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ORIGINAL ARTICLE

Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer

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Abstract
Goals of work The aims of this study were to assess the safety and antiemetic efficacy of multiple-day dosing of palonosetron plus dexamethasone in patients receiving highly emetogenic multiple-day cisplatin-based chemotherapy for germ cell tumors.
Materials and methods Forty-one men undergoing 5-day cisplatin-based chemotherapy for testicular cancer received palonosetron 0.25 mg IV once daily 30 min before chemotherapy on days 1, 3, and 5 plus IV dexamethasone 20 mg before chemotherapy on days 1 and 2, and 8 mg PO bid on days 6 and 7 and 4 mg bid on day 8. Safety and efficacy were assessed in 24-h intervals for 9 days. Efficacy endpoints included emesis, intensity of nausea and its interference with patient functioning, and rescue antiemetic use. A subset of patients ($n=11$) was studied for electrocardiograph effects and pharmacokinetic evaluation.
Main results This multiple-day antiemetic regimen was safe, with headache and constipation the most common treatment-related adverse events, mostly mild. Neither adverse events nor electrocardiographic changes appeared to increase in frequency, duration, or intensity over time despite a 1.42-fold systemic accumulation of palonosetron with repeated doses. The majority of patients had no emesis at any time throughout days 1–5 (51%) or days 6–9 (83%), had no moderate-to-severe nausea, and did not require rescue medication. Most patients reported that nausea had no significant effect on daily functioning on days 1–4 (72%) and days 5–9 (85%).
Conclusions Palonosetron on days 1, 3, and 5, along with a regimen of dexamethasone, was safe and well tolerated and effectively controlled both nausea and emesis in patients undergoing 5-day cisplatin-based chemotherapy for testicular cancer.

Keywords Palonosetron · Multiple-day · Chemotherapy-induced nausea and vomiting · Cisplatin · Testicular cancer

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Introduction

The introduction of 5-HT_3 receptor antagonists has significantly improved control of chemotherapy-induced nausea

and vomiting (CINV) for patients undergoing treatment for cancer. The 5-HT_3 receptor antagonists provide superior control of emesis and nausea, with fewer side effects compared with metoclopramide [4, 15, 21] or other previously standard regimens [19]. The addition of a corticosteroid, usually dexamethasone, to a 5-HT_3 receptor antagonist further improves control of CINV [17, 19, 23].

Nonetheless, patients continue to rank CINV among the most distressing experiences of cancer treatment [14]; chemotherapy-induced emesis interferes with daily functioning and significantly impairs quality of life [22]. CINV also can cause medical complications, such as dehydration, and may affect a patient's ability to continue with scheduled chemotherapy (CT) cycles [16]. Thus, good control of emesis and reduction in the intensity and duration of nausea are important clinical objectives for the patient and also may help to optimize cancer treatment.

With single-day CT, distinct phases of CINV have been identified: an acute phase, usually beginning immediately after CT administration and resolving within about 24 h and a delayed phase, usually defined as starting 24 or more hours after CT and lasting for up to 120 h or more depending on the CT regimen used [10]. In multiple-day emetogenic regimens, the overlap of acute and delayed CINV confounds antiemetic prophylaxis[1] [5, 10]. In previous clinical trials with short-acting 5-HT_3 receptor antagonists with or without dexamethasone, patients receiving multiple-day cisplatin experienced the highest incidence of nausea and vomiting on days 3 through 5 when the interaction of acute and delayed CINV is at its height [2, 11].

Patients treated with multiple-day CT regimens are at risk for CINV with each day's treatment. Multiple-day dosing with a 5-HT_3 receptor antagonist has been shown to provide reasonable control over CINV in patients receiving 4- or 5-day courses of cisplatin-based CT such as routinely employed in germ cell tumor patients [6]. The addition of a corticosteroid with a 5-HT_3 receptor antagonist provides improved control of acute and delayed CINV compared with 5-HT_3 receptor antagonists alone [11]. It is currently unknown whether daily dexamethasone for five consecutive days of cisplatin provides more harm than benefit due to the potential adverse effects of longer duration dexamethasone [25].

