated that a single intravenous (i.v.) dose of palonosetron 0.25 mg provided superior protection against both acute and delayed emesis compared with single-dose ondansetron or dolasetron [26–28]. In another recently published phase II dose-ranging study in patients receiving highly emetogenic (cisplatin) chemotherapy, a single i.v. dose of palonosetron monotherapy resulted in protection from acute emesis (with no rescue medication) in 40% to 50% of patients treated at the 3 (∼0.25 mg), 10 (∼0.75 mg), 30, or 90 mcg/kg dose levels; two pre-selected suboptimal doses (0.3 and 1 mcg/kg) were less efficacious, and all doses studied were well tolerated [29].

The current phase III pivotal comparative trial was conducted to evaluate the safety and efficacy of single-dose palonosetron 0.25 mg and 0.75 mg (confirming the lowest fully effective dose) compared with single-dose ondansetron 32 mg in preventing CINV following highly emetogenic chemotherapy.

methods

patients

All patients provided written informed consent before enrollment. Eligible patients were males and females ≥18 years of age with histologically or cytologically confirmed malignant disease, naïve or non-naïve to chemotherapy, with a Karnofsky index ≥50%, scheduled to receive a single dose of highly emetogenic chemotherapy (i.e. cisplatin ≥60 mg/m^2, cyclophosphamide >1500 mg/m^2, carmustine [BCNU] >250 mg/m^2, dacarbazine [DTIC], or mechlorethamine) on day 1. Patients with known hepatic, renal, or cardiovascular dysfunction, or patients who had experienced (at maximum) mild nausea following any previous chemotherapy, were allowed per investigator discretion.

Patients were excluded if they had received, or were scheduled to receive, any drug with potential anti-emetic efficacy within 24 h of study initiation and throughout day 5. Patients with any vomiting, retching, or National Cancer Institute Common Toxicity Criteria grade 2 or 3 nausea in the 24 h preceding chemotherapy, patients with ongoing vomiting from any organic etiology, or those with a history of moderate to severe nausea or vomiting following any previous chemotherapy were excluded. Also excluded were patients with active seizure disorders requiring anticonvulsant medication, those scheduled to receive any other chemotherapeutic agent with an emetogenicity level ≥4 [1] or radiotherapy of the upper abdomen or cranium on day 2 through day 6, or those with known contraindication to 5-HT_3 receptor antagonists. Administration of low to moderately emetogenic chemotherapy agents (not greater than Hesketh level 3 emetogenicity) was permitted during days 2–6.

study design

This was a phase III, multinational, randomized, double-blind, double-dummy, stratified, parallel-group, active-comparator trial conducted between July 2000 and December 2001. Eligible patients were randomized to receive 1 of 3 treatments administered as a single fixed i.v. dose 30 min before chemotherapy initiation on day 1: palonosetron 0.25 mg, palonosetron 0.75 mg, or ondansetron 32 mg. Use of a single dose of prophylactic corticosteroid (dexamethasone 20 mg i.v. 15 min before chemotherapy initiation) was allowed at physician discretion, but not required.

Randomization of patients in this study was stratified by factors known to influence emetic risk, including dexamethasone use (yes/no), gender (male/female), and prior chemotherapy (naïve/non-naïve) to ensure balance between treatment groups. Subjects were followed for 5 days for the efficacy endpoints and 15 days for safety endpoints. The study was conducted according to the Declaration of Helsinki, and written approval was obtained from the ethics committees and institutional review boards at each site in all participating countries before study commencement.

