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ORIGINAL ARTICLE

Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV)

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Abstract
Purpose Preventing chemotherapy-induced nausea and vomiting (CINV) is integral to treatment success in patients with cancer. This analysis was undertaken to assess the relative efficacy and safety of palonosetron versus older $5HT_3$ RAs in preventing CINV associated with moderately or highly emetogenic chemotherapy.
Methods Patient-level data from four randomized, double-blind, phase III trials comparing palonosetron 0.25 or 0.75 mg with ondansetron 32 mg, dolasetron 100 mg, or granisetron 40 μg/kg were analyzed. Endpoints included complete response (CR: no emesis and no rescue antiemetics) in the acute (0–24 h), delayed (>24–120 h), and overall (0–120 h) postchemotherapy periods (primary), complete control (CC: no emesis, no rescue antiemetics, and no more than mild nausea), number of emetic episodes, and nausea severity.
Results CR rates were significantly higher for palonosetron ($n=1,787$) versus older $5HT_3$ RAs ($n=1,175$) in the delayed (57 vs 45 %, $P<0.0001$) and overall periods (51 vs 40 %, $P<0.0001$); odds ratios (95 % CI) in the acute, delayed, and overall periods were 1.15 (0.98–1.34), 1.62 (1.40–1.88), and 1.56 (1.34–1.81), respectively. Significant differences in CC rates and nausea severity were observed for the delayed and overall periods and in emetic episodes for all three periods. The incidence of treatment-related adverse events was similar with palonosetron (0.25 mg, 20.0 %; 0.75 mg, 26.5 %) and older $5HT_3$ RAs (27.5 %).
Conclusions Palonosetron is more effective than older $5HT_3$ RAs for controlling CINV in the delayed and overall post-chemotherapy periods.

Keywords Palonosetron · Serotonin antagonists · CINV · Nausea · Vomiting · Cancer chemotherapy

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Introduction

Patients with cancer who receive chemotherapy often experience nausea and vomiting (chemotherapy-induced nausea and vomiting, CINV), the onset of which can be acute (starting within minutes to hours following treatment and generally resolving within 24 h) or delayed (starting more than 24 h after treatment and lasting for up to several days) [1]. The time course and severity of CINV vary depending on the specific chemotherapeutic agents administered, their dosages and routes of administration, and patient factors such as age, gender, history of alcohol use, and type of cancer [1–3]. Delayed CINV, which tends to be more common than acute CINV, is less responsive to antiemetic therapy [4, 5]. Delayed nausea also tends to be more severe than acute nausea [4, 5]. Although delayed nausea can occur in the absence of acute

CINV [6], both types are important targets for antiemetic therapy because the risk of delayed CINV is greater if acute CINV is poorly controlled [7]. Further, the risk of CINV in general is highly related to its occurrence in a previous cycle of chemotherapy [8, 9].

Adverse consequences of CINV may include metabolic derangements, nutritional deficiencies and anorexia, esophageal tears, wound dehiscence, deterioration of performance and mental status, and degeneration of self-care and functional ability [1]. Further, CINV may lead to the discontinuation of potentially beneficial or curative anticancer treatments [1] and significantly affects quality of life [9]. Controlling CINV is therefore integral to treatment success in patients with cancer.

The first generation of $5HT_3$ receptor antagonists ($5HT_3$ RAs), such as ondansetron, dolasetron, and granisetron revolutionized CINV management. These antiemetic agents are broadly effective in controlling acute CINV associated with moderately (MEC) or highly emetogenic chemotherapy (HEC) [10].

The $5HT_3$ RA palonosetron differs from other $5HT_3$ RAs in its pharmacokinetic/pharmacodynamic profile and may be uniquely suited to treat delayed CINV. Specifically, palonosetron has a longer elimination half-life ($t_{½}$) and a distinctly different receptor-binding profile compared with older $5HT_3$ RAs [11], uniquely triggers $5HT_3$ receptor internalization, and induces prolonged inhibition of receptor function [12]. Palonosetron also inhibits substance P responses in a serotonin-independent manner [13].