Palonosetron is a unique 5-HT_3 receptor antagonist with a plasma terminal phase elimination half-life of approximately 40 h [24]. In head-to-head studies, a single 0.25-mg IV dose of palonosetron was more effective than single-dose ondansetron[2] or dolasetron[3] for prevention of emesis on days 1 through 5 after moderately emetogenic CT [8, 12]. Palonosetron has been studied against moderately and highly emetogenic single-day CT regimens and is used as a single 0.25-mg IV dose for the prevention of acute and delayed CINV associated with moderately emetogenic CT and acute CINV associated with highly emetogenic CT. Previous studies have shown that a wide range of doses (from 0.3 to 90 μg/kg) of palonosetron were safe and well tolerated in healthy volunteers and cancer patients [1, 3, 8, 9, 12, 24]. Moreover, Hunt et al. [18] have demonstrated that dosing of 0.25 mg IV palonosetron on three consecutive days in healthy subjects was safe and well tolerated, with a predictable accumulation ratio of 2:1 based on the elimination half-life [18].

Given the high receptor binding affinity and prolonged half-life of palonosetron, we hypothesized that alternate-day dosing (days 1, 3, and 5), combined with a standard dexamethasone regimen, during multiple-day cisplatin-based CT would be safe and would effectively mitigate acute and delayed CINV.

Materials and methods

Adult men (aged ≥18 years) with histologically or serologically confirmed testicular cancer and Karnofsy index ≥50% who were scheduled to receive a 5-day cisplatin-based CT regimen (Table 1) were eligible for this phase 2, multicenter open-label study.

Subjects with known mild-to-moderate hepatic (bilirubin <3 mg/dl), renal (serum creatine <3 mg/dl), or cardiovascular disease were enrolled at the discretion of investigators. Prior CT was allowed. Exclusion criteria included use of any investigational drugs within 30 days of study enrollment, use of any drug from any class with potential antiemetic activity within 24 h of study day 1 or during the study, previous treatment with palonosetron, any vomiting or retching or grade 2 to 4 nausea in the 24 h before study day 1, ongoing vomiting of any organic etiology, or receipt of upper abdomen or cranial radiotherapy within 1 week of or during the study. It was anticipated that 40 patients would be enrolled to ensure that 35 patients completed the study per protocol. The protocol was approved by the institutional review board at each of the four participating

[1] Kytril® (2005) (granisetron hydrochloride) Injection. Prescribing information. Roche Laboratories, Inc. Nutley, NJ, USA November 2005.

[2] Zofran® (2006) (ondansetron hydrochloride) Injection. Prescribing information. GlaxoSmithKline, Research Triangle Park, NC, USA. February 2006.

[3] Anzemet® (2006) Injection (dolasetron meselate injection). Prescribing information. Sanofi-Aventis US, L.L.C., Bridgewater, NJ, USA, June 2006.

Table 1 Eligible cisplatin regimens

Regimen	Dosage
EP	Etoposide 100 mg/m^2 days 1–5 and cisplatin 20 mg/m^2 on days 1–5
BEP	Bleomycin 30 U weekly and etoposide 100 mg/m^2, cisplatin 20 mg/m^2, both on days 1–5
VIP	Etoposide 75 mg/m^2, ifosfamide 1.2 g/m^2, cisplatin 20 mg/m^2, all on days 1–5

centers, and all patients provided written informed consent before enrollment in the study.

All patients received the same antiemetic regimen of 0.25 mg IV palonosetron (MGI PHARMA[4], Bloomington, MN, USA) administered as a 30-s infusion 30 min before CT on days 1, 3, and 5 plus dexamethasone 20 mg IV 30 min before CT on days 1 and 2, 8 mg orally bid on days 6 and 7, and 4 mg orally bid on day 8. The choice of rescue medication to treat vomiting or nausea was left to the discretion of the investigator.

Safety and efficacy were assessed over nine 24-h periods, beginning with the initiation of CT (day 1) and ending on study day 10. In a subset of patients (n=11) at one center, 12-lead electrocardiogram (ECG) was performed 20 min before (baseline) and 20 min after administration of palonosetron (days 1 and 5). In the same subset of patients, blood samples for pharmacokinetic (PK) testing were collected 10 min before and 1 to 2 min and again 30 min after palonosetron administration and at the end of the day's CT.

All adverse events, whether or not related to the study drug, were assessed during each CT visit and at all follow-up visits. The safety cohort consists of all patients who received at least one dose of palonosetron and had at least one post-dose safety assessment.

The intent-to-treat (ITT) cohort consists of all patients who received at least one dose of palonosetron and CT. The per-protocol efficacy cohort consists of all patients who received (1) palonosetron on days 1, 3, and 5; (2) the scheduled CT regimen on days 1 through 5; and (3) had efficacy assessments completed for nine 24-h periods.