efficacy parameters

The primary efficacy endpoint in this study was the proportion of patients with a complete response (CR; defined as no emetic episodes and no rescue medication use) during the acute phase (0–24 h post-chemotherapy). Secondary efficacy variables included CR rates for the delayed (24–120 h post-chemotherapy) and overall (0–120 h post-chemotherapy) phases, complete control rates (CC; defined as no emetic episodes, no rescue medication use, and no more than mild nausea), number of emetic episodes, time to first emetic episode, time to first administration of rescue medication, time to treatment failure (i.e. time to first emetic episode or time to administration of rescue therapy, whichever occurred first), and severity of nausea, using a categorical scale of none, mild, moderate, or severe. Patient diaries were used for recording of any emetic episodes, nausea or rescue anti-emetics in daily (24-h) intervals. An emetic episode was defined as one occurrence of vomiting or a sequence of occurrences in very close succession not relieved by a period of relaxation of at least 1 min, any number of episodes of unproductive emesis (retches) in a unique 5-min period, or an episode of retching of <5 min duration combined with vomiting not relieved by a period of relaxation of 1 min.

The effect of CINV on daily activities was measured using the Functional Living Index–Emesis (FLIE). The FLIE is a validated nausea- and vomiting-specific, patient-reported outcome instrument comprising nine items in each of two domains [30, 31]. Responses to each of the 18 items were marked by the patient on a seven-point, 100-mm visual analog scale with anchors of 'a great deal' and 'none'/'not at all.' Higher scores corresponded to less effect on daily activities. No impact of CINV on daily life (NIDL) was defined by a score >6 on the seven-point FLIE scale. FLIE questionnaires were completed on day 2, reflecting the acute impact of CINV on daily

life activities during the first 24 h (day 1) following chemotherapy, and on day 5, reflecting the delayed impact (days 2–4) of CINV on daily life activities.

study visits and assessment procedures

Patients were randomized on day 1 and study drug was administered 30 min before initiation of highly emetogenic chemotherapy. On day 2 (approximately 24 h after study drug administration) and once between days 6–8, patients returned to the clinic for evaluations including ECG measurement, adverse event (AE) and concomitant medication recording, and laboratory assessments. Patients were also contacted by phone for AE and concomitant medication recording through day 15.

statistical analysis

The intent-to-treat (ITT) cohort included all randomized patients who received chemotherapy and study drug ($n = 667$). The safety cohort (safety analysis) included all patients who received study drug and had at least one safety assessment after treatment ($n = 673$). The ITT cohort was used for the primary efficacy analysis.

The primary efficacy hypothesis was that at least one dose of palonosetron was not inferior to the ondansetron dose using a maximum delta of 15% for CR at 24 h. To test the hypothesis of the non-inferiority of at least one of the two doses of palonosetron, the lower bound of the two-sided, 97.5% confidence interval (CI) of the difference between the proportions of CR in each dose of palonosetron and ondansetron was compared to the pre-set threshold (–15% difference). Assuming a responder rate of 50% in the palonosetron and ondansetron groups, a sample size of 212 evaluable patients per group was needed to ensure an overall power of 90% for each comparison.

Response rate comparisons through 120 h were pre-planned secondary analyses for the ITT cohort and stratified subgroups. Additionally, logistic regression analysis was applied to further investigate the influence of gender, chemotherapeutic history, concomitant dexamethasone use, and type of chemotherapy on CR rates. The Chi-square test was used to analyze CC rates, the proportion of patients receiving rescue medication, and the proportion of patients with FLIE scores indicating no impact on daily life for the domains of nausea, vomiting, and combined (i.e. total). The number of emetic episodes and severity of nausea were compared between treatment groups using the Kruskal-Wallis/Wilcoxon test. Differences between the treatment groups in time to first emetic episode, time to first administration of rescue medication, and time to treatment failure were analyzed using Kaplan-Meier estimates and the log-rank test. Safety data were analyzed descriptively. A two-sided Fisher's exact test and the Chi-square test were used subsequently to evaluate between-group differences in CR rates and secondary efficacy parameters, respectively, for the subgroup receiving dexamethasone.

results

patient characteristics and baseline demographics

Patients were enrolled and evaluated between July 2000 and December 2001 in 76 centers on two continents (North America and Europe). A total of 673 patients were randomized and received a single i.v. dose of 1 of the 3 treatments: palonosetron 0.25 mg ($n = 225$), palonosetron 0.75 mg ($n = 225$), or ondansetron 32 mg ($n = 223$). Six patients from a disqualified site who received study medication were excluded from the ITT analysis.