In the clinical setting, palonosetron improved rates of CINV prevention relative to older $5HT_3$ RAs in four phase III trials in patients receiving either MEC (30–90 % frequency of emesis) [14, 15] or HEC (>90 % frequency of emesis) [16, 17]. The present analysis utilized pooled data from these four trials to compare the relative effectiveness of palonosetron versus older $5HT_3$ RAs for preventing CINV in patients with cancer scheduled to receive either MEC or HEC and to compare the tolerability of palonosetron with that of older $5HT_3$ RAs. These studies were selected because patient-level data were available for analysis.

Patients and methods

Pooled patient-level data from four multicenter, randomized, double-blind, parallel-group phase III trials were analyzed (Table 1). Two of the trials were conducted in patients scheduled to receive MEC [14, 15] and two in patients scheduled to receive HEC [16, 17]. Of note, 64 % of patients in the study by Eisenberg et al. received anthracycline+cyclophosphamide (AC) [15], which is currently classified as HEC [1] (at the time of the study, AC was classified as MEC). Three trials were conducted in Europe or North America [14–16] and one in Japan [17]. All four studies were approved by institutional review boards or independent ethics committees at each site where they were performed. Written informed consent was obtained from all participating patients before any study-related procedure was initiated.

Methods of included trials

The methods for each study have been described in detail [14–17]. Briefly, patients enrolled in the four studies were

Table 1 Studies pooled for analysis (all were randomized, double-blind, controlled clinical trials)

Study	$5HT_3$ RA treatment groups[a]	*N* (ITT)	Emetogenicity of chemotherapy
Gralla et al. [14]	Palonosetron 0.25 mg	189	MEC
	Palonosetron 0.75 mg	189	
	Ondansetron 32 mg	185	
Eisenberg et. al [15]	Palonosetron 0.25 mg[b]	189	MEC
	Palonosetron 0.75 mg[b]	189	
	Dolasetron 100 mg[b]	191	
Aapro et al. [16]	Palonosetron 0.25 mg[b]	223	HEC
	Palonosetron 0.75 mg[b]	223	
	Ondansetron 32 mg[b]	221	
Saito et al. [17]	Palonosetron 0.75 mg[c]	555	HEC
	Granisetron 40 μg/kg[c]	559	

$5HT_3$ RA $5HT_3$ receptor antagonist, *HEC* highly emetogenic chemotherapy, *ITT* intent-to-treat, *IV* intravenously, *MEC* moderately emetogenic chemotherapy

[a] All $5HT_3$ RAs were administered as a single IV dose 30 min before the scheduled chemotherapy regimen

[b] Patients could also receive dexamethasone (20 mg IV, 15 min before chemotherapy)

[c] All patients also received dexamethasone (16 mg IV, 45 min before $5HT_3$ RAs, plus another IV [8 mg] or oral dose [4 mg] on days 2 and 3 after chemotherapy)

required to be at least 18 years of age, have a histologically or cytologically confirmed malignancy, and have a Karnofsky Performance Scale score of ≥50 %. Eligible patients were randomly assigned to receive single intravenous (IV) doses of palonosetron (0.25 or 0.75 mg) or older $5HT_3$ RAs: ondansetron (32 mg), dolasetron (100 mg), and granisetron (40 μg/kg), all of which were administered 30 min before the scheduled chemotherapy regimens. Consistent with guidelines at the time of the studies, concomitant steroids were permitted [15, 16] or required [17] in three of the four studies. In each study, the primary efficacy endpoint was the complete response (CR) rate (defined as no emesis and no rescue medication) in the acute (0–24 h), delayed (>24–120 h), and/or overall (0–120 h) postchemotherapy treatment periods. Secondary efficacy endpoints included the complete control (CC) rate (defined as no emesis, no rescue medication, and no more than mild nausea) during the acute, delayed, and overall postchemotherapy treatment periods; numbers of emetic and nausea episodes; and nausea severity (rated on a four-point Likert scale from 0=none to 3=severe). Safety assessments included adverse events (AEs), vital signs, laboratory test results, and electrocardiographic (ECG) findings.

Statistical analysis

For this analysis, data from patients treated with ondansetron, dolasetron, or granisetron were pooled, and all data from all patients treated with palonosetron were pooled. Because the older $5HT_3$ RAs have similar efficacy in preventing CINV when administered at therapeutically equivalent doses [10], pooling of the data for these agents was considered valid. Similarly, as there are few differences in efficacy between the 0.25- and 0.75-mg doses of palonosetron [14–16], pooling of data for the two doses was also considered valid.

