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

R. Gralla1, M. Lichinitser2, S. Van der Vegt3, H. Sleeboom4, J. Mezger5, C. Peschel6, G. Tonini7, R. Labianca8, A. Macciocchi9 & M. Aapro10*

*Correspondence to: Dr M. Aapro, IMO, Clinique de Genolier, 1 Route du Muids, CH-1272 Genolier, Vaud, Switzerland. Tel: +41-22-3669136; Fax: +41-22-3669131; E-mail: aapro@cdg.ch

Received 10 June 2003; revised 17 July 2003; accepted 21 July 2003

Background: Although all first-generation 5-HT3 receptor antagonists demonstrate efficacy in preventing acute chemotherapy-induced nausea and vomiting (CINV), effective prevention of delayed CINV has not yet been achieved. This study compared the efficacy and tolerability of palonosetron, a novel, second-generation 5-HT3 receptor antagonist, with ondansetron.

Patients and methods: In this multicenter, randomized, double-blind, stratified, phase III study, 570 adult cancer patients were randomized to receive a single i.v. dose of palonosetron 0.25 mg, palonosetron 0.75 mg or ondansetron 32 mg, each administered 30 min before initiation of moderately emetogenic chemotherapy. The primary end point was the proportion of patients with no emetic episodes and no rescue medication [complete response (CR)] during the 24 h after chemotherapy administration (acute period). Secondary end points included efficacy in treatment of delayed CINV (≤ 5 days post-chemotherapy) and overall tolerability.

Results: 563 patients were evaluable for efficacy. CR rates were significantly higher (P <0.01) for palonosetron 0.25 mg than ondansetron during the acute (0–24 h) (81.0% versus 68.6%, respectively), delayed (24–120 h) (74.1% versus 55.1%) and overall (0–120 h) (69.3% versus 50.3%) periods. CR rates achieved with palonosetron 0.75 mg were numerically higher but not statistically different from ondansetron during all three time intervals. Both treatments were well tolerated.

Conclusions: A single i.v. dose of palonosetron 0.25 mg was significantly superior to i.v. ondansetron 32 mg in the prevention of acute and delayed CINV.

Key words: chemotherapy-induced nausea and vomiting, emesis, 5-HT3 receptor antagonist, ondansetron, palonosetron

Introduction

Four selective 5-HT3 (serotonin-3) receptor antagonists are available for use in North America and/or Europe for the prevention of acute chemotherapy-induced nausea and vomiting (CINV): dolasetron, ondansetron, granisetron and tropisetron. Although these agents have some pharmacological differences in 5-HT3 receptor binding affinity, selectivity and metabolism, these minor variations have not resulted in clinically meaningful differences in efficacy amongst them. Therefore, according to current evidence-based and consensus guidelines, these 5-HT3 receptor antagonists are equivalent with regard to efficacy and are therapeutically interchangeable when used at equipotent doses [1–4].

All first-generation 5-HT3 receptor antagonists demonstrate considerable efficacy in preventing acute CINV [5], with acute response rates as single agents ranging from 50% to 70% [6]. The effectiveness of the 5-HT3 receptor antagonists as single agents in preventing delayed CINV is less well established, with a proportion of patients who receive these agents continuing to experience nausea and vomiting after receiving moderately or highly emetogenic chemotherapy [7–11]. Therefore, the development of new agents with the potential to more effectively prevent CINV is warranted. Of interest is whether distinct, major pharmacological differences in a 5-HT3 receptor antagonist would produce meaningful improvements over a currently available 5-HT3 receptor
antagonist in controlling CINV in patients receiving emetogenic chemotherapy.