Efficacy was assessed daily based on the number of emetic episodes (vomiting and retching), use of rescue medication, and intensity and duration of nausea. Complete response was defined as no emetic episodes plus no use of rescue medications for the assessed time period. Nausea intensity (none, mild, moderate, or severe) was rated four times each day at 6-h intervals. The Osoba nausea module, which assesses five patient-rated items using a four-point scale (1 = none, 2 = a little bit, 3 = quite a bit, and 4 = very much), was used to evaluate the effect of nausea on patients' quality of life [20]. The Osoba nausea module questionnaire asks to what extent nausea (1) interferes with appetite, (2) affects sleep, (3) interferes with physical activity, (4) interferes with social life, and (5) interferes with enjoyment of life [20]. Interference with functioning due to nausea was assessed using the Osoba nausea module at three time points during the study: baseline, on day 5 (for the day 1 through day 4 time interval) and on day 10 (covering days 5 through 9).

PK parameters evaluated included maximum plasma concentration (C_{max}), area under the plasma concentration–time curve to last time measured ($AUC_{0\text{-}t}$), time to occurrence of C_{max} (T_{max}), and the accumulation ratio of day 5 to day 1 $AUC_{(0\text{-}t)}$.

Results

A total of 41 patients from four sites in the US were enrolled between April 18, 2005 and January 31, 2006. Patient characteristics are summarized in Table 2. All 41 patients were included in the ITT and safety cohorts. Thirty-nine patients completed the study. One patient withdrew on day 3 due to hospitalization for fluid overload secondary to aggressive hydration and asymptomatic sinus bradycardia for which the patient had a history, and one withdrew on day 4 due to nausea and vomiting. Twenty-eight patients met all requirements for the per-protocol cohort.

Table 2 Summary of patient characteristics

	ITT/safety cohort (n=41)	PK/ECG cohort (n=11)
Age, years (mean±SD)	33.3±10.03	33.6±8.43
Ethnicity, n (% white)	39 (95)	11 (100)
Chemotherapy-naïve, n (%)[a]	35 (85)	9 (82)
Alcohol consumption, n (%)		
No/rarely	22 (54)	5 (45)
Occasionally/regularly	19 (46)	6 (55)
Chemotherapy regimen, n (%)		
BEP	49 (98)	11 (100)
EP	1 (2)	0

BEP Bleomycin/etoposide/cisplatin, *EP* etoposide/cisplatin, *ITT* intent-to-treat, *PK* pharmacokinetics, *ECG* electrocardiogram

[a] A total of six patients received prior chemotherapy for testicular cancer, including one patient with three cycles, two patients with two cycles, and one patient with three previous cycles.

[4] Aloxi® (palonosetron HCl) injection. Prescribing information. Helsinn Birex Pharmaceuticals Ltd., Damastown, Dublin, Republic of Ireland: 2005; MGI PHARMA, INC., Bloomington, MN, USA, January 2006.

Table 3 Summary of efficacy results (ITT population; *N*=41)

Study day	No emesis patients (%)	Max nausea none/mild patients (%)	No rescue patients (%)	CR, % (95% CI)
1	88	85	88	82.9 (67.9, 92.8)
2	88	80	83	75.6 (59.7, 87.6)
3	83	71	68	65.9 (49.4, 79.9)
4	68	59	46	41.5 (26.3, 57.9)
5	71	63	63	56.1 (39.7, 71.5)
1–5	51	34	42	34.1 (20.1, 50.6)
6–9	83	76	63	61.0 (44.5, 75.8)

CR Complete response, *ITT* intent-to-treat

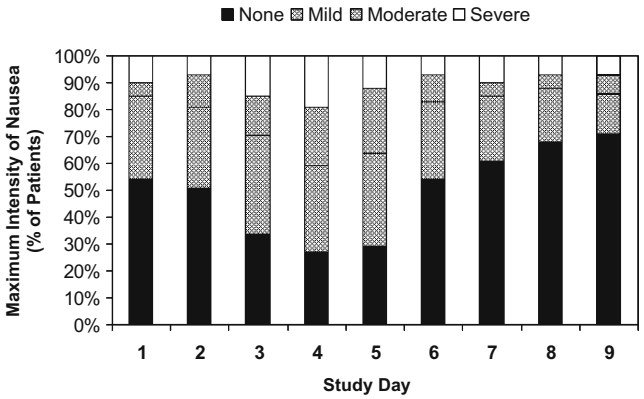

Fig. 2 Maximum intensity of nausea at any time on each study day (ITT population, *N*=41)

Efficacy results

Daily efficacy results for days 1−5 and cumulative results for the 5 days of CT administration (0 to 120 h) and days 6 through 9 (121 to 216 h) are shown in Table 3. Multiple-day dosing of palonosetron plus dexamethasone prevented emesis for most patients each day throughout the study (Fig. 1). Even on days 4 and 5, when a complex overlap of acute and delayed cisplatin-induced emesis was most likely present, 68 and 71% of patients, respectively, reported no emetic episodes.