A logistic regression model was used to analyze pooled data from the four phase III trials and was fitted for CR and CC endpoints with terms for palonosetron 0.25, palonosetron 0.75, HEC, MEC, and Japanese study. In addition, a goodness-of-fit test (Hosmer–Lemeshow) was applied to ensure the consistency of effect of the endpoint across various strata of variables in the model. Interaction terms were assessed for significance. If the term was deemed not significant, it was removed from the model. The model was then refitted, and the model-fit and goodness-of-fit tests were reapplied. This process was repeated, eliminating each nonsignificant variable, one at a time, until all nonsignificant variables had been eliminated or the Hosmer–Lemeshow goodness-of-fit test had become significant. The process also was repeated for the subgroups of patients who had lung cancer or breast cancer. For descriptive purposes, if both the model-fit and Hosmer–Lemeshow goodness-of-fit tests were statistically significant (suggesting poor model fit across the strata, even though the model fit was good), the statistically significant model was displayed with a note of pooled consistency of fit across various strata (i.e., a statistically significant Hosmer–Lemeshow goodness-of-fit test statistic).

Observed rates of each efficacy outcome were compared between the palonosetron (pooled doses) and older $5HT_3$ RA groups using Cochran–Mantel–Haenszel tests.

For the safety analyses, a comparative descriptive assessment of AE rates in the four studies was performed.

Results

A total of 2,962 patients were included in the analysis: 1,787 received palonosetron and 1,175 received older $5HT_3$ RAs. Demographic and clinical characteristics of the analysis population are shown in Table 2. Data are shown separately for MEC and HEC studies. Additionally, data are shown for patients who received AC treatment in any study. Mean body weight was slightly lower in the groups containing Japanese patients in the study of HEC-induced CINV [17]. The majority of patients receiving HEC also received a corticosteroid (dexamethasone) concomitantly, while the majority of patients receiving MEC did not (Table 2); all patients in the Saito et al. study [17], approximately 67 % of patients in the Aapro et al. study [16], 5 % of patients in the Eisenberg et al. study [15]), and no patients in the Gralla et al. study [14] received corticosteroids.

Complete response rates

CR rates were significantly higher for palonosetron (pooled doses) relative to older $5HT_3$ RAs during the delayed phase ($P<0.0001$), and overall phase ($P<0.0001$), but not the acute phase ($P=0.091$) (Fig. 1a). Likewise, odds ratios (ORs, 95 % CI) reflected a significantly greater likelihood of CR with palonosetron versus older $5HT_3$ RAs in the delayed (OR, 1.62 [1.40–1.88]) and overall phases (OR, 1.56 [1.34–1.81]), but not the acute phase (OR, 1.15 [0.98–1.34]).

Complete control rates

Analysis of the CC data showed that palonosetron provided higher CC rates than older $5HT_3$ RAs in the delayed ($P<0.0001$) and overall ($P<0.0001$) phases, but not the acute phase ($P=0.137$) (Fig. 1b). ORs (95 % CI) for the acute, delayed, and overall phases were 1.12 (0.96–1.31), 1.49 (1.29–1.73), and 1.50 (1.29–1.74), respectively.

Number of emetic episodes

The frequency of emetic episodes was significantly different for palonosetron and older $5HT_3$ RAs during the acute ($P=0.007$), delayed ($P<0.0001$), and overall ($P<0.0001$) phases (Fig. 2).

Table 2 Pooled demographic and clinical characteristics of patients treated with palonosetron (PALO) or other $5HT_3$ RAs in four randomized controlled clinical trials (analysis population)