Palonosetron is a highly potent, selective, second-generation 5-HT3 receptor antagonist with a 5-HT3 receptor binding affinity that is ∼100-fold higher than other 5-HT3 receptor antagonists (pKᵢ 10.5 compared with 8.91 for granisetron, 8.81 for tropisetron, 8.39 for ondansetron, 7.6 for dolasetron) [12–14]. Palonosetron also has an extended plasma elimination half-life of ∼40 h [15], significantly longer than others in its class (ondansetron, 4 h [16]; tropisetron, 7.3 h [17]; dolasetron, 7.5 h [18]; granisetron, 8.9 h [19]). A prior dose-ranging phase II trial of palonosetron in patients receiving highly-emetogenic chemotherapy identified 0.25 and 0.75 mg as minimal effective doses for phase III investigation [20]. The current phase III, randomized, double-blind, stratified, non-inferiority study was conducted with the main objective of comparing the efficacy and tolerability of single, fixed, intravenous (i.v.) doses of palonosetron 0.25 and 0.75 mg with a single i.v. dose of ondansetron 32 mg in the prevention of acute and delayed CINV following administration of moderately emetogenic chemotherapy.

Patients and methods

Patient selection

Eligible patients were ≥18 years of age with histologically or cytologically confirmed malignant disease, either chemotherapy naïve or non-naïve (having experienced a maximum of mild nausea previously) and scheduled to receive moderately emetogenic chemotherapy. The inclusion/exclusion criteria can be summarized as follows: patients who were scheduled to receive chemotherapy with any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan or mitoxantrone; methotrexate >250 mg/m²; cyclophosphamide <1500 mg/m²; doxorubicin >25 mg/m²; or cisplatin <50 mg/m² (infused over 1–4 h). Patients with hepatic, renal or cardiovascular impairment were enrolled at the investigator’s discretion. Patients were excluded if they were unable to understand or cooperate with study procedures. Other exclusion criteria were as follows: the taking of any drug with antiemetic activity within 24 h prior to treatment until day 5 (including corticosteroids); evidence of seizure disorder requiring anti-convulsants (unless clinically stable with no seizure activity); vomiting, retching or National Cancer Institute (NCI) Common Toxicity Criteria grade 2 or 3 nausea in the 24 h preceding chemotherapy; or were scheduled for radiation of upper abdomen or cranium on days 2–6.

Study design and treatment regimen

This multicenter, phase III, randomized, controlled, double-blind, non-inferiority study was conducted in 58 European centers (Germany, Italy, UK, The Netherlands and Russia) from 1 August 2000 to 2 October 2001. On day 1, eligible patients were randomized using the TrialLine® interactive voice system to receive a single i.v. dose of palonosetron 0.25 mg, palonosetron 0.75 mg (each palonosetron dose was infused over 30 s) or ondansetron 32 mg infused over 15 min, administered 30 min before the first dose of moderately emetogenic chemotherapy. Patients were stratified at randomization by gender and prior chemotherapy experience. For the study to remain blind, a double-dummy technique was used. No patient received pretreatment with corticosteroids. After the start of chemotherapy, rescue medication was permitted at the investigator’s discretion. The study protocol was approved by the ethics committee at each participating site and the study was conducted according to the Declaration of Helsinki. All patients gave written informed consent.

Efficacy parameters

The primary end point of the study was the proportion of patients achieving a complete response (CR; defined as no emetic episode and no use of rescue medication) during the first 24 h following chemotherapy administration (i.e. efficacy in preventing acute CINV). An emetic episode was defined as one episode of vomiting or a sequence of episodes in very close succession not relieved by a period of relaxation of at least 1 min; any number of unproductive emetic episodes (retches) in any given 5 min period; or an episode of retching lasting <5 min combined with vomiting not relieved by a period of relaxation of at least 1 min. Secondary end points included the following: the proportion of patients achieving a CR during the delayed 24–120-h time period and the cumulative overall 0–120-h time period, as well as CR rates during successive 24-h time periods (i.e. 24–48, 48–72, 72–96, 96–120 h); the proportion of patients achieving complete control (CC; defined as no emetic episode, no need for rescue medication and no more than mild nausea) for the 0–24, 24–120 and 0–120 h intervals; number of emetic episodes daily and cumulatively for the 24–120 and 0–120 h intervals; time to first emetic episode; severity of nausea measured daily for the 0–120 h interval by a four-point Likert scale (used in previous studies to evaluate patient perceptions of cancer treatment-related side-effects) [21–23]; time to administration and need for rescue medication; time to treatment failure (first emetic episode or first need of rescue medication, whichever occurred first); patient global satisfaction with antiemetic therapy, as measured by a visual analog scale (VAS) daily for the 0–120 h interval; and quality of life (QoL), measured via a modified functional living index—emesis (FLIE) questionnaire, which specifically addresses the impact of nausea and emesis on daily functioning, for the first 24 h and the standard FLIE for the 24–96-h interval.