Palonosetron plus dexamethasone also prevented severe nausea for most patients (Fig. 2), with 59% or more of patients reporting no, or, at maximum, mild nausea at any time on each study day.

The median duration of nausea of any intensity was 16 h over the 216-h study period. The median duration of mild nausea was 11 h; of moderate nausea, 1 h; and severe nausea, 0 h. Patients reported little interference with daily functioning as a result of nausea (Fig. 3) during the first 4 days or during the following five post-chemotherapy days.

More than 60% of patients required no rescue medication on any study day except day 4 (when 46% required no rescue medication). Overall, rescue medication was used on a median of 1 day during the 9-day study.

Complete response (defined as no emesis and no rescue medication) rates are shown in Table 3.

Safety results

The most common (≥10%) treatment-emergent adverse events, regardless of cause, were fatigue, dyspepsia, headache, constipation, nausea, and anxiety. A total of ten patients (24.4%) reported adverse events judged by investigators to be possibly or probably related to palonosetron therapy. The most common such adverse events are listed in Table 4. All events were mild in severity, except for one instance each of headache, constipation, and abdominal pain, which were reported as moderate. Palonosetron-related adverse events did not increase in number, duration, or severity over the study period.

In the subset of patients assessed with ECG, ten patients completed ECGs on days 1 and 5, and one patient had ECGs only on day 5. No clinically significant changes in ECG intervals, rhythms, or patterns were seen, and no patients developed prolongation of QT or QTc. No ventricular arrhythmias or clinically significant abnormali-

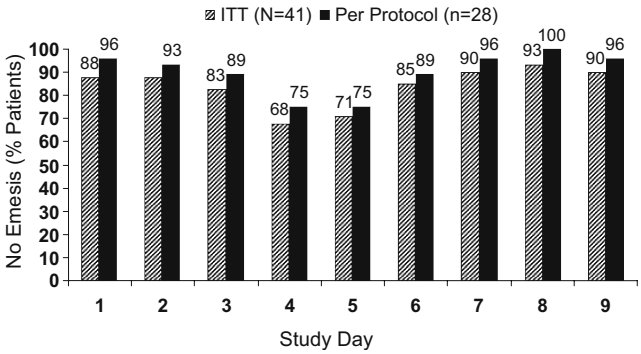

Fig. 1 The proportion of patients with no emetic episodes on study days 1 through 9 in the ITT (*N*=41) and per protocol (*n*=28) populations

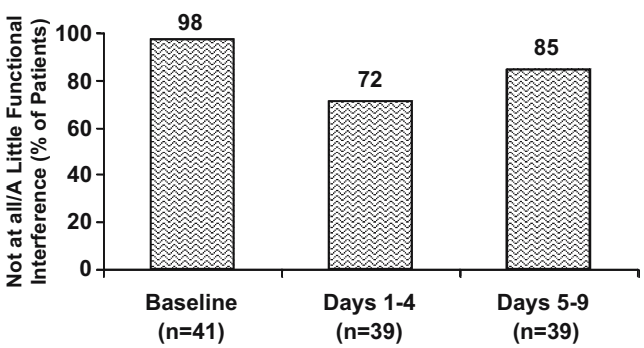

Fig. 3 The proportion of patients reporting no or little interference with functioning attributable to nausea (Osoba nausea module)

Table 4 Incidence of palonosetron-related adverse events (safety cohort; *N*=41)

Adverse event	Patients, *n* (%)[a]
Headache	7 (17.1)
Constipation	4 (9.8)
Abdominal pain	1 (2.4)
Fatigue	1 (2.4)
Asthenia	1 (2.4)

[a] Patients could report more than one adverse event.

ties of axis, chamber enlargement, or conduction were seen. No changes in T waves or significant U waves were seen with treatment. In addition, no cumulative effect on cardiac ventricular repolarization was observed, and ECG intervals did not appear to change with the systemic accumulation of palonosetron.

There were no deaths during the study or within 30 days of the last dose of palonosetron. A total of seven serious adverse events occurred in four patients during the study; none of these were considered related to palonosetron treatment.