Demographic data for the ITT cohort ($n = 667$) are presented in Table 1. Because of the stratified design of the study, the distribution of patients by gender, chemotherapeutic history, and dexamethasone use was similar across all treatment groups.

Table 1. Baseline demographic and clinical characteristics (ITT cohort, total $n = 667$)

Characteristic	Palonosetron 0.25 mg i.v. ($n = 223$)		Palonosetron 0.75 mg i.v. ($n = 223$)		Ondansetron 32 mg i.v. ($n = 221$)	
	Mean	SD	Mean	SD	Mean	SD
Age, years	53.4	13.7	50.6	14.1	50.9	14.2
Height, cm	164.6	9.5	164.4	10.8	164.6	11.2
Weight, kg	67.4	14.1	69.5	15.7	67.8	15.4
	n	%	*n*	%	*n*	%
Gender						
Female	115	51.6	113	50.7	113	51.1
Ethnicity						
White, Caucasian	140	62.8	130	58.3	127	57.5
Black	6	2.7	8	3.6	8	3.6
Hispanic	75	33.6	81	36.3	85	38.5
Other	2	0.9	4	1.8	1	0.5
Alcohol consumption						
No	115	51.6	110	49.3	116	52.5
Chemotherapeutic history						
Naïve	133	59.6	129	57.8	131	59.3
Tumor type[a]						
Ovarian	38	16.9	41	18.2	39	17.5
Lung	35	15.6	30	13.3	33	14.8
Hodgkin's	23	10.2	14	6.2	17	7.6
Gastric	9	4.0	12	5.3	14	6.3
Breast	13	5.8	6	2.7	14	6.3
Chemotherapy[a]						
Cisplatin	184	82.5	189	84.8	181	81.9
Cyclophosphamide	57	25.6	53	23.8	59	26.7
Dacarbazine	28	12.6	24	10.8	30	13.6
Dexamethasone use						
Yes	150	67.3	150	67.3	147	66.5

[a]Reported for the most common categories in the safety cohort ($n = 673$) (incidence ≥5% in any group).
ITT, intent to treat; SD, standard deviation.

The majority (59%) of patients were chemotherapy-naïve, with no relevant differences between treatment groups with respect to renal, hepatic, or cardiovascular impairment or Karnofsky index. Treatment groups were similar with regard to prior and concomitant diseases and concomitant medications. Prophylactic dexamethasone was administered to 67.3% of patients in each of the palonosetron groups and to 66.5% of patients in the ondansetron group. Ovarian cancer, lung cancer, and Hodgkin's disease were the most frequently reported primary cancers for patients in all treatment groups. Of the chemotherapeutic agents received on day 1, high-dose cisplatin and cyclophosphamide were the most common chemotherapy agents administered in all treatment groups, received by 83% and 25% of patients, respectively. The median dose of cisplatin was 80 mg/m^2, administered over 2.9 h.

efficacy endpoints—full trial population

Complete response rates for the ITT population during the acute phase were 59.2% for palonosetron 0.25 mg, 65.5% for palonosetron 0.75 mg, and 57.0% for ondansetron (Table 2).

