Palonosetron versus older 5-HT_3 receptor antagonists for nausea prevention in patients receiving chemotherapy: a multistudy analysis

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Background No clinical standard currently exists for the optimal management of nausea induced by emetogenic chemotherapy, particularly delayed nausea.
Objective To compare the efficacy and safety of palonosetron with older 5-HT_3 receptor antagonists (RAs) in preventing chemotherapy-induced nausea.
Methods Data were pooled from 4 similarly designed multicenter, randomized, double-blind, clinical trials that compared single intravenous doses of palonosetron 0.25 mg or 0.75 mg with ondansetron 32 mg, dolasetron 100 mg, or granisetron 40 µg/kg, administered 30 minutes before moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC). Pooled data within each chemotherapy category (MEC: n = 1,132; HEC: n = 1,781) were analyzed by a logistic regression model. Nausea endpoints were complete control rates (ie, no more than mild nausea, no vomiting, and no rescue medication), nausea-free rates, nausea severity, and requirement for rescue antiemetic/antinausea medication over 5 days following chemotherapy. Pooled safety data were summarized descriptively.
Results Numerically more palonosetron-treated patients were nausea-free on each day, and fewer had moderate-severe nausea. Similarly, usage of rescue medication was less frequent among palonosetron-treated patients. Complete control rates for palonosetron and older 5-HT_3 RAs in the acute phase were 66% vs 63%, 52% vs 42% in the delayed phase (24-120 hours), and 46% vs 37% in the overall phase. The incidence of adverse events was similar for palonosetron and older 5-HT_3 RAs.
Limitations This post hoc analysis summarized data for palonosetron and several other 5-HT_3 RAs but was not powered for statistical comparisons between individual agents. Because nausea is inherently subjective, the reliability of assessments of some aspects (eg, severity) may be influenced by interindividual variability.
Conclusion Palonosetron may be more effective than older 5-HT_3 RAs in preventing nausea, with comparable tolerability.
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Patients who receive cancer chemotherapy are at risk for nausea and vomiting. The incidence and severity of these effects depend on the inherent emetogenic potential of the chemotherapeutic agents and their dosage and administration schedules, and patient factors such as younger age, female gender, low use of alcohol, and perceived susceptibility to nausea.[1-3] Chemotherapy-induced nausea and vomiting (CINV) may be responsible for numerous adverse outcomes, including nutritional deficiencies and anorexia, esophageal tears, deterioration of performance and mental status, functional ability, and discontinuation of potentially effective cancer treatment.[1] Therefore, overall control of CINV is an important primary goal of preventive treatment.

CINV may occur acutely after the start of chemotherapy, or it can be delayed, not appearing until the second day after start of chemotherapy and continuing for 5 or more days.[1] Although delayed CINV can occur independently of acute CINV, the risk of delayed CINV is greater if acute CINV is poorly controlled.[4] Delayed CINV may be more common.[5] In particular, delayed nausea seems to be

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more common and often more severe than acute nausea and it may be resistant to common preventive treatments.[6] Indeed, although vomiting can often be controlled by prophylactic antiemetic therapy administered before emetogenic chemotherapy, patients may still experience acute or delayed nausea.[5] Thus, nausea is generally more difficult to control than vomiting,[1] and controlling delayed nausea in particular presents a challenge.

CINV seems to result from the release of 5-hydroxytryptamine (5-HT; serotonin) from chemotherapy-damaged enterochromaffin cells in the small intestine and the subsequent activation of 5-HT_3 receptors on the vagal afferent nerves and stimulation of CNS centers involved in mediating emesis.[7,8] Substance P and neurokinin-1 (NK-1) receptors also seem to play a role in CINV, particularly in the delayed phase.[7]

5-HT_3 receptor antagonists (RA) have been widely studied and are standard therapies for cancer patients receiving emetogenic chemotherapy. Older 5-HT_3 RA agents such as ondansetron, granisetron, dolasetron, and tropisetron have proven effective in preventing acute CINV in 50%-80% of patients on moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) regimens.[9] However, many patients continue to have acute and/or delayed CINV despite such treatment.[5,10]

Palonosetron is a newer 5-HT_3 RA with a distinct molecular and pharmacologic profile, including structural differences,[11] stronger binding affinity for the 5-HT_3 receptor,[12] a different binding profile (ie, allosteric binding, positive cooperativity, and receptor internalization, leading to longer binding, as well as persistent functional effects[11] and a longer elimination half-life (about 40 hours)[12,13] relative to older agents. Palonosetron also inhibits substance P-mediated responses independent of serotonin[14] and has been found to uniquely inhibit cross-talk between 5-HT_3 and NK-1 receptor pathways.[15] Palonosetron has not been associated with significant QT interval prolongation,[16-18] an effect observed with other 5HT_3 RAs.[1,19] A recent analysis of data from 5 randomized, double-blind, comparative trials (n = 2,057) found that palonosetron was significantly more effective than were older 5-HT_3 RAs (ondansetron, dolasetron, granisetron) in preventing acute and delayed CINV associated with MEC or HEC, whether or not corticosteroids were used concomitantly.[20] Another recent study reported a lower incidence of nausea with palonosetron (n = 39) compared with granisetron (n = 49) in patients with advanced colorectal cancer who received mFOLFOX6 and FOLFIRI.[21]