Variable	Moderately emetogenic chemotherapy[a]		Highly emetogenic chemotherapy[b]		Anthracycline+ cyclophosphamide[c] chemotherapy		All patients	
	PALO[d] (±Dex) (*n* = 765)	$5HT_3$ RAs[d] (±Dex) (*n* = 381)	PALO (±Dex)[e] (*n* = 1,022)	$5HT_3$ RAs (±Dex)[e] (*n* = 794)	PALO (±Dex) (*n* = 748)	$5HT_3$ RAs (±Dex) (*n* = 495)	PALO (±Dex) (*n* = 1,787)	$5HT_3$ RAs (±Dex) (*n* = 1,175)
Age (year), mean (SD)	55.0 (12.1)	54.6 (12.0)	55.6 (12.4)	56.0 (12.1)	52.1 (11.1)	51.9 (10.9)	55.3 (12.3)	55.6 (12.1)
Height (cm), mean (SD)	162.6 (9.0)	163.0 (8.9)	161.9 (9.4)	161.1 (9.4)	159.5 (7.7)	158.5 (7.8)	162.2 (9.2)	161.7 (9.3)
Weight (kg), mean (SD)	70.9 (15.1)	71.8 (15.8)	62.5 (13.3)	60.7 (12.7)	66.4 (14.7)	63.2 (14.4)	66.1 (14.7)	64.3 (14.7)
Gender, *n* (%)								
Male	173 (23)	88 (23)	460 (45)	347 (44)	54 (7)	25 (5)	633 (35)	435 (37)
Female	592 (77)	293 (77)	562 (55)	447 (56)	694 (93)	470 (95)	1,154 (65)	740 (63)
Alcohol use, *n* (%)								
None	426 (56)	215 (56)	467 (46)	362 (46)	555 (74)	363 (73)	893 (50)	577 (49)
Rarely	203 (27)	98 (26)	200 (20)	132 (17)	96 (13)	73 (15)	403 (23)	230 (20)
Occasionally/sometimes	100 (13)	43 (11)	149 (15)	113 (14)	97 (13)	59 (12)	249 (14)	156 (13)
Regularly/daily	34 (5)	25 (7)	205 (20)	187 (24)	555 (74)	363 (73)	239 (13)	212 (18)
Tobacco use, *n* (%)								
Nonsmoker	506 (66)	242 (64)	469 (46)	361 (46)	555 (74)	363 (73)	975 (55)	603 (51)
Ex-smoker	137 (18)	74 (19)	377 (37)	312 (39)	96 (13)	73 (15)	514 (29)	386 (33)
Smoker	121 (16)	65 (17)	175 (17)	121 (15)	97 (13)	59 (12)	296 (17)	186 (16)
Corticosteroid use, *n* (%)								
Yes	23 (3)	8 (2)	861 (85)	711 (91)	268 (36)	257 (52)	884 (50)	719 (62)
No	742 (97)	373 (98)	149 (15)	74 (9)	480 (64)	238 (48)	891 (50)	447 (38)
Primary cancer, *n* (%)								
Blood	44 (6)	22 (6)	51 (5)	22 (3)	48 (6)	23 (5)	95 (5)	44 (4)
Breast	469 (61)	241 (63)	262 (26)	256 (32)	635 (85)	446 (90)	731 (41)	497 (42)
CNS	1 (<1)	2 (1)	4 (<1)	1 (<1)	0	0	5 (<1)	3 (<1)
Colorectal	42 (6)	12 (3)	7 (1)	3 (<1)	0	0	49 (3)	15 (1)
Endocrine	7 (1)	3 (1)	12 (1)	5 (1)	3 (<1)	0	19 (1)	8 (1)
GI	13 (2)	8 (2)	24 (2)	15 (2)	1 (<1)	0	37 (2)	23 (2)
Genitourinary	65 (9)	34 (9)	147 (14)	76 (10)	27 (4)	8 (2)	212 (12)	110 (9)
Head and neck	12 (2)	7 (2)	77 (8)	32 (4)	2 (<1)	3 (1)	89 (5)	39 (3)
Hepatobiliary	8 (1)	2 (1)	4 (<1)	1 (<1)	0	0	12 (1)	3 (<1)
Respiratory	84 (11)	37 (10)	384 (38)	343 (43)	22 (3)	9 (2)	468 (26)	380 (32)
Sarcoma	7 (1)	7 (2)	11 (1)	6 (1)	7 (1)	2 (<1)	18 (1)	13 (1)
Skin	5 (1)	2 (1)	22 (2)	17 (2)	0	1 (<1)	27 (2)	19 (2)

$5HT_3$ RAs other $5HT_3$ receptor antagonists (ondansetron, dolasetron, or granisetron), *Dex* dexamethasone, *ITT* intent-to-treat, *IV* intravenous, *PALO* palonosetron

[a] Agents associated with a 30–90 % frequency of emesis [1]