Table 2. Complete response rates (ITT cohort, total $n = 667$)

Time period, h	Palonosetron 0.25 mg i.v. ($n = 223$)			Palonosetron 0.75 mg i.v. ($n = 223$)			Ondansetron 32 mg i.v. ($n = 221$)
	%	97.5% CI PAL minus OND	P value[a]	%	97.5% CI PAL minus OND	P value[a]	%
Acute phase							
0–24	59.2	−8.8%, 13.1%	0.701	65.5	−2.3%, 19.2%	0.079	57.0
Delayed phase							
24–120	45.3	−4.6%, 17.3%	0.180	48.0	−1.9%, 20.0%	0.056	38.9
Overall phase							
0–120	40.8	−2.9%, 18.5%	0.095	42.2	−1.6%, 19.8%	0.051	33.0

[a]P values represent adjusted post-hoc, two-sided, Fisher's exact test comparisons of palonosetron with ondansetron, significance level = 0.025.
CI, confidence interval; PAL, palonosetron; OND, ondansetron.

The primary efficacy endpoint was achieved; palonosetron was not inferior to ondansetron during the first 24 h after chemotherapy, as the lower bounds of the 97.5% CI of the difference in CR rates between palonosetron and ondansetron (–8.8% and –2.3% for palonosetron 0.25 mg and 0.75 mg, respectively) were greater than the pre-set threshold of –15%. Efficacy comparisons are reported for the clinically relevant endpoints and the dexamethasone subgroup using both pre-specified primary and secondary analyses and post hoc analyses.

Palonosetron produced numerically higher CR rates compared with ondansetron during the delayed and overall phases (Table 2). During the acute phase, CC rates for palonosetron 0.25 mg and 0.75 mg were slightly higher than ondansetron 32 mg (56.5%, 61.0%, and 51.6%, respectively). Throughout the delayed and overall phases, the treatments were comparable with respect to CC. Time to first emetic episode was significantly longer for patients treated with palonosetron 0.25 mg (median >120 h) and palonosetron 0.75 mg (median >120 h) compared with patients treated with ondansetron (median 42.7 h) ($P = 0.023$ and $P = 0.006$, respectively), with no difference between palonosetron doses. Slightly more patients in the ondansetron group used rescue medication during the acute phase (22.6% for ondansetron, 19.7% and 17.0% for the palonosetron groups). The difference between palonosetron and ondansetron was more pronounced on days 2 and 3 (6%–7% difference), although rescue medication use rates were not statistically significantly different on any day or during the overall time phase. Acute emesis was prevented in 68.2% and 60.2% of patients in the palonosetron 0.25-mg and ondansetron groups, respectively ($P = 0.079$). There were significantly more patients free from emetic episodes in the palonosetron 0.25-mg group compared with the ondansetron group during both the delayed (56.5% versus 46.6%, $P = 0.037$) and overall (51.1% versus 39.4%, $P = 0.013$) phases. There were also significantly fewer patients experiencing an emetic episode in the palonosetron 0.75 mg group compared with the ondansetron group during the acute ($P = 0.007$), delayed ($P = 0.029$), and overall ($P = 0.007$) time phases.

Subgroup analyses by gender showed a trend in male patients toward less emesis and nausea, reflected in higher CR and CC rates, longer times to first emesis or treatment failure, and less interference with daily functioning than in the female subgroup. For female patients, differences favoring palonosetron over ondansetron were observed for CR and CC rates, number of emetic episodes, and time to first emesis. Subgroup analyses by chemotherapy history showed a trend toward higher response rates, including less emesis and nausea, for non-naïve patients, with no consistent differences between treatment groups.

efficacy endpoints—addition of dexamethasone

A large proportion of the ITT population (447 patients, 67.0%) received concomitant dexamethasone on day 1, and these patients were stratified for balance between the treatment groups. These patients had similar characteristics to the full ITT population, but a slightly higher percentage of the subgroup were chemotherapy-naïve (61.9%), more received cisplatin (89.9%), and fewer received cyclophosphamide (21.9%). The patient characteristics for this subgroup were well balanced between treatment groups.