The present analysis evaluates the safety and efficacy of palonosetron compared with older 5-HT_3 RAs in preventing nausea in the acute phase (0-24 h) and the delayed phase (24-120 h) after emetogenic chemotherapy. Data were derived from 4 similarly designed comparative studies of palonosetron compared with ondansetron, dolasetron, or granisetron in patients treated with emetogenic chemotherapy.[22-25] The primary published reports of the 4 studies focused on the occurrence of emetic episodes; here we report an analysis of pooled data for nausea endpoints.

Patients and methods

The studies in the present analysis were multicenter, randomized, double-blind, parallel-group investigations in patients with various types of cancer who were scheduled to receive emetogenic chemotherapy at sites in Europe or North America[22-24] (in 2000-2001) or in Japan (in 2006-2007).[25] In 2 studies,[22,23] the patients' chemotherapy regimens were associated with a moderate risk of emesis (MEC; frequency of emesis 30%-90%[1,7]). In the other 2 studies,[24,25] the chemotherapy regimens were associated with a high risk of emesis (HEC; frequency of emesis > 90%[1,7]). All 4 trials were approved by institutional review boards or independent ethics committees at each study site and written informed consent was obtained from all of the patients before any study-related procedures were initiated.

Patients enrolled in the 4 clinical trials were required to be at least 18-20 years of age, have histologically or cytologically confirmed malignant disease, and a Karnofsky Performance Scale score of ≥ 50%. Exclusion criteria were similar for all 4 trials and included vomiting, retching, or nausea severity of grade ≥ 2 (National Cancer Institute Common Terminology Criteria for Adverse Events) in the 24 hours preceding chemotherapy; ongoing emesis from any organic etiology; use of any drug with potential antiemetic activity from 24 hours before treatment until study day 5 (except dexamethasone in the HEC studies); active seizure disorder requiring anticonvulsant therapy (unless clinically stable); and known hypersensitivity to any 5-HT_3 RA.[22-25]

Treatments

Eligible patients in the 4 studies were randomly assigned to receive treatment with palonosetron (0.25 mg or 0.75 mg) or another 5-HT_3 RA (ondansetron 32 mg, dolasetron 100 mg, or granisetron 40 μg/kg). Investigators and patients were blinded to treatment assignment. Each drug was administered intravenously before the scheduled chemotherapy regimen on study day 1; dexamethasone was permitted or required in the HEC studies. Rescue antiemetic/antinausea medication (metoclopramide, prochlorperazine, antihistamines, or other agents) was permitted for patients who experienced nausea and emesis during follow-up.

Assessments and nausea prevention endpoints

After chemotherapy administration (on study day 1), clinical efficacy was assessed for 5 days and safety for 8-15 days by patient-reported outcomes, depending on the study.

All of the assessments were completed at clinic visits or by follow-up telephone contact. Patients were given common diaries for documenting clinical and safety outcomes, including all episodes of emesis and nausea, the severity of nausea, and the use of rescue medication for each of the 5 days of follow-up (24-hour intervals).

The nausea outcomes evaluated in this analysis included: the complete control rate (defined as no more than mild nausea, no emetic episodes, and no use of rescue medication) during the acute (0-24 h), delayed (24-120 h), and overall (0-120 hours) postchemotherapy phases, and each of the 5 successive 24-hour phases; nausea-free rate (percentage of patients with no nausea on each day); nausea severity (rated on a 4-point categorical scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe); and use of rescue antiemetic/antinausea medication.

Safety and tolerability

In all of the studies, safety was assessed by recording of adverse events (AEs) reported by patients at study visits and during follow-up phone contacts, vital signs, laboratory results (including hematology, blood chemistry, and urinalysis), and electrocardiogram (ECG) recordings.

Statistical analysis

Data for palonosetron compared with the other 5-HT_3 RAs were pooled within each chemotherapy category (MEC, HEC) for this analysis. Because the study participants had similar demographic characteristics (apart from ethnicity) and were selected using similar inclusion and exclusion criteria, post hoc pooling of the derived data was considered valid. Pooling of data for the older 5-HT_3 RAs was also considered valid based on similar clinical efficacy at therapeutically equivalent doses.[9] Pooling of data for the 2 palonosetron doses (0.25 mg and 0.75 mg) was deemed valid, as few dose-dependent differences in overall efficacy for CINV have been noted in previous studies.[22-24]

Nausea outcomes were summarized for the intent-to-treat (ITT) cohorts of each study. The ITT population comprised all randomized patients who received study medication and the scheduled chemotherapy regimen (consistent with the definition used in the individual studies). Safety was summarized for all patients who received study medication and had at least 1 safety assessment (the safety cohort).