[b] Agents associated with >90 % frequency of emesis [1]

[c] Patients who received AC chemotherapy in any of the four studies

[d] Pooled data for the palonosetron 0.25 and 0.75 mg arms, and the other $5HT_3$ RA (ondansetron 32 mg and dolasetron 100 mg) arms of the two studies of moderately emetogenic chemotherapy [14, 15]

[e] Pooled data for the palonosetron 0.25 mg and/or 0.75 mg ± dexamethasone arms, and the other $5HT_3$ RA (ondansetron 32 mg ± dexamethasone and granisetron 40 μg/kg + dexamethasone) arms of the two studies of highly emetogenic chemotherapy [16, 17]

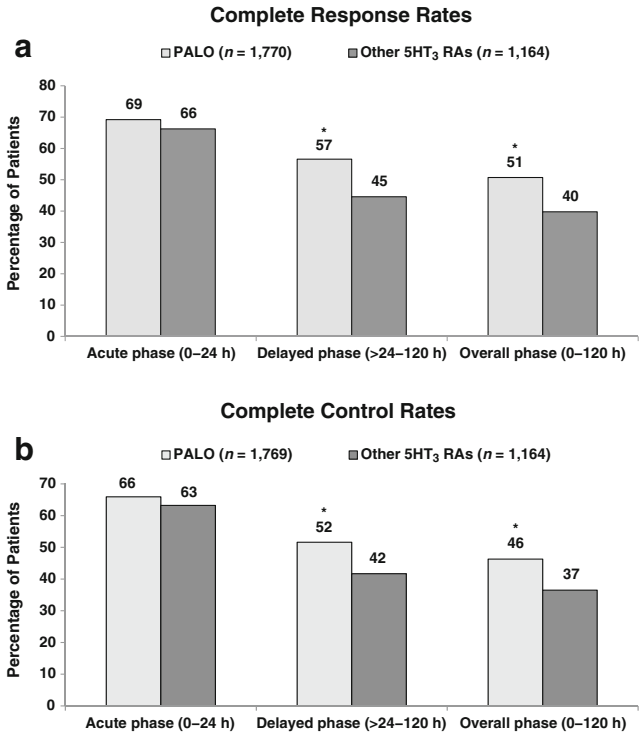

Fig. 1 **a**, **b** Complete response rates for all patients/complete control rates for all patients. **a** Significant differences between the palonosetron and other $5HT_3$ RAs groups were observed in the delayed and overall phases. *Complete response* no emetic episodes and no usage of rescue medication, *PALO* palonosetron, *other 5HT₃ RAs* other $5HT_3$ receptor antagonists (ondansetron, dolasetron, and granisetron). *$P<0.0001$, palonosetron versus other $5HT_3$ RAs. **b** Significant differences between the palonosetron and other $5HT_3$ RAs groups were observed in the delayed and overall phases. *Complete control* no emetic episodes, no usage of rescue medication, and no more than mild nausea; *PALO* palonosetron; *other 5HT₃ RAs* other $5HT_3$ receptor antagonists (ondansetron, dolasetron, and granisetron). *$P<0.0001$, palonosetron versus other $5HT_3$ RAs

Frequency and severity of nausea episodes

The severity of nausea episodes was not significantly different with palonosetron and older $5HT_3$ RAs during the acute postchemotherapy phase ($P=0.165$). However, there were significant differences in the delayed ($P=0.0002$) and overall phases ($P=0.011$) (Fig. 3). In terms of frequency of nausea, in the acute phase, 56 % of the palonosetron group and 54 % of the older $5HT_3$ RA group reported no episodes of nausea; in the delayed phase, the rates were 44 and 36 %, respectively, and in the overall phase, the rates were 39 and 33 %, respectively.

Safety and tolerability

The incidence of treatment-related AEs was similar for the three overall treatment groups: palonosetron 0.25 mg (20.0 %), palonosetron 0.75 mg (26.5 %), and older $5HT_3$ RAs (27.5 %) (Table 3). The percentages of patients with treatment-related AEs was less than one third of the percentages of patients with all-cause AEs, suggesting that most reported AEs were likely due to the patients' cancer and/or the chemotherapy regimens (Table 3). The most common treatment-related AEs were constipation (palonosetron 0.25 mg [4.4 %], palonosetron 0.75 mg [11.5 %], older $5HT_3$ RAs [9.2 %]) and headache (palonosetron 0.25 mg [9.0 %], palonosetron 0.75 mg [7.4 %], older $5HT_3$ RAs [7.4 %]) (Table 3).