Pharmacokinetic results

Mean plasma concentration–time plots after IV administration of palonosetron on days 1, 3, and 5 are shown in Fig. 4. On days 1, 3 and 5, the observed mean C_{max} values were 1.92, 2.50, and 2.58 ng/ml, respectively, with a coefficient of variation (CV) between 57 and 84%. The observed mean T_{max} values were 0.04, 0.08, and 0.06 h after day 1, day 3, and day 5 of IV bolus administration of palonosetron, respectively. Mean $AUC_{(0\text{-}t)}$ values were 1.27, 1.55, and 1.68 $ng{\cdot}h^{-1}\ ml^{-1}$ on day 1, day 3 and day 5, respectively, with CV between 32 and 39%. Comparison of $AUC_{(0\text{-}t)}$ over the same sampling interval of 0 to 2.5 h on day 5 to day 1 resulted in a mean accumulation ratio of 1:42; these results are consistent with the long plasma terminal elimination half-life of palonosetron observed in previous PK studies in healthy subjects and cancer patients. Metabolite M9 concentrations were low and near the lower limit of quantitation; therefore, no M9 PK analysis could be performed.

Discussion

Multiple-day moderately and highly emetogenic chemotherapy regimens often are used for treatment of cancer, and patients treated with these regimens are at high risk for developing CINV with each day of treatment. Antiemetic guidelines from ASCO, MASCC, and NCCN have recommended administration of a 5-HT_3-receptor antagonist before CT on each day of the multiple-day regimens [5, 10, 13]. A standard antiemetic regimen for patients receiving 5-day cisplatin regimens for testicular cancer is a short-acting 5-HT_3 receptor antagonist at least once per day on days 1 through 5 plus dexamethasone on days 1 and 2 and 6 through 8 [7]. Historically, this regimen prevents emesis in up to 95 to 100% of patients on day 1, and about 55 to 58% overall on days 1 through 5 [7]. Nausea is usually minimal on days 1 and 2, most severe on days 4 and 5, and continues through day 8 [7]. Palonosetron, a longer acting 5-HT_3 receptor antagonist with higher $5HT_3$ receptor binding affinity, was approved for the prevention of CINV with a single, weekly IV administration. Therefore, palonosetron generally has not been used in patients who are receiving multiple-day regimens and who may benefit from its less frequent use compared with older 5-HT_3 agents.

This study evaluated the safety and efficacy of a multiple-day regimen of palonosetron plus dexamethasone for control of CINV in men receiving a 5-day cisplatin-based CT

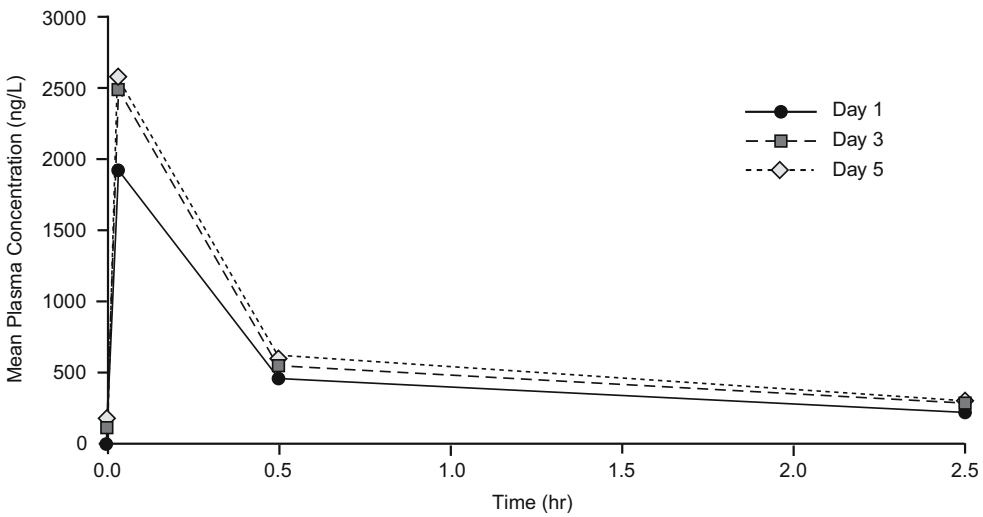

Fig. 4 Mean plasma concentration–time plots after IV administration of palonosetron on days 1, 3, and 5

regimen for treatment of testicular cancer. Because of the longer terminal phase elimination half-life of palonosetron, in the present study, it was administered every other day (days 1, 3, and 5), rather than everyday as has been done in studies with short-acting $5HT_3$ receptor antagonists, such as ondansetron, plus the recommended dexamethasone regimen.