Results

The 4 clinical trials enrolled a total of 2,978 patients who received either MEC (n = 1,162) or HEC (n = 1,816) and who were randomly assigned to receive antiemetic treatment. Sixty-five patients were excluded from the ITT analysis for various reasons, including nonreceipt of study medications (n = 40), chemotherapy deemed to be of insufficient emetogenic potential (n = 6) , and enrollment at a disqualified investigative site (n = 19). Thus, the overall ITT population for the present analysis was 2,913 patients (MEC: n = 1,132 [palonosetron: n = 756; other 5-HT_3 RA: n = 376]; HEC: n = 1,781 [palonosetron: n = 1,001; other 5-HT_3 RA: n = 780]).

Demographic characteristics of the pooled ITT cohorts are shown in Table 1. The characteristics of the patients in the individual treatment arms within each study type were generally similar; however, there were some differences between patients in the MEC and HEC studies (eg, ethnicity, body weight) that reflect differences based on the geographical location of the studies. Most MEC recipients (≥ 97%) did not receive corticosteroids before or concomitantly with 5-HT_3 RA treatment, whereas most of the HEC patients (> 85%) did receive them. In the HEC study by Aapro and colleagues,[24] about 67% of patients in each treatment arm received concomitant dexamethasone; in the other HEC study (Saito and colleagues[25]), all of the patients received dexamethasone with the 5-HT_3 RA. The most common tumors in the 4 clinical trials were breast and lung cancers.

Nausea outcomes

Nausea-free days and nausea severity. In the MEC studies, a numerically greater percentage of patients who received palonosetron were nausea-free on each of the 5 days after starting chemotherapy compared with the patients who received other 5HT_3 RAs (Figure 1). The 6% difference (55% vs 49%, respectively) observed on day 1 expanded to a 12% difference on day 2 (52.4% vs 39.9%) and remained a 12% difference on day 3 (57.1% vs 45.5%). Fewer palonosetron recipients had moderate-to-severe nausea, particularly on days 2 and 3 (21.0% vs 30.1% and 14.7% vs 23.9%; Figure 2).

In the HEC studies, the percentage of patients who were nausea-free was similar for palonosetron and other 5-HT_3 RAs on study day 1. Thereafter, the percentage of nausea-free patients was slightly higher for palonosetron than for other 5HT_3 RAs (Figure 1). Nausea severity ratings were slightly more favorable with palonosetron (Figure 2), but the differences compared with the other 5-HT_3 RAs were smaller than in the MEC studies. The greatest differences in the incidence of moderate-to-severe nausea were on days 4 and 5 (14.8% vs 20.4% and 10.8% vs 16.8%, respectively).

Requirement for rescue antiemetic/antinausea medication. The most commonly used rescue antiemetic/antinausea agents were metoclopramide and prochlorperazine. In the MEC studies, rates of rescue medication use in patients who received palonosetron vs older 5-HT_3 RAs were: day 1: 17% vs 19%; day 2: 20% vs 25%; day 3: 16% vs 21%; day

TABLE 1 Pooled demographic patient data (intent-to-treat cohorts)