Study visits and evaluation procedures

Consenting patients were initially screened for eligibility within 7 days prior to study commencement. During this time period the following were recorded: physical examination; vital signs and weight; laboratory tests [complete blood count (CBC) with differential, platelet counts, blood chemistry and urine analysis]; past medical history; concomitant medications; and history of nausea and vomiting. Follow-up included clinic visits on day 2 (at 24–30 h post-chemotherapy) and once between days 6 and 8. Follow-up, via the telephone, occurred on days 5 and 15. All subjects were followed for a total of 15 days. Patient diaries were used to record the following: emetic episodes; use of rescue medication, whichever occurred first; patient global satisfaction with antiemetic therapy, as measured by a visual analog scale (VAS) daily for the vomiting; and quality of life (QoL), measured via FLIE questionnaire, which specifically addresses the impact of nausea and emesis on daily functioning, for the first 24 h and the standard FLIE for the 24–96-h interval.

Safety was assessed by the following: adverse event (AE) reporting for a period of 15 days (30 days for serious AEs); vital sign measurements; laboratory tests performed 24 h and 1 week after study drug administration (including hematology, blood chemistry, liver function tests and urine analysis); physical examination; and electrocardiogram (ECG) recordings performed 24 h and 1 week after study drug administration. A subset of patients (total, n = 49; palonosetron 0.25 mg group, n = 20; palonosetron 0.75 mg group, n = 15; ondansetron 32 mg group, n = 14) had an additional ECG evaluation 15 min after study drug administration (around the peak of plasma concentrations), according to study protocol.

Statistical analysis and sample size calculation

The primary efficacy hypothesis of the study was that at least one dose of palonosetron was non-inferior to the ondansetron dose using a maximum of 15% in the CR rate. For a one-sided test of equivalence (α = 0.0125), a sample size of 180 evaluable patients
per group was needed to ensure 80% power for each comparison (overall power = 90%). Assuming a 5% dropout rate, 189 patients per group needed to be enrolled.

To demonstrate the non-inferiority of at least one dose of palonosetron to ondansetron, the lower boundary of the two-sided 97.5% confidence intervals (CI) for the difference (palonosetron minus ondansetron) between the proportion of patients achieving a CR during the first 24 h after chemotherapy administration was calculated and compared with the preset threshold (–15% difference). Subsequent analyses comparing CR rates between each palonosetron dose and ondansetron by means of Fisher’s exact test were also conducted. The χ² test was utilized to analyze CC rates and the proportion of patients receiving rescue medication. Number of emetic episodes, severity of nausea, patient global satisfaction and QoL assessments were compared between treatment groups using the Kruskal–Wallis or Wilcoxon tests. Differences between treatment groups with respect to time to first emetic episode, time to first administration of rescue medication and time to treatment failure were analyzed using Kaplan–Meier estimates and the log-rank test.

Analysis of the primary end point was performed for the intention-to-treat (ITT) cohort (all randomized patients who received chemotherapy and study drug) and the per-protocol (PP) cohort (all patients who completed study day 1 and who were compliant with the study protocol). Results for the ITT cohort analysis were interpreted in a confirmatory manner, whereas results of analyses performed for the PP cohort were only descriptive. All secondary efficacy analyses were performed for the ITT cohort and the results were interpreted in a descriptive manner. The proportion of patients achieving a CR at further time points was examined using the same statistical methods as for the primary efficacy variable. Subgroup analyses were used to identify differences in response based on gender and chemotherapeutic history. The equivalence of the two palonosetron doses with respect to CR was also evaluated (α = 0.05).