Discussion

This analysis of pooled patient-level data from four multicenter, phase III, randomized, double-blind, comparative trials demonstrates that palonosetron has a safety profile similar to that of older $5HT_3$ RAs but provides superior prophylaxis of CINV. Palonosetron demonstrated significantly higher complete

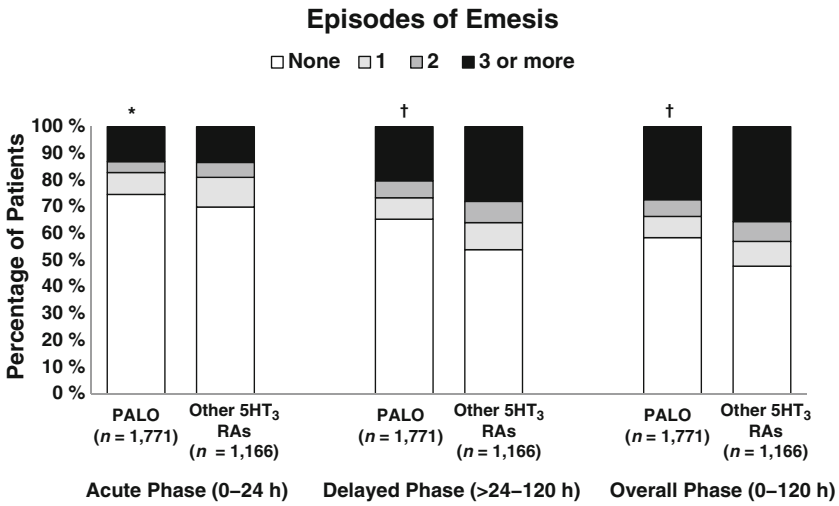

Fig. 2 Episodes of emesis in the acute, delayed, and overall postchemotherapy phases. Significant differences between the palonosetron and other $5HT_3$ RAs groups were observed in the acute, delayed, and overall phases. *PALO* palonosetron, *other 5HT₃ RAs* other $5HT_3$ receptor antagonists (ondansetron, dolasetron, and granisetron). *$P=0.0066$, palonosetron versus other $5HT_3$ RAs; †$P<0.0001$, palonosetron versus other $5HT_3$ RAs

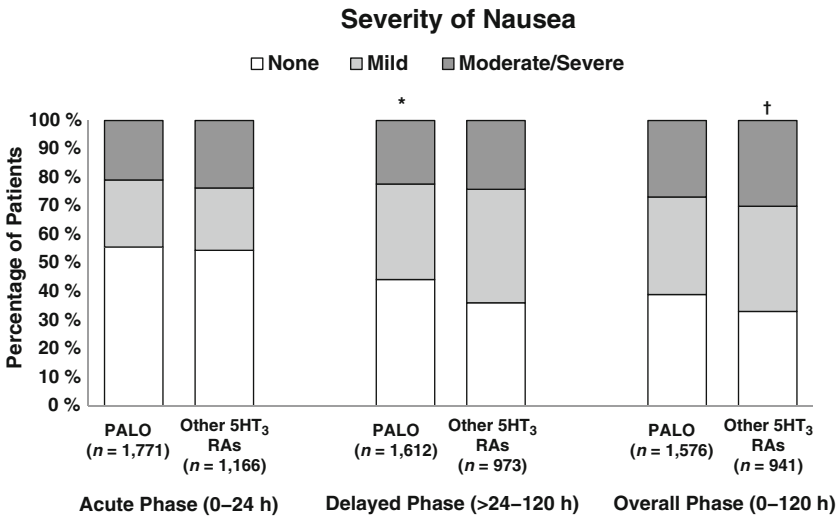

Fig. 3 Severity of nausea in the acute, delayed, and overall postchemotherapy phases. Significant differences between the palonosetron and other $5HT_3$ RAs groups were observed in the delayed and overall phases. *PALO* palonosetron, other $5HT_3$ RAs other $5HT_3$ receptor antagonists (ondansetron, dolasetron, and granisetron). *$P=0.0002$, palonosetron versus other $5HT_3$ RAs; †$P=0.0112$, palonosetron versus other $5HT_3$ RAs

response (CR) and complete control (CC) rates than older $5HT_3$ RAs (ondansetron, dolasetron, and granisetron) during the delayed (>24-120 h), and overall (0–120 h) postchemotherapy periods. The number of emetic episodes and severity of nausea were also significantly different for palonosetron compared with older $5HT_3$ RAs.