Variable	Moderately emetogenic chemotherapy[a,22,23]		Highly emetogenic chemotherapy[b,24,25]	
	PALO 0.25 mg and 0.75 mg[c] (n = 756)	OND 32 mg and DOL 100 mg[c] (n = 376)	PALO 0.25 mg and 0.75 mg (± Dex)[d] (n = 1,001)	OND 32 mg and GRAN 40 µg/kg (± Dex)[d] (n = 780)
Mean age, y	54.9	54.4	55.5	56.0
Mean height, cm	162.6	163.0	161.8	161.2
Mean weight, kg	70.9	71.8	62.5	60.8
Gender, n (%)				
Male	172 (22.8)	87 (23.1)	447 (44.7)	343 (44.0)
Female	584 (77.2)	289 (76.9)	554 (55.3)	437 (56.0)
Ethnicity, n (%)				
White	493 (65.2)	242 (64.4)	270 (27.0)	127 (16.3)
Black	20 (2.6)	10 (2.7)	14 (1.4)	8 (1.0)
Hispanic	230 (30.4)	116 (30.9)	156 (15.6)	85 (10.9)
Japanese/Asian	9 (1.2)	6 (1.6)	560 (55.9)	559 (71.7)
Other	4 (0.5)	2 (0.5)	1 (0.1)	1 (0.1)
Alcohol use, n (%)				
None	422 (55.8)	212 (56.4)	458 (45.8)	355 (45.5)
Rarely	201 (26.6)	97 (25.8)	199 (19.9)	132 (16.9)
Occasionally/sometimes	97 (12.8)	43 (11.4)	146 (14.6)	108 (13.8)
Regularly/daily	34 (4.5)	24 (6.4)	197 (19.7)	185 (23.7)
Tobacco use, n (%)				
Nonsmoker	498 (65.9)	240 (63.8)	462 (46.2)	353 (45.3)
Ex-smoker	135 (17.9)	72 (19.1)	239 (23.9)	187 (24.0)
Smoker	122 (16.1)	64 (17.0)	170 (17.0)	120 (15.4)
Chemotherapy history, n (%)				
Naïve	411 (54.4)	203 (54.0)	781 (78.0)	647 (82.9)
Non-naïve	345 (45.6)	173 (46.0)	220 (22.0)	133 (17.1)
Corticosteroid use (pretreatment or concomitantly), n (%)				
Yes	23 (3.0)	8 (2.1)	855 (85.4)	706 (90.5)
No	733 (97.0)	368 (97.9)	146 (14.6)	74 (9.5)
Common tumor types, n (%)				
Breast	464 (61.4)	236 (62.8)	256 (25.6)	250 (32.1)
Lung	75 (9.9)	34 (9.0)	349 (34.9)	330 (42.3)
Colon/rectum	36 (4.8)	11 (2.9)	0	0
Ovarian	19 (2.5)	10 (2.7)	76 (7.6)	39 (5.0)
Hodgkin	4 (0.5)	2 (0.5)	36 (3.6)	17 (2.2)
Gastric	12 (1.6)	6 (1.6)	19 (1.9)	14 (1.8)

Dex, dexamethasone; DOL, dolasetron; GRAN, granisetron; IV, intravenous; OND, ondansetron; PALO, palonosetron

[a]Agents associated with a 30%-90% frequency of emesis. [b]Agents associated with > 90% frequency of emesis. [c]Combined data for the palonosetron 0.25 mg and 0.75 mg arms, and the ondansetron 32 mg and dolasetron 100 mg arms of the MEC studies. [d]Combined data for the palonosetron 0.25 mg and/or 0.75 mg ± dexamethasone arms, and the ondansetron 32 mg ± dexamethasone and granisetron 40 µg/kg + dexamethasone arms of the HEC studies.

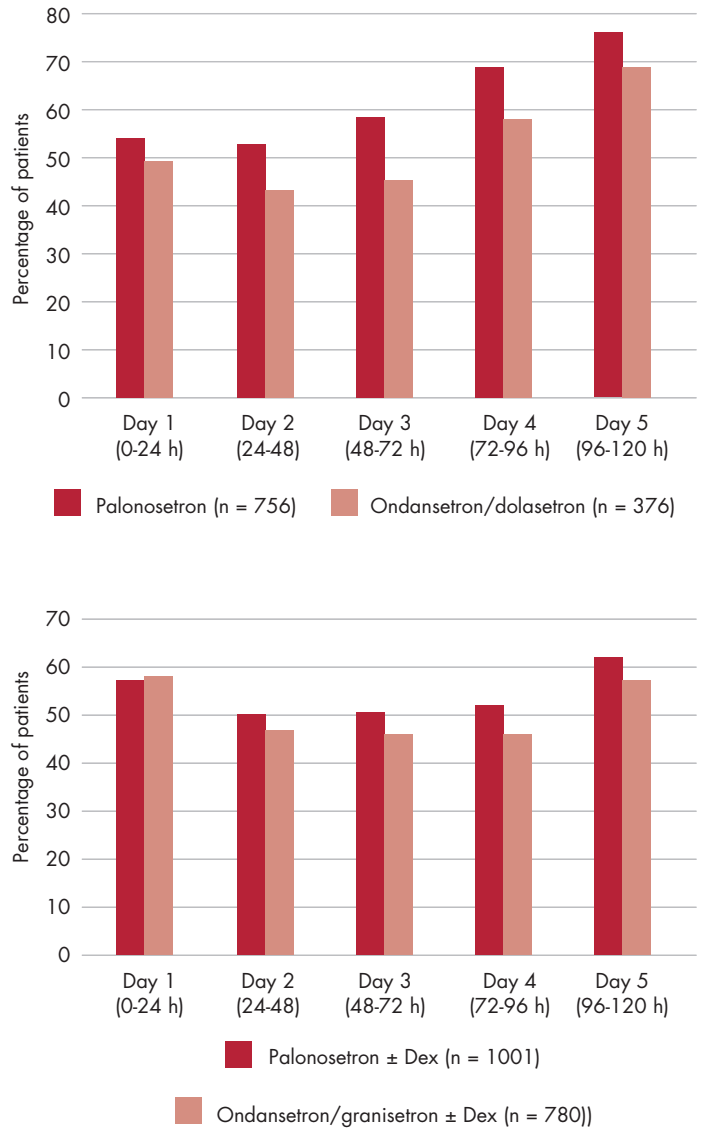

FIGURE 1 Percentage of MEC and HEC recipients who had no nausea on days 1 to 5: pooled data for palonosetron versus older agents.[22-25]

HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy

4: 11% vs 13%; and day 5: 8% vs 7%. In the HEC studies, rates of rescue medication use for palonosetron and other 5-HT_3 RAs were about 17% in each group on day 1; about 21% vs 23% on day 2; about 18% vs 21% on day 3; 18% vs 23% on day 4; and about 15% vs 18% on day 5.

Complete control rates. Overall, for MEC and HEC studies combined, the pooled complete control rates for palonosetron (0.25 mg and 0.75 mg) were higher than the rates for other 5HT_3 RAs in the delayed phase (52% vs 42%; $P < .0001$, respectively) and overall phase (46% vs 37%; $P < .0001$), but not the acute phase (66% vs 63%; $P = .137$.[26] Among patients who received MEC, complete control rates were numerically higher for palonosetron on each of the 5 study days after chemotherapy (Figure 3). The largest differences in complete control rates between palonosetron and the other 5-HT_3 RAs were on day 2 (63.2% vs 50.3%, respectively) and day 3 (70.9% vs 54.3%). Among patients who received HEC, the pooled complete control rates for palonosetron were numerically higher than for other 5HT_3 RAs on day 3 through day 5.

Tolerability and safety

An analysis of pooled safety data from the 4 studies showed no clinically relevant difference in the incidence of AEs between palonosetron and the older 5-HT_3 RAs (Table 2). Most AEs were likely attributable to the patients' cancer and/or the chemotherapy regimens administered. This was presumed because the number of AEs considered to have a definite, probable, possible, or unknown relationship to the study medication was about one-third of the all-cause AE total (across all studies).

In MEC studies, the proportion of patients with a treatment-related AE was 21.4% for palonosetron recipients and 22.8% for those who received older 5-HT_3 RAs. For HEC studies, the percentages were 27.3% and 30.4%, respectively. More than 90% of the AEs reported for each treatment were mild or moderate in intensity (grade 1-2 Common Terminology Criteria for Adverse Events). Across all studies, the most common treatment-related AEs associated with palonosetron and other 5-HT_3 RAs, were headache (8.0% and 7.5%, respectively), constipation (9.3% and 9.3%), dizziness (0.8% and 1.1%), and diarrhea (0.6% and 0.8%).

Although serious AEs (SAEs) were reported for about 3.5% of patients in both groups (palonosetron and older 5-HT_3 RAs), only 2 patients were deemed to have treatment-related SAEs (both in the study by Saito and colleagues[25]). One patient had hepatitis, possibly related to palonosetron; the other had QTc prolongation, possibly related to granisetron. These events were confirmed as "in remission" or "recovering" 8 days after administration of the study drugs. All other SAEs were considered unrelated or unlikely to be related to the study medications.

Discussion

Chemotherapy-induced nausea is more difficult to control than vomiting.1 Nausea that occurs in the delayed (24-120 h) postchemotherapy phase, in particular, may be inadequately controlled by older antiemetic/antinausea medications.[6] Thus, there is concern about the optimal management of nausea after the administration of emetogenic cancer chemotherapy.

The present analysis includes the largest randomized,

TABLE 2 Pooled safety data (safety cohorts)