Changes in laboratory values with respect to toxicity grades were investigated for each time point within each group using the Wilcoxon signed rank test. All other safety parameters were analyzed descriptively, with ECG data summarized highlighting differences from baseline values for quantitative variables and frequencies of treatment-emergent abnormalities. Shift tables were used to evaluate categorical changes with respect to toxicity grades in hematology and blood chemistry parameters. Changes in laboratory values with respect to NCI-adapted toxicity grades were investigated within each group using the Wilcoxon matched pairs signed rank test. Vital signs and physical examination data were listed and summarized. ECG data were summarized highlighting differences from the baseline values for quantitative variables and the frequencies of treatment-emergent abnormalities. In particular, electrocardiographic intervals QT and QTc mean changes from baseline were calculated at each time point, including the maximum mean change from baseline.

**Results**

**Patient characteristics and baseline demographics**

Demographic data and baseline characteristics for patients in the ITT cohort are presented in Table 1. Of the 570 patients randomized, seven did not receive study medication. Therefore, a total of 563 patients were evaluable for efficacy in the ITT cohort. Of these patients, 562 were evaluable for safety. Five patients withdrew from the study: one in the palonosetron 0.25 mg group (patient’s decision), two in the palonosetron 0.75 mg group (one, patient’s decision; one, non-serious AE), and two in the ondansetron group (one, patient’s decision; one, serious AE). The percentages of patients with protocol violations were similar in the three treatment groups, with the majority of violations (4.7%) in all treatment groups due to the taking of rescue medication before the first emetic episode on study day 1.

The majority (72.1%) of patients evaluated were female, Caucasian (98.9%) and had received chemotherapy previously (58.4%). The most common cancer type was breast cancer (57% of patients), followed by lung (8%), bladder (5%), colon (4%), rectal (3%), small-cell lung (3%) and gastric (3%) cancer. The most common chemotherapeutic agents administered on study day 1 (received by >10% of patients) were cyclophosphamide (63%), doxorubicin (48%), cisplatin (18%), methotrexate (16%) and carboplatin (12%). All three treatment groups were comparable regarding the type and dose of chemotherapy administered. No patient received prophylactic corticosteroids.

**Primary efficacy analysis**

**Complete response: study day 1 (acute CINV).** The proportion of patients in the ITT cohort achieving a CR during the first 24 h after administration of moderately emetogenic chemotherapy is presented in Table 2. Non-inferiority of both doses of palonosetron compared with ondansetron was demonstrated, as the lower bounds of the 97.5% CI of the difference with ondansetron (1.8% and –6.1%, respectively) were greater than the preset threshold of –15% difference. Moreover, palonosetron 0.25 mg was statistically significantly superior to ondansetron in preventing acute emesis (lower bound of the 97.5% CI >0; P = 0.009).

**Secondary efficacy parameters**

**Complete response: study days 2–5 (delayed CINV).** For the delayed (24–120 h) and overall (0–120 h) time periods, the proportion of patients achieving a CR was significantly greater for palonosetron 0.25 mg compared with ondansetron (Table 2). For the daily assessments through study day 4 (96 h), CR rates were significantly higher with palonosetron 0.25 mg than ondansetron. Palonosetron 0.75 mg was as effective as ondansetron at all time points.

**Complete control: study days 1–5 (acute and delayed CINV).** Palonosetron 0.25 mg and 0.75 mg produced significantly higher CC rates compared with ondansetron during the delayed (24–120 h) interval (66.7% versus 50.3%; P = 0.001), and the overall (0–120 h) interval (63.0% versus 44.9%; P = 0.001). Palonosetron 0.25 mg was superior to ondansetron on study days 2 (P = 0.001), 3 (P = 0.001) and 4 (P = 0.003), with palonosetron 0.75 mg superior to ondansetron on study days 3 (P = 0.004) and 4 (P = 0.006). On all other days, both palonosetron doses were as effective as ondansetron.