The most noteworthy differences between palonosetron and older $5HT_3$ RAs occurred in the delayed phase and throughout the overall 5-day evaluation period. Palonosetron therefore provides an effective option for delayed onset CINV, an effect of chemotherapy that previously had been more difficult to manage due to the limited efficacy of older $5HT_3$ RAs in this context [5, 6]. Further, palonosetron may be more effective in controlling nausea [18] (particularly delayed nausea), which remains a challenge despite the antiemetic efficacy of the older $5HT_3$ RAs [19, 20]. The observed advantage of palonosetron in efficacy during the delayed phase may be explained by differences in binding characteristics of palonosetron (i.e., a longer elimination half-life relative to other $5HT_3$ RAs [11] and triggering of receptor internalization leading to prolonged inhibition of receptor function and NK_1 cross talk [12]). All of the studies evaluated outcomes following a single dose of palonosetron or other $5HT_3$ RAs given on day 1 of chemotherapy; outcomes may differ with the use of multi-day antiemetic treatment regimens.

Table 3 Pooled safety data from the four randomized, double-blind studies comparing single IV doses of palonosetron with other $5HT_3$ RAs in patients receiving either moderately or highly emetogenic chemotherapy

Adverse event	PALO 0.25 mg ($n=609$)	PALO 0.75 mg ($n=1,182$)	$5HT_3$ RAs[a] ($n=1,178$)
Total AEs (all-cause), *n* (%)	425 (69.8)	1,004 (84.9)	985 (83.6)
Treatment-related AEs, *n* (%)	122 (20.0)	313 (26.5)	324 (27.5)
Most common treatment-related AEs[b], *n* (%)			
Constipation	27 (4.4)	136 (11.5)	108 (9.2)
Headache	55 (9.0)	87 (7.4)	87 (7.4)
ALT increased	1 (0.2)	25 (2.1)	37 (3.1)

Other 5HT₃ RAs other $5HT_3$ receptor antagonists (ondansetron, dolasetron, or granisetron), *AE* adverse event, *ALT* alanine aminotransferase, *PALO* palonosetron

[a] Ondansetron 32 mg, dolasetron 100 mg, or granisetron 40 μg/kg

[b] Adverse events occurring in ≥3 % of patients in any treatment group

The incidence of treatment-related AEs with palonosetron in this analysis was similar to that of older $5HT_3$ RAs, with a lower incidence of AEs associated with the 0.25 mg dose of palonosetron relative to the 0.75 mg dose. The most common treatment-related AEs were constipation and headache. Safety concerns with $5HT_3$ RAs include the potential for QTc prolongation [21], which has been the subject of recent safety communications from the US FDA (dolasetron: http://www.fda.gov/Drugs/DrugSafety/ucm237081.htm; ondansetron: http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm). Notably, QTc prolongation with ondansetron appears to be dose dependent, which led to the removal of the 32-mg IV single daily dose from the ondansetron label (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm310219.htm). IV dolasetron is no longer recommended due to an increased risk of cardiac arrhythmias [1]. Notably, recent studies evaluating the electrocardiographic effects of palonosetron in cancer patients found no significant changes in QTc interval [22, 23], and a thorough ECG study using moxifloxacin as a positive control found that doses up to 2.25 mg were not associated with clinically significant changes in QTc or other ECG parameters [24].