As is observed in general with 5-HT_3 receptor antagonists, the most common adverse events related to multiple-day treatment with palonosetron were headache and constipation. All events in the present study were mild in nature, except for one moderate event each of headache, constipation, and abdominal pain. In this study, the frequency and intensity of these two most common side effects were not quantitatively different from that previously seen for palonosetron or the 5-HT_3 receptor antagonists as a class.

Multiple-day dosing of palonosetron resulted in a 1.42-fold accumulation seen in the day 5 to day 1 $AUC_{(0\text{-}t)}$ ratio, consistent with the approximately 40-h plasma elimination half-life of palonosetron. However, there was no evidence of cumulative toxicity or any increase in the number or intensity of adverse events as a result of systemic accumulation of palonosetron when the drug was given three times over 5 days. There was no evidence of cardiac effects, and there were no new safety findings in this trial, which is consistent with findings from the three pivotal phase 3 trials that included 192 patients with pre-existing cardiac impairment and over 300 patients at least 65 years of age in which one third of patients received palonosetron 0.75 mg (three times the approved dose). Overall, the incidence of treatment-related events was similar to that seen in other trials and in clinical practice.

In terms of efficacy, with multiple-day administration of palonosetron, approximately half of the ITT population of this study had no emetic episodes during CT (days 1–5) or throughout the entire study period (days 1–9). Overall, about one third of patients in the study had a complete response to therapy. Importantly, although the majority of the ITT population reported some nausea during at least one interval in the study, more than two thirds reported little or no functional impact on activities of daily living due to nausea.

Nausea continues to be an area of unmet need in the treatment of these patients and can have significant effects on health-related quality of life and ability to maintain daily activities. In an effort to address this unmet need and assess the study treatment's possible benefits in this area, nausea data collection for this trial was designed to be more rigorous and more frequent than in previous trials reported in the literature [2, 11]. The incidence, duration, and intensity of nausea were recorded by 6-h intervals not only during the 5-day treatment period but also in the 4-day period after completion of CT. A more complete understanding of the time course and intensity of nausea in these patients should allow for modification of antiemetic regimens in future trials.

Most patients experienced at least one episode of nausea during the 216-h study period. Further, the highest incidence, greatest intensity, and longest duration of nausea were reported on days 3 to 5 of this study. Even so, on any given study day, the majority of patients reported having no or mild nausea. For the entire 216-h study period, patients reported having no nausea for a median of 200 h (equivalent to 8.3 of the nine study days) and having mild nausea for a median of 11 h. In addition, most patients reported little or no interference with functioning attributable to nausea in either the interval covering days 1 through 4 (assessed the day immediately after that when the observed nausea control rates were lowest) or between days 5 through 9. This result suggests that nausea episodes did not interfere with patients' social, physical, or other functioning. Considered together with the nausea duration data, the lack of interference with

Table 5 Comparison of efficacy results from published studies with multiple-day dosing of ondansetron or ondansetron plus dexamethasone with efficacy results from the current study of multiple-day palonosetron plus dexamethasone[a]

Antiemetic regimen	Day 1 *n* (%)	Day 2 *n* (%)	Day 3 *n* (%)	Day 4 *n* (%)	Day 5 *n* (%)	Days 1–5 *n* (%)
OND + DEX days 1−5 (*N*=24)[b]	24 (100)	21 (88)	16 (67)	16 (67)	11 (73) (*n*=15)	14 (58)
OND days 1−5 (*N*=22) or OND days 1–5 + DEX days 1–2 + CHLOR days 1−5 (*N*=22)[c]	18 (82) 21 (95)	16 (73) 22 (100)	11 (50) 20 (91)	12 (55) 17 (77)	14 (64) 12 (60)	7 (32) 12 (55)
PALO days 1, 3, 5 + DEX days 1, 2, 6−8 (*N*=41)[d]	36 (88)	36 (88)	34 (83)	28 (68)	29 (71)	21 (51)

bid Two times per day, *CHLOR* chlorpromazine, *CT* chemotherapy, *DEX* dexamethasone, *IV* intravenous, *OND* ondansetron, *PALO* palonosetron, *qd* one time per day, *tid* three times per day

[a] Efficacy results are for percent of patients experiencing no emesis.