	Moderately emetogenic chemotherapy[a,22,23]		Highly emetogenic chemotherapy[b,24,25]	
Adverse event (AE)	**PALO 0.25 and 0.75 mg[c] (n = 763)**	**OND 32 mg and DOL 100 mg[c] (n = 381)**	**PALO 0.25 and 0.75 mg (± Dex)[d] (n = 1,007)**	**OND 32 mg and GRAN 40 µg/kg (± Dex)[d] (n = 785)**
At least 1 AE, n (%)	543 (71.2)	269 (70.6)	885 (87.9)	716 (91.2)
Treatment-related[e] AE, n (%)	163 (21.4)	87 (22.8)	275 (27.3)	239 (30.4)
Serious AE, n (%)	27 (3.5)	14 (3.7)	35 (3.5)	28 (3.6)
Treatment-related serious AE, n (%)	0	0	1 (0.1)[f]	1 (0.1)[f]
Withdrew due to treatment-related AE, n (%)	1 (0.1)	0	1 (0.1)	0
Most common treatment-related AEs, n (%)				
Headache	77 (10.1)	42 (11.0)	64 (6.4)	45 (5.7)
Constipation	41 (5.4)	15 (3.9)	124 (12.3)	93 (11.8)
Dizziness	6 (0.8)	10 (2.6)	8 (0.8)	3 (0.4)
Diarrhea	6 (0.8)	4 (1.0)	4 (0.4)	5 (0.6)
Asthenia	5 (0.7)	1 (0.3)	5 (0.5)	2 (0.3)
Fatigue	4 (0.5)	4 (1.0)	0	0
Anxiety	4 (0.5)	0	0	0
Increased ALT (> 1 toxicity grade)	2 (0.3)	1 (0.3)	6 (0.6)	19 (2.4)
Increased AST (> 1 toxicity grade)	3 (0.4)	0	3 (0.3)	15 (1.9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events (National Cancer Institute); Dex, dexamethasone; DOL, dolasetron; GRAN, granisetron; IV, intravenous; OND, ondansetron; PALO, palonosetron

[a,1]Agents associated with a 30%-90% frequency of emesis. [b,1]Agents associated with >90% frequency of emesis. [c]Combined data for the palonosetron 0.25 mg and 0.75 mg arms, and the ondansetron 32 mg and dolasetron 100 mg arms of the MEC studies. [d]Combined data for the palonosetron 0.25 mg and/or 0.75 mg ± dexamethasone arms, and the ondansetron 32 mg ± dexamethasone and granisetron 40 µg/kg + dexamethasone arms of the HEC studies. [e]Adverse events considered to have a definite, probable, possible, or unknown relationship to the study medications. [f]One case of hepatitis with palonosetron and one of QTc prolongation with granisetron was considered possibly related to the study medication.

double-blind comparative clinical trials that have been conducted of palonosetron versus older 5-HT_3 RAs.[22-25] The pooled data indicate palonosetron (0.25 mg or 0.75 mg) is more effective in preventing nausea than ondansetron, dolasetron, or granisetron. The differences in nausea outcomes were most pronounced in the delayed phase (24-120 h) and on study days 2, 3, and 4. This finding was true in patients who received MEC and those receiving HEC. However, as expected, complete control rates and nausea-free rates were lower in the HEC studies (regardless of study medication).

It is likely the pharmacokinetic and pharmacodynamic properties of palonosetron contribute to the apparent improvement over older 5-HT_3 RAs in preventing nausea in the delayed postchemotherapy phase. In addition to a longer elimination half-life (t½) that contributes to a longer duration of action,[12,13] palonosetron has a distinctly different receptor binding profile: it acts as an allosteric antagonist with positive cooperativity to the 5-HT_3 receptor, whereas ondansetron and granisetron exhibit simple bimolecular binding.[11] Thus, palonosetron binds more strongly, is a more efficient receptor antagonist, and is less likely to be displaced by serotonin. Moreover, unlike ondansetron, granisetron, and dolasetron, palonosetron reportedly triggers 5-HT_3 receptor internalization, thereby inducing prolonged inhibition of receptor function.[27]

NK-1–dependent mechanisms reputedly have an important role in the genesis of delayed CINV (through substance P acting centrally at NK-1 receptors), and NK-1 RAs such as aprepitant have inhibited delayed CINV more effectively than have older 5-HT_3 RAs such as ondansetron and granisetron.[28] Evidence suggests that the inhibitory effects of palonosetron on the substance P response can occur in the absence of serotonin, and a synergistic effect of palonosetron and the NK-1 RA netupitant on inhibition of the substance P response.[29] Palonosetron also inhibited cisplatin-induced substance P enhancement (dose dependently) in experimental animals.[15] Because substance P is an