The efficacy findings are similar to those reported in other recent meta-analyses of the efficacy of palonosetron versus

older $5HT_3$ RAs (ondansetron, dolasetron, and granisetron) in preventing CINV in patients receiving MEC or HEC [25–27]. For example, the analysis by Botrel, which included data from 2,057 patients from five randomized, double-blind, comparative trials, showed that palonosetron 0.25 mg is significantly more effective than older 5HT3 RAs in preventing both acute and delayed nausea and vomiting, regardless of the concomitant use of corticosteroids [25]. The relative risks (RRs, 95 % CI) were 0.86 (0.76–0.96, $P=0.007$) for acute nausea, 0.82 (0.75–0.89; $P<0.00001$) for delayed nausea, 0.76 (0.66–0.88; $P=0.0002$) for acute vomiting, and 0.76 (0.68–0.85, $P<0.00001$) for delayed vomiting [25]. Likun et al. [27] analyzed data from eight clinical trials ($n=3,592$) and found that palonosetron (0.25 and 0.75 mg, combined) was significantly more effective than first-generation $5HT_3$ RAs in preventing CINV in the acute (OR: 0.76 [0.66–0.88], $P=0.0003$), delayed (OR: 0.62 [0.54–0.71], $P<0.00001$), and overall phases (OR 0.64 [0.56–0.74], $P<0.00001$). Most recently, an analysis of data from nine studies ($n=3,463$) demonstrated significantly greater efficacy with palonosetron 0.25 mg (based on RR for complete response) compared with first-generation $5HT_3$ RAs in the acute (1.11 [1.05–1.17]), delayed (1.26 [1.16–1.36]), and overall phases (1.25 [1.14–1.37]) [26]. Results were similar for palonosetron 0.75 mg [26]. These previous meta-analyses included data from the four studies analyzed here, as well as data from additional studies. Limiting our analysis to the pivotal clinical trials that formed the basis for FDA approval of palonosetron potentially introduces some degree of bias, as not all publicly available data were included. Other meta-analyses, which analyzed both abstracted (literature-based) data and patient-level data, yielded similar results, demonstrating similar efficacy and safety of the 0.25 and 0.75 mg doses of palonosetron. This analysis is generally in agreement with other meta-analyses and utilizes patient-level data to demonstrate a benefit for palonosetron compared with older $5HT_3$ RAs. We would not expect substantially different results were the other published studies included.

The overall body of evidence supporting the efficacy of palonosetron in managing CINV has led to its inclusion in several clinical practice guidelines. Specifically, the Multinational Association of Supportive Care in Cancer (MASCC), the European Society of Medical Oncology (ESMO) [19], the American Society of Clinical Oncology (ASCO) [20], and the National Comprehensive Cancer Network (NCCN) [1] recommend palonosetron as the preferred $5HT_3$ RA for prevention of CINV associated with MEC. In addition, MASCC and ESMO recommend palonosetron as the preferred $5HT_3$ RA for AC (doxorubicin or epirubicin and cyclophosphamide) regimens when an NK_1 RA is not available [19]. MASCC/ESMO and ASCO guidelines recommend palonosetron among other $5HT_3$ RAs for HEC [19, 20], while NCCN guidelines denote palonosetron 0.25 mg as the preferred $5HT_3$ RA for acute and delayed emesis prevention during intravenous chemotherapy with high emetic risk [1]. Adherence to practice guidelines improves CINV prevention outcomes; a recent study demonstrated that guideline-consistent CINV prophylaxis was associated with significantly greater odds of CR (OR 1.43 [1.04–1.97]; $P=0.027$) [28].

The substantial economic burden associated with management of CINV includes resource utilization and costs related to inpatient, outpatient, and emergency department visits [29, 30]. Improved CINV prevention, therefore, may result in economic benefits. For example, among patients with breast or lung cancer on HEC or MEC, the risk of CINV events requiring hospital or emergency department visits was significantly reduced with palonosetron as compared to other 5-HT_3 RA-based regimens [31]. Another study demonstrated that palonosetron was associated with significantly fewer extreme CINV events, resulting in a substantial reduction in both the use of rescue antiemetics and staff management time [32]. In addition, because patients who experience CINV during one cycle of chemotherapy are more likely to experience CINV in subsequent cycles [33], the economic benefits of preventing CINV during an initial cycle of chemotherapy would be expected to extend to subsequent cycles.

In summary, the data from the current analysis support previous findings of improved prevention of CINV relative to older $5HT_3$ RAs and further demonstrate an advantage of palonosetron in preventing delayed CINV. Improved prophylaxis against CINV, especially in the first cycle of chemotherapy, might provide additional benefit in helping to prevent the occurrence of CINV in subsequent cycles of chemotherapy, thereby facilitating treatment adherence.

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