[b] Ondansetron 0.3 mg/kg bid days 1–5 + dexamethasone 20 mg qd days 1–5 [4]

[c] Ondansetron 0.15 mg/kg tid days 1–5 OR ondansetron 0.15 mg/kg tid days 1–5 + dexamethasone 8 mg pre-CT/4 mg bid days 1–2 + chlorpromazine 50 mg qid days 1–5 [13]

[d] Palonosetron 0.25 mg qd IV days 1, 3, 5 + dexamethasone 20 mg qd days 1, 2; 8 mg bid days 6, 7; 4 mg bid day 8

functioning suggests that any nausea episodes, including those of moderate and severe nausea, were quite manageable. This interpretation is supported by the finding that more than one third of the study population used no rescue medications at any time during the entire 216-h study period.

Patients receiving a 5-day CT regimen were most affected by CINV on days 4 and 5. This is to be expected because of the potential combination of acute and delayed CINV on these days. On day 4, neither palonosetron nor dexamethasone was given; on day 5, palonosetron alone was administered. Still, a majority of patients had no emesis on these days when treated with the multiple-day palonosetron regimen. Results indicated that at all other 24-h intervals, patients experienced few symptoms and, contrary to the previous observations reported by investigators experienced with this patient population, few patients had significant vomiting or nausea on days 6−9 of this study.

We based our dexamethasone dose and schedule upon the previous experience at Indiana University. We have had concern about utilizing dexamethasone for days 1–5 of cisplatin, and then followed by lower doses on days 6–8 to mitigate cisplatin delayed nausea and vomiting. Other authors have described adverse events with shorter courses of dexamethasone [25]. It remains unknown whether administering dexamethasone on each day of cisplatin treatment might be shown to further reduce CINV on days 4 and 5. In addition, combining palonosetron and dexamethasone with aprepitant or with olanzapine also has yet to be defined, as we strive to improve patient outcomes after multiple-day chemotherapy.

The majority of our patients had not undergone prior chemotherapy treatment. Because of the small number of non-naïve patients, no analysis of their response versus that for the chemotherapy-naïve patients was conducted.

The emesis prevention results with palonosetron plus dexamethasone are comparable to those of published studies evaluating 5-day treatment with ondansetron plus either a day 1 through 5 regimen or a day 1 and day 2 regimen of dexamethasone during multiple-day cisplatin-based therapy (Table 5). Palonosetron administered on days 1, 3, and 5, plus a standard regimen of dexamethasone, was safe and well tolerated in patients with germ cell tumors receiving highly emetogenic multiple-day cisplatin-based CT. This palonosetron antiemetic regimen was effective in preventing both emesis and significant nausea throughout a 9-day study period in the majority of patients. Importantly, interference with patient functioning attributable to nausea was minimal during both intervals assessed in this study. Pharmacokinetic results were similar to values in previous studies with multiple-day dosing of palonosetron in healthy subjects [18] or higher dose (up to 90 μg/kg) single administration in cancer patients [1, 3, 8, 9, 12, 24], suggesting predictable plasma accumulation of drug with multiple doses. Multiple-day dosing of palonosetron plus dexamethasone seems to provide at least comparable overall protection from chemotherapy-induced vomiting and nausea as the current standard 5-day ondansetron-based regimen.

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References

1. Aapro M, Grunberg S, Manikhas G, Olivares G, Suarez T, Tjulandin S, Bertoli L, Yunus F, Morrica B, Lordick F, Macciocchi A (2006) A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol 17:1441–1449
2. Baltzer L, Pisters KMW, Kris MG et al (1993) High-dose ondansetron plus dexamethasone for the prevention of nausea and vomiting with multiple-day cisplatin chemotherapy [abstract]. J Clin Oncol 12:462 (Abstract 1607)
3. Cartmell A, Ferguson S, Yanagihara R et al (2003) Protection against chemotherapy-induced nausea and vomiting (CINV) is maintained over multiple cycles of moderately or highly emetogenic chemotherapy by palonosetron (PALO), a potent 5-HT3 receptor antagonist (RA) [abstract and poster]. Proc Am Soc Clin Oncol 22:756 (Abstract 3041)
4. De Mulder PH, Seynaeve C, Vermorken JB, van Liessum PA, Mols-Jevdevic S, Allman EL, Beranek P, Verweij J (1990) Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. A multicenter, randomized, double-blind, crossover study. Ann Intern Med 113:834–840
5. De Mulder PHM, Roila F, Kris MG, Marty MM (1998) Consensus regarding multiple day and rescue antiemetic therapy. Support Care Cancer 6:248–252
6. Einhorn LH, Nagy C, Werner K, Finn AL (1990) Ondansetron: a new antiemetic for patients receiving cisplatin chemotherapy. J Clin Oncol 8:731–735
7. Einhorn LH, Rapoport B, Koeller J, Grunberg SM, Feyer P, Rittenberg C, Aapro M (2005) Antiemetic therapy for multiple-day chemotherapy and high-dose chemotherapy with stem cell transplant: review and consensus statement. Support Care Cancer 13:112–116
8. Eisenberg P, Figueroa-Vadillo J, Zamora R, Charu V, Hajdenberg J, Cartmell A, Macciocchi A, Grunberg S, 99–04 Palonosetron Study Group (2003) Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT_3 receptor antagonist. Results of a phase III, single-dose trial versus dolasetron. Cancer 98:2473–2482