**Time to treatment failure**

Time to treatment failure was significantly longer following treatment with palonosetron 0.25 mg than treatment with ondansetron (P < 0.001) (Figure 1). Although the median time to treatment failure (time to first emetic episode or first use of rescue medication, whichever occurred first) was >120 h in all treatment groups, the first quartile of palonosetron 0.25 mg showed a time to treatment failure more than twice as long as that observed with ondansetron (46.5 versus 19.5 h, respectively).
Additional secondary end points

Palonosetron 0.25 mg was consistently superior to ondansetron \((P \leq 0.05)\) in the number of emetic episodes [during the acute \((0–24 \text{ h})\), delayed \((24–120 \text{ h})\) and overall \((0–120 \text{ h})\) intervals, as well as on study days 2 and 3], the proportion of patients with no emetic episodes (study days 1–3 and delayed and overall intervals) (Figure 2) and the proportion of nausea-free patients (study days 3–5). For these same end points, palonosetron 0.75 mg was superior to ondansetron on study day 3, delayed and overall intervals (% no emesis), and study days 4–5 (% no nausea). Only a few patients required rescue medication during the delayed \((24–120 \text{ h})\) period (palonosetron 0.25 mg, 15.9%; palonosetron 0.75 mg, 22.8%; ondansetron, 24.3%) and during the overall \((0–120 \text{ h})\) period (18.5%, 23.8% and 27.0%, respectively) \((P \geq 0.05\) for each study day and during the cumulative delayed and overall study periods), with metoclopramide used most frequently.

A subset analysis by gender showed a trend in males for higher CR rates, higher CC rates, less severe nausea, longer time to treatment failure, longer time to first emetic episode and less rescue medication compared with female patients. A subset analysis by chemotherapeutic history showed that chemotherapy-naïve patients tended to have less severe nausea than non-naïve patients.

Adverse events

A total of 562 patients were evaluable for safety. Of the patients in the palonosetron 0.25 mg, palonosetron 0.75 mg and ondansetron groups, 114 (61.0%), 125 (66.5%) and 120 (64.2%) experienced at least one AE. Most AEs were mild in intensity, with the majority (84%) assessed as associated with the patient’s cancer and/or chemotherapy treatment and not related, or unlikely to be related, to study medication. Post hoc analysis revealed no differences in the duration of AEs commonly associated with 5-HT\(_3\) receptor antagonist therapy (i.e. headache, constipation, diarrhea, fatigue) in patients treated with palonosetron compared with ondansetron.

Table 3 provides a list of treatment-emergent, drug-related AEs. Adverse reactions (i.e. AEs considered to be treatment related) occurred in 16% of patients in each of the palonosetron groups and in 13.9% of patients in the ondansetron group. The most common
adverse reaction reported in all treatment groups was headache (palonosetron 0.25 mg, 4.8%; palonosetron 0.75 mg, 5.3%; ondansetron, 5.3%). There were two withdrawals during the study due to AEs, one non-serious AE (debility) assessed as possibly related to study medication in the palonosetron 0.75 mg group, and one serious AE (pulmonary embolism resulting in death) assessed as not related to study medication in the ondansetron group. Three other deaths were reported during the study; all were assessed as unlikely to be related to, or as definitely unrelated to, study medication.

Fifteen patients (five per treatment group) experienced serious AEs; all were assessed by the investigators as not related to, or unlikely to be related to, study medication. No significant changes related to study drug were observed with respect to laboratory
parameters, vital sign measurements and ECG recordings, with no pronounced differences in these parameters observed between treatment groups. The mean post-dose change from baseline in QTc (Fridericia correction) was 1 ms for palonosetron 0.25 mg, 2 ms for palonosetron 0.75 mg and 5 ms for ondansetron. Overall, no significant safety concerns were raised in this study.

Discussion

Conventional thinking regarding the activity of the available 5HT3 receptor antagonists is that they are all similar. The results of this study suggest that palonosetron’s major pharmacological differences may translate into improved control of CINV in patients receiving moderately emetogenic chemotherapy. In this study, a single i.v. dose of palonosetron was superior to ondansetron in preventing acute CINV, as indicated by the CR rates and a number of secondary efficacy assessments within the 24 h following chemotherapy administration. This advantage was observed comparing palonosetron to the highest recommended i.v. dose of ondansetron. CR rates observed in this study for ondansetron were similar to those reported previously, with earlier studies reporting CR rates ranging from 69% to 73% for acute emesis (following a single dose) and 45% for delayed emesis (following multiple doses) [24, 25]. The consistency of these CR rates with those reported in the current study (69% for acute emesis, 50% for delayed emesis) highlights the validity of the current study.