Secondary descriptive subgroup analyses showed that patients treated with palonosetron 0.25 mg or 0.75 mg who received dexamethasone on day 1 had numerically higher CR rates than those treated with ondansetron 32 mg plus dexamethasone during the acute time phase (64.7% and 62.7%, respectively, versus 55.8%) (Figure 1). For the delayed and overall phases, significantly higher CR rates were seen for single doses (of the approved dose) of palonosetron 0.25 mg plus dexamethasone compared with ondansetron plus dexamethasone (42.0% versus 28.6%; $P = 0.021$ and 40.7% versus 25.2%; $P = 0.005$, respectively).

Significantly more patients pre-treated with dexamethasone in the palonosetron 0.25-mg group were free from acute and delayed (and overall) emesis compared with ondansetron (Figure 2). With concomitant dexamethasone there was a small incremental increase of 7% in the percentage of patients protected from any acute nausea for both palonosetron groups, to 58%, compared to patients in the ondansetron plus dexamethasone group. Differences in nausea-free rates were numerically higher for the palonosetron plus dexamethasone group on each day, but not statistically superior; the greatest magnitude difference between groups was on day 3, when 49% of palonosetron 0.25-mg patients and 38% of ondansetron patients were free from any nausea. Additionally, fewer patients

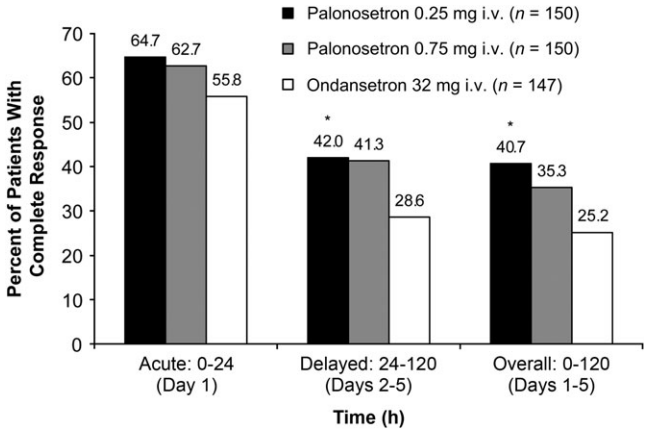

Figure 1. Complete response rates in patients receiving study drug plus prophylactic dexamethasone during the acute, delayed, and overall phases following chemotherapy (total $n = 447$). *97.5% CI for the difference between palonosetron 0.25 mg i.v. and ondansetron and two-sided Fisher's exact test indicates palonosetron superiority ($\alpha = 0.025$).

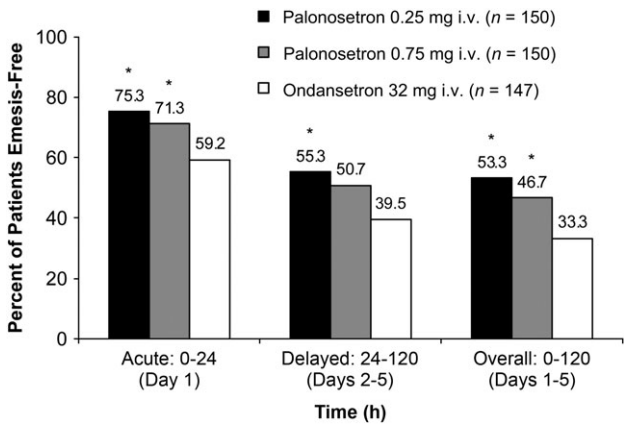

Figure 2. Proportion of patients receiving study drug plus prophylactic dexamethasone with no emetic episodes during the acute, delayed, and overall phases (total $n = 447$). *$P<0.05$ for palonosetron versus ondansetron (Chi-square test).

treated with palonosetron 0.25 mg plus dexamethasone experienced moderate to severe nausea on day 1 compared to patients treated with ondansetron plus dexamethasone (19% versus 28%), and the rates of moderate to severe nausea remained somewhat lower for the palonosetron 0.25-mg group on each subsequent day through day 5.