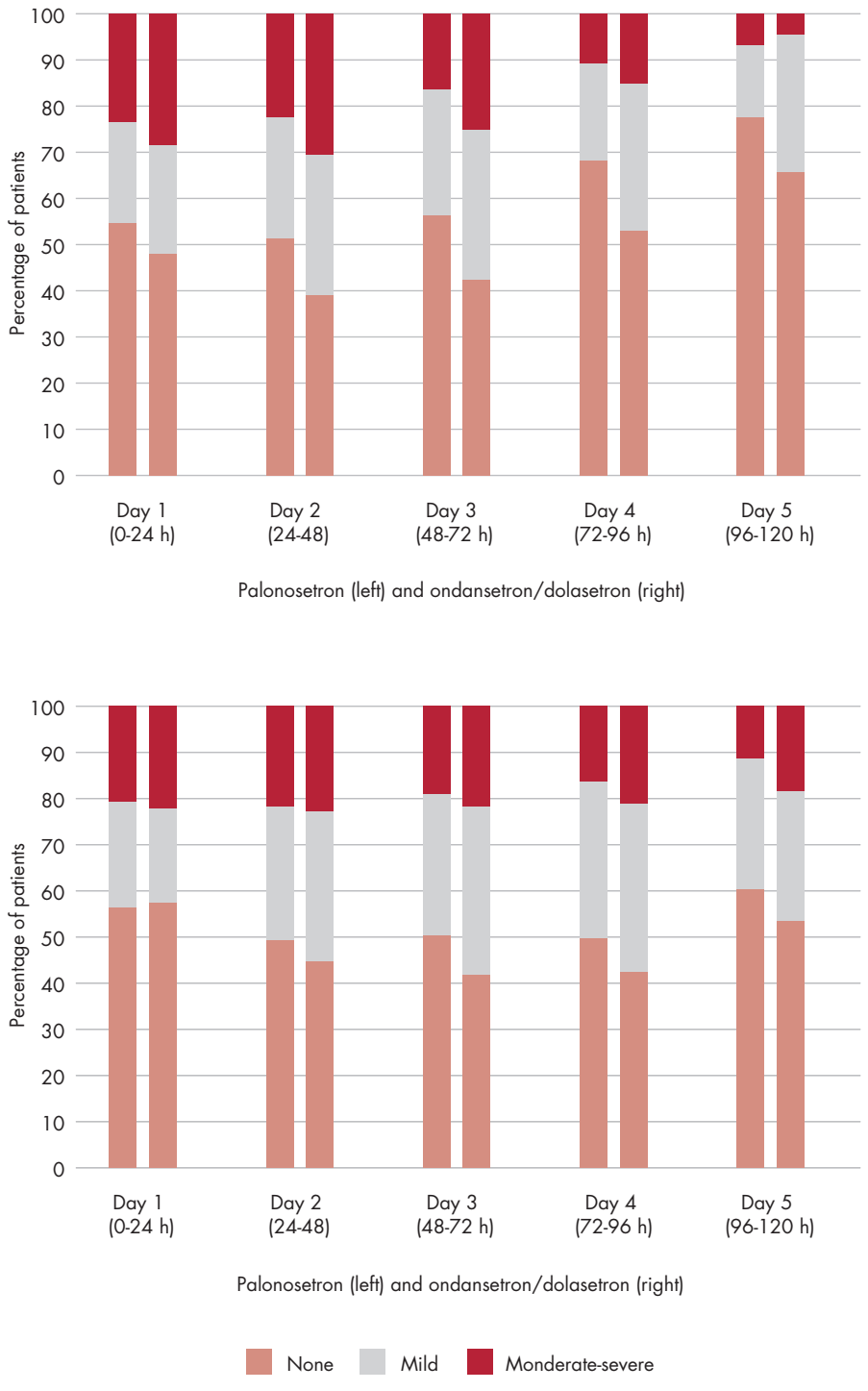

FIGURE 2 Severity of nausea in the MEC and HEC studies on days 1 to 5: pooled data for palonosetron versus older agents.[22-25] The majority of patients in the HEC studies received dexamethasone concomitantly.

HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy

agonist at the NK-1 receptor, this suggests that palonosetron, even though it does not bind to the NK-1 receptor, may have the ability to inhibit cross-talk between 5-HT_3 and NK-1 receptors.[15] These effects, which have not been observed with other 5HT_3 RAs, also help to explain the greater efficacy of palonosetron in preventing delayed nausea.

The findings of the present analysis complement those of an earlier meta-analysis of data from 5 randomized, double-blind trials of palonosetron compared with older 5-HT_3 RAs in 2,057 patients receiving cancer chemotherapy.[20] The studies in the meta-analysis included 3 of the studies analyzed here[22-24] but not the large study by Saito and colleagues[25] and evaluated only the 0.25-mg dose of palonosetron.[20] In that analysis, palonosetron was associated with less nausea than were ondansetron, dolasetron, and granisetron in the acute phase (fixed effect: response rate, 0.86; 95% CI, 0.76-0.96; P = .007) and the delayed phase (fixed effect: RR, 0.82; 95% CI, 0.75-0.89; P < .0001).20 Our analysis differed in that the MEC and HEC data were considered separately. Our results therefore further support the previous findings and also demonstrate that the differences between palonosetron and older 5-HT_3 RAs are less pronounced among patients who receive highly emetogenic regimens.