9. Eisenberg P, MacKintosh FR, Ritch P, Cornett PA, Macciocchi A (2004) Efficacy, safety, and pharmacokinetics of palonosetron in patients receiving highly emetogenic, cisplatin-based chemotherapy: a dose-ranging, clinical study. Ann Oncol 15:330–337
10. Ettinger DS, Bierman PJ, Bradbury B et al for the National Comprehensive Cancer Network (2004) Clinical practice guidelines in oncology: antiemesis. J Natl Compr Canc Netw 2:470–490
11. Fox SM, Einhorn LH, Cox E, Powell N, Abdy A (1993) Ondansetron versus ondansetron, dexamethasone, and chlorpromazine in the prevention of nausea and vomiting associated with multiple-day cisplatin chemotherapy. J Clin Oncol 11:2391–2395
12. Gralla R, Lichinitser M, Van Der Vegt S, Sleeboom H, Mezger J, Peschel C, Tonini G, Labianca R, Macciocchi A, Aapro M (2003) Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 14: 1570–1577
13. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, Clark-Snow R, Gill DP, Groshen S, Grunberg S, Koeller JM, Morrow GR, Perez EA, Silber JH, Pfister DG (1999) Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. J Clin Oncol 17:2971–2994
14. Griffin AM, Butow PN, Coates AS, Childs AM, Ellis PM, Dunn SM, Tattersall MH (1996) On the receiving end V: patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 7:189–195
15. Hainsworth J, Harvey W, Pendergrass K, Kasimis B, Oblon D, Monaghan G, Gandara D, Hesketh P, Khojasteh A, Harker G, York M, Siddiqui T, Finn A (1991) A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. J Clin Oncol 9:721–728
16. Hesketh PJ (2000) Comparative review of 5-HT_3 receptor antagonists in the treatment of acute chemotherapy-induced nausea and vomiting. Cancer Invest 18:163–173
17. Hesketh PJ, Harvey WH, Harker WG, Beck TM, Ryan T, Bricker LJ, Kish JA, Murphy WK, Hainsworth JD, Haley B, Plagge P, Flack NE (1994) A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. J Clin Oncol 12:596–600
18. Hunt TL, Gallagher SC, Cullen MT Jr, Shah AK (2005) Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. J Clin Pharmacol 45:589–596
19. Jantunen IT, Kataja VV, Muhonen TT (1997) An overview of randomized studies comparing 5-HT_3 receptor antagonists to conventional anti-emetics in the prophylaxis of acute chemotherapy-induced vomiting. Eur J Cancer 33:66–74
20. Martin CG, Rubenstein EB, Elting LS, Kim YJ, Osoba D (2003) Measuring chemotherapy-induced nausea and emesis. Cancer 98:645–655
21. Marty M, Pouillart P, Scholl S, Droz JP, Azab M, Brion N, Pujade-Lauraine E, Paule B, Paes D, Bons J (1990) Comparison of the 5-hydroxytryptamine$_3$ (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. N Engl J Med 322:816–821
22. Osoba D, Zee B, Warr D, Kaizer L, Latreille J, Pater J (1996) Quality of life studies in chemotherapy-induced emesis. Oncology 53(Suppl):92–95
23. Roila F, Tonato M, Cognetti F, Cortesi E, Favalli G, Marangolo M, Amadori D, Bella MA, Gramazio V, Donati D, Ballatori E, Del Favero A (1991) Prevention of cisplatin-induced emesis: a double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. J Clin Oncol 9:675–678
24. Stoltz R, Cyong JC, Shah A, Parisi S (2004) Pharmacokinetic and safety evaluation of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in US and Japanese healthy subjects. J Clin Pharmacol 44:520–531
25. Vardy J, Chiew KS, Galica J, Pond GR, Tannock IF (2006) Side effects associated with the use of dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy. Br J Cancer 94:1011–1015