The percentage of patients using rescue antiemetic medication was 10% higher for the ondansetron plus dexamethasone group than for the palonosetron 0.25-mg plus dexamethasone group (50% versus 40%), and the median time to first administration of rescue medication was longer for the palonosetron group (>120 h) than for the ondansetron group (102.9 h).

The time to treatment failure (time to first emesis or rescue) was longer for both palonosetron plus dexamethasone groups (48.2 h and 42.2 h) than for the ondansetron plus dexamethasone group (27.4 h), with log-rank test results showing pronounced differences between the treatment groups ($P = 0.032$) (Figure 3).

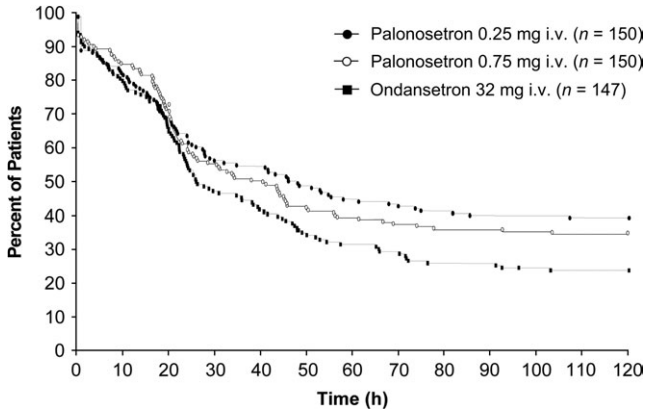

Figure 3. Kaplan-Meier plot of time to treatment failure (first emesis or rescue use). $P = 0.032$ Log-Rank test for palonosetron 0.25 mg i.v. plus dexamethasone, palonosetron 0.75 mg i.v. plus dexamethasone, and ondansetron 32 mg i.v. plus dexamethasone.

Results of the FLIE analysis indicate less impact from CINV on daily functioning in all patients receiving dexamethasone compared to those who were not pre-treated. In the groups receiving concomitant dexamethasone on day 1, the percentage of patients reporting NIDL (score >6 on seven-point FLIE scale) in the nausea, vomiting, and combined (total) domains was slightly higher for palonosetron 0.25 mg than for ondansetron 32 mg. The differences in FLIE scores between patients receiving palonosetron 0.25 mg plus dexamethasone or ondansetron 32 mg plus dexamethasone were greatest during the acute phase, and differences in impact on daily functioning from nausea were more pronounced than for vomiting during both the acute and delayed phases. In the acute phase, 74% of palonosetron-treated patients and 66% of ondansetron-treated patients reported NIDL from nausea; 81% and 71% of patients, respectively, reported NIDL from vomiting; and 78% and 68%, respectively, reported NIDL for the combined nausea and vomiting domain. During the 24–96 h (delayed) reporting interval, 55% of patients in the palonosetron group and 46% of patients in the ondansetron group reported NIDL from nausea; 67% and 66% of patients, respectively, reported NIDL from vomiting; and 59% and 52%, respectively, reported NIDL for the combined nausea and vomiting domain.

adverse events

A total of 673 patients who received palonosetron (with or without concomitant dexamethasone) were evaluated in the safety cohort. In the palonosetron 0.25-mg, palonosetron 0.75-mg, and ondansetron 32-mg groups, 72%, 79%, and 73% of patients, respectively, reported any AE. Palonosetron and ondansetron were well tolerated, with >90% of AEs mild or moderate in intensity. The majority (approximately 80%) of AEs were judged by the investigator as not related to study medication. The proportion of patients with drug-related AEs (i.e. adverse reactions) was similar across treatment groups (Table 3). The most frequently reported drug-related AEs were headache (palonosetron 0.25 mg, 8.0% of patients; palonosetron 0.75 mg, 12.4%; ondansetron 32 mg, 10.8%) and constipation (4.4%, 7.6%, and 2.2%, respectively).