Because the study drug was administered only on study day 1 as a single i.v. dose, we were able to explore the rate of delayed CINV and determine the efficacy of palonosetron in preventing CINV during the 24–120-h period following administration of moderately emetogenic chemotherapy. Our results showed the superiority of palonosetron over ondansetron in preventing delayed CINV, as measured by CR and CC rates, as well as with respect to number of emetic episodes, per cent of patients with no nausea and time to treatment failure. It should be noted that both chemotherapy-naive and non-naive patients were included in this study to provide a more realistic, heterogeneous patient group, similar to that seen in the clinical setting.

Superiority of palonosetron in the prevention of delayed CINV has also been demonstrated in a similarly designed phase III trial of palonosetron and dolasetron in patients receiving moderately emetogenic chemotherapy [26]. The observed sustained efficacy of a single dose of palonosetron in preventing delayed emesis is a clinically important finding, as currently available 5-HT3 receptor antagonists do not demonstrate substantial efficacy in delayed emesis, despite repeated dosing [9, 10, 27] and concomitant use with corticosteroids [3]. The prolonged antiemetic efficacy of palonosetron is possibly related to its high 5-HT3 receptor binding affinity and long plasma elimination half-life of approximately 40 h.

All treatments were well tolerated, with no significant differences between groups. Most AEs (including serious AEs) were assessed as unlikely to be related to study medication, but rather to the patient’s underlying cancer or chemotherapeutic treatment. Consistent with previous studies of 5-HT3 receptor antagonists, headache was the most frequently reported drug-related AE (i.e. adverse reaction) in all treatment groups [4, 28–30]. There were no significant treatment-related changes in laboratory measures, vital signs or ECG. No safety concerns were raised in this study.

Doses of palonosetron chosen for investigation in this study were based on a phase II dose-finding study, which revealed palonosetron 3.0 µg/kg (fixed dose of ~0.25 mg) as the minimum effective dose for preventing CINV after administration of highly emetogenic chemotherapy, with doses up to 90 µg/kg (fixed dose of ~6.0 mg) also safe and effective [20]. Findings from this phase II study supported the selection of 3.0 µg/kg and 10 µg/kg doses (corresponding to fixed doses of ~0.25 mg and ~0.75 mg, respectively) for use in the current phase III study. Our results show that palonosetron 0.25 and 0.75 mg are similar in overall efficacy, suggesting that the 0.25 mg dose can be found on the plateau of the efficacy dose–response curve. The statistically non-significant difference in efficacy between palonosetron 0.25 mg and 0.75 mg is not unlike the results observed with other 5-HT3 receptor antagonists, such as dolasetron [28].

Our results demonstrate that a single i.v. dose of palonosetron results in prolonged protection against nausea and emesis following moderately emetogenic chemotherapy. Palonosetron is superior to ondansetron in preventing both acute and delayed CINV. Thus, palonosetron, a novel second-generation 5-HT3 receptor antagonist, would be a significant and important addition to antiemetic therapy.

Acknowledgements

This study was sponsored by Helsinn Healthcare SA, Lugano, Switzerland.

The following 99-03 Palonosetron Study Group investigators included patients in this study. Our sincere thanks go to the patients and the team that took care of them: G. Adam, Asklepios

---

Table 3. Treatment-related adverse events* reported by >2% of patients (safety cohort, n = 562)

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>PAL 0.25 mg (n = 187)</th>
<th>PAL 0.75 mg (n = 188)</th>
<th>OND 32 mg (n = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>4.8</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>1.6</td>
<td>6</td>
</tr>
</tbody>
</table>

*Adverse events judged by the investigator to have a definite, possible, probable or unknown relationship to study medication.

PAL, palonosetron; OND, ondansetron.
References


13. Wong EH, Clark R, Leung E et al. The interaction of RS 25259-197, a potent and selective antagonist at 5-HT 3 receptors, with ondansetron, ondansetron hydrochloride injection (ondansetron hydrochloride injection) pre-