Safety data from the present analysis also are consistent with those of Botrel and colleagues.[20] Both analyses found that the tolerability profiles of palonosetron and older 5-HT_3 RAs are comparable. There were no clinically relevant differences between palonosetron and the other therapies in the incidence of AEs. Most AEs were attributable to the patients' cancer and/or the chemotherapy regimens, because the percentages of patients with treatment-related AEs were similar. The most frequently reported AEs for all 4 studies were headache, constipation, and dizziness. With respect to laboratory values, vital signs, and ECG findings, there were no pronounced differences between palonosetron and older 5-HT_3 RAs. The studies

analyzed here did not thoroughly evaluate QTc measures; however, recent studies in patients with cancer[17,18] and a thorough QTc study in healthy subjects that used a positive control (ie, moxifloxacin)[16] demonstrated no significant QTc changes associated with palonosetron. This is in contrast to evidence of significant dose-related QTc prolongation with ondansetron, which led to the removal of the 32-mg single dose from its label,[30] and an increased risk of cardiac arrhythmias with IV dolasetron, which is no longer recommended.[1]

This analysis of the efficacy and safety of palonosetron versus older 5-HT_3 RAs (ondansetron, dolasetron, and granisetron) in patients receiving emetogenic cancer chemotherapy suggests that palonosetron may have an advantage in preventing nausea, particularly in the delayed post-chemotherapy phase (24-120 h) and throughout 5 days after chemotherapy administration. In addition, palonosetron was as well tolerated as the older agents. These findings are consistent with and further support various guidelines from the Multinational Association of Supportive Care in Cancer, the European Society of Medical Oncology,[31] the American Society of Clinical Oncology,[32] and the National Comprehensive Cancer Network,[1] which recommend palonosetron as the preferred 5-HT_3 RA for prevention of CINV with MEC,[1,31,32] as the preferred 5-HT_3 RA for AC (doxorubicin and cyclophosphamide) or regimens when an NK-1 RA is not available[31] and as either preferred1 or among other 5-HT_3 RAs[31,32] for HEC.

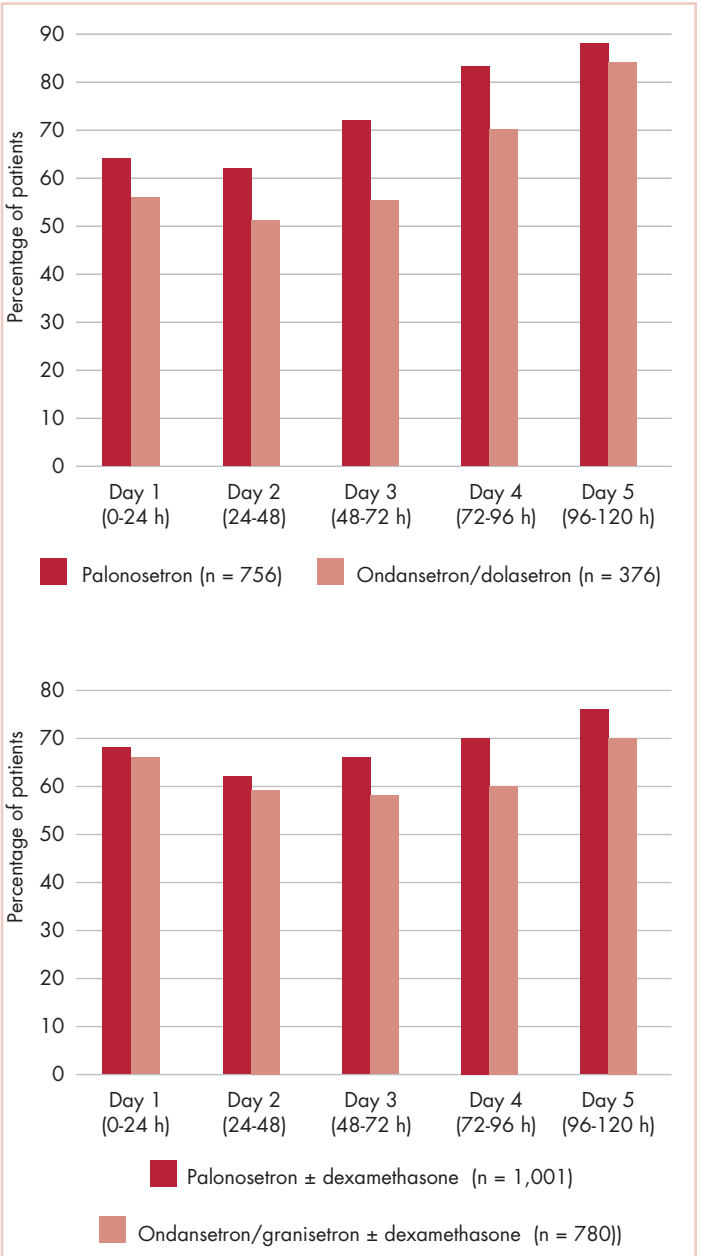

FIGURE 3 Pooled complete control rates for palonosetron versus older agents, by chemotherapy category and time period.[22-25] Complete control = no more than mild nausea, no emetic episodes, and no need for rescue medication.

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