Table 3. Treatment-related adverse events occurring in ≥2% of patients in any treatment group (safety cohort, total $n = 673$)

Adverse event	Palonosetron 0.25 mg i.v. ($n = 225$)		Palonosetron 0.75 mg i.v. ($n = 225$)		Ondansetron 32 mg i.v. ($n = 223$)	
	n	%	*n*	%	*n*	%
Headache	18	8.0	28	12.4	24	10.8
Constipation	10	4.4	17	7.6	5	2.2
Diarrhea	3	1.3	1	0.4	5	2.2

The incidence and duration of serious AEs was low and similar between treatment groups, and all serious AEs were determined to be not related or unlikely related to study drugs.

There were no pronounced differences between treatment groups for vital sign changes or laboratory test results. With respect to ECG recordings, the mean post-dose change in QTc interval (Fredericia correction) from baseline was 3 ms, 2 ms, and 5 ms for palonosetron 0.25 mg, palonosetron 0.75 mg, and ondansetron, respectively. Overall, no significant safety concerns were identified in the study.

discussion

In this phase III pivotal trial of patients receiving highly emetogenic chemotherapy, single-dose palonosetron was effective in preventing both acute and delayed CINV. In the prevention of acute CINV, palonosetron 0.25 mg and 0.75 mg were at least as effective as ondansetron 32 mg. Serotonin antagonists are believed to be effective in acute CINV because serotonin is released rapidly from the enterochromaffin cells in the gastrointestinal tract in the first 24 h [32, 33]. Serotonin release initiates the stimulation of the chemoreceptor trigger zone in the central nervous system, resulting in nausea and vomiting [34]. In humans, a peak in the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) is observed in urine at 4 h, with levels returning to baseline within 24 h [35]. Other factors that may play a role in acute CINV in humans are less well understood but could include dopaminergic receptor mechanisms, central serotonin receptor mechanisms, and the neurokinin-1 receptor pathway. Although the exact mechanism of delayed CINV, especially in humans, is not well understood, it is increasingly clear that several neurotransmitters are involved, including serotonin, dopamine, and substance P [5, 32, 36–41].

Both chemotherapy-naïve and non-naïve patients were included in the current trial to provide a more real-world, heterogeneous patient group, similar to that seen in a clinical setting. The inclusion of patients who had previously received chemotherapy, experiencing at maximum mild chemotherapy-induced nausea, is a source of potential bias in this trial. Those who experienced no nausea during initial treatment may not be susceptible to this side effect, while those who experienced mild nausea may be more likely to experience worse nausea during re-treatment. The proportion of patients who experienced no versus mild nausea during prior chemotherapy was not determined. Another limitation of this trial is the heterogeneity of chemotherapy regimens of the study patients. Different regimens may be associated with different patterns and intensities of nausea and vomiting and, for some agents and regimens, their association with delayed emesis is not well understood.

Although use of a corticosteroid (such as dexamethasone) with a serotonin antagonist is generally recommended for patients receiving highly emetogenic chemotherapy [2, 3, 32, 40, 42], its mechanism of action remains somewhat unclear, and physicians may be hesitant to use corticosteroids in certain cases either due to patient co-morbidities or to the potential toxicity of the corticosteroid medications themselves [43].

Approximately two thirds of patients in all arms of this trial received dexamethasone. This frequency of corticosteroid use is consistent with that reported in other large studies of anti-emetics in which corticosteroids were also allowed at physician discretion [44, 45]. Extended administration of corticosteroids has been used for prevention of delayed emesis. However, even a single dose of dexamethasone may provide significant antiemetic protection throughout the delayed period [46].

This trial was designed prior to the publication of anti-emetic consensus guidelines in the late 1990s that highlighted the benefit of adding dexamethasone to a 5-HT_3 receptor antagonist and continuing dexamethasone therapy during the delayed period of emetic risk. In addition, it was designed as a non-inferiority trial as, at the time, there was no evidence to suggest superiority of one 5-HT_3 receptor antagonist over another. Therefore, the primary analysis was for non-inferiority of palonosetron versus the United States Food and Drug Administration–approved dose of ondansetron, allowing concomitant use of dexamethasone only at the investigator's discretion, according to the standards of therapy and accepted guidance for the conduct of well-controlled phase III clinical trials at the time of study planning. With the knowledge we now have regarding CINV prevention, the pre-planned and post hoc secondary subgroup analyses of subjects who received concomitant dexamethasone on day 1 is extremely relevant. These analyses showed that palonosetron plus dexamethasone was statistically superior to ondansetron plus dexamethasone in providing protection from both acute and delayed emesis and numerically superior to ondansetron plus dexamethasone in providing protection from nausea.

Improved protection against both emesis and nausea has the potential to reduce interference with functioning across many domains of health-related quality of life, which was demonstrated in this trial as decreased impairment in patients' ability to perform their usual daily activities. Palonosetron and ondansetron had a similar incidence and pattern of AEs, with most being mild and not related to study medication. Therefore, palonosetron offers a more favorable efficacy profile than ondansetron, with a safety profile consistent to that of the 5-HT_3 class of anti-emetics.

Efficacy findings for ondansetron during the acute interval in the current trial are consistent with those previously reported for highly emetogenic CINV, thus providing external validation of the acute control rates for ondansetron observed in this trial. The emesis prevention rate for ondansetron plus dexamethasone during the first 24 h in the current trial was 59%, compared with 61% previously reported for three 0.15-mg/kg doses plus dexamethasone 20 mg [47].

In this trial, a single dose of palonosetron was more efficacious than single-dose ondansetron in preventing emesis induced by highly emetogenic chemotherapy throughout the 5-day study period. Results of the phase III studies evaluating single-dose palonosetron following moderately emetogenic chemotherapy also showed it to be more effective than first-generation 5-HT_3 receptor antagonists in the prevention of acute and delayed emesis [26–28].

The NK-1 receptor antagonist aprepitant has been shown to have additive activity with 5-HT_3 receptor antagonists plus dexamethasone in preventing CINV caused by highly emetogenic chemotherapy including cisplatin [48]. A small open-label study evaluated the efficacy of the combination of aprepitant and dexamethasone (3-day regimen) with palonosetron (given only on day 1) in 58 patients receiving moderately to moderately-highly emetogenic chemotherapy [49]. Results showed that 88% of patients had a CR (no emetic episodes with no rescue medication) in the acute phase, and 78% of patients had a CR in the delayed phase; 91% of patients were free from emesis throughout the 5-day study [49]. These promising results suggest that the addition of dexamethasone (and aprepitant as indicated) to palonosetron could provide extra clinical benefit in the overall prevention of nausea and vomiting associated with emetogenic chemotherapy regimens.

In summary, the current trial showed that single, fixed, i.v. doses of palonosetron 0.25 mg and 0.75 mg were safe and effective in preventing acute and delayed CINV following highly emetogenic chemotherapy. When used as monotherapy, palonosetron was at least as effective as ondansetron in preventing acute CINV, with a trend toward greater efficacy than ondansetron in preventing delayed CINV. In this trial the approved 0.25-mg dose of palonosetron was as effective as the 0.75-mg dose for prevention of CINV [25]. In addition, and as per current anti-emetic guidelines, palonosetron 0.25 mg administered with dexamethasone was significantly more effective than ondansetron with dexamethasone in preventing CINV during the overall 5-day period after chemotherapy. To achieve the current 'gold standard' for emesis and nausea prevention throughout the acute and delayed periods, dexamethasone and aprepitant should be added to the antiemetic regimen in the 3 to 4 days following high-emetic-risk chemotherapy. With its proven efficacy, extended duration of action, and excellent safety profile, palonosetron is a safe and effective alternative to currently marketed first-generation 5-HT_3 receptor antagonists in the prevention of highly emetogenic CINV.

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