Palonosetron Hydrochloride in the Treatment of Chemotherapy-Induced Nausea and Vomiting

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) is among the most unpleasant and stressful aspects of chemotherapy. Poorly controlled nausea and vomiting may have negative impacts on clinical treatment and quality of life. Clinical trials aimed at the prevention of CINV have focused on both acute and delayed phases of CINV. The use of first generation serotonin subtype 3 serotonin (5-HT$_3$) receptor antagonists has significantly improved symptom control in acute CINV. However, they are less effective in controlling delayed CINV. Palonosetron is a second generation 5-HT$_3$ receptor antagonist with high potency, selectivity, prolonged half-life, and a unique allosteric binding mechanism. Previous trials which compared palonosetron to other first generation 5-HT$_3$ antagonists had used the prevention of delayed CINV as a secondary end point. Recent data have demonstrated palonosetron, when used with a corticosteroid, was superior to granisetron in the prevention of delayed CINV as a primary end point. This article will review recently published literature focusing on mechanism of action, metabolism, pharmacokinetics, clinical efficacy, and safety of palonosetron in the treatment of CINV, specifically delayed CINV.

Keywords: palonosetron, chemotherapy-induced nausea and vomiting, 5-HT$_3$ receptor antagonist

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Introduction
Chemotherapy-induced nausea and vomiting (CINV) can be a significant problem for cancer patients. Patients have consistently reported that nausea and vomiting are among the most unpleasant and stressful aspects of chemotherapy.\textsuperscript{1,2} More than eighty percent of all cancer patients will experience some degree of CINV if they receive no or an inadequate prophylactic antiemetic regimen.\textsuperscript{1,3–6} In addition, 10\%–44\% of cancer patients will experience anticipatory nausea and vomiting, which can be secondary to inadequate antiemetic control during previous chemotherapy administration.\textsuperscript{1,5} Consequences of poorly controlled nausea and vomiting include negative impact on quality of life (physical and cognitive), electrolyte abnormalities, dehydration, anxiety, increase in costs (longer hospital stays, extra hospital stays, addition of medications), and patients delaying or refusing further treatment.\textsuperscript{7–13}

Prevention studies for CINV have demonstrated a model consisting of 3 general time periods of chemotherapy-induced nausea and vomiting: acute, delayed, and anticipatory.\textsuperscript{1,14–16} Acute CINV is defined as nausea and vomiting occurring within the first 24 hours after chemotherapy administration.\textsuperscript{1,16} Delayed CINV is defined as nausea and vomiting starting after 24 hours of chemotherapy administration and continuing up to 5 days typically caused by doxorubicin, cyclophosphamide, cisplatin, carboplatin, and ifosfamide.\textsuperscript{1,16} The acute and delayed phases of CINV may overlap; therefore, “overall response” (0–120 hours) may be a more useful endpoint for future studies. Anticipatory nausea and vomiting occurs prior to chemotherapy administration and is associated with age <50, treatment greater than 6 months, highly emetogenic chemotherapy (HEC), history of anxiety, depressive disorders, and poor antiemetic control with prior therapy.\textsuperscript{1,17} As prevention strategies have improved in recent years, the incidence of anticipatory nausea and vomiting has declined. Acute, delayed, and anticipatory CINV can be prevented in the majority of patients who receive an appropriate prophylactic antiemetic regimen.

The severity and incidence of CINV is largely influenced by the emetogenicity of the chemotherapy agent;\textsuperscript{1,18,19} patient risk factors (Table 1);\textsuperscript{1,15} co-existing conditions such as constipation, hepatic metastasis, bowel obstruction, increased intracranial pressure, acute and chronic pain, fluid and electrolyte abnormalities; co-administered medications such as opioids, antibiotics, and digoxin; and psychophysiologic issues.\textsuperscript{20} Emetogenicity of a chemotherapy agent is based upon the dose, route, and schedule; however co-administration of chemotherapy agents and duration of treatment increases the potential of CINV.\textsuperscript{1,18,19} The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the Multinational Association of Supportive Care in Cancer (MASCC) have defined 4 categories of emetic risk of chemotherapy agents: minimal (<10\% of patients will experience CINV without prophylaxis), low (10\%–30\% of patients will experience CINV without prophylaxis), moderate (30\%–90\% of patients with experience CINV without prophylaxis), and high (>90\% of patients will experience CINV without prophylaxis). Based on these categories, guidelines for the prevention of acute and delayed CINV have been developed by ASCO, NCCN, and MASCC.\textsuperscript{16,21,22} A prophylactic 3-drug regimen consisting of dexamethasone, a 5-HT\textsubscript{3} receptor antagonist, and aprepitant/fosaprepitant is recommended for the prevention of acute CINV associated with HEC.\textsuperscript{16,21,22} A prophylactic 2-drug regimen consisting of dexamethasone and a 5-HT\textsubscript{3} receptor antagonist is recommended for the prevention of delayed CINV associated with HEC, aprepitant should continue on days 2 and 3, and dexamethasone on days 2, 3 and 4.\textsuperscript{16,21,22} For the prevention of delayed CINV associated with MEC, dexamethasone remains the

<table>
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<th>Table 1. Patient risk factors of CINV.\textsuperscript{1,13}</th>
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<td>Prior treatment, especially if poorly controlled</td>
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<td>Age (children &gt; adults)</td>
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<td>&lt;100 grams of alcohol per day</td>
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cornerstone of treatment, although guidelines vary regarding the addition or substitution of aprepitant and 5-HT₃ receptor antagonists.¹⁶,²¹,²²

There are various pharmacotherapy options available; however, steroids and 5-HT₃ receptor antagonists are the most widely used options for the prevention of CINV based on clinical efficacy and the practice guidelines.¹⁶,²¹,²³⁻³⁰ First generation 5-HT₃ receptor antagonists (ondansetron, granisetron, dolasetron and tropisetron) were first introduced in the 1990s and improved the management of acute CINV due to MEC and HEC. Various studies have shown that a 5-HT₃ receptor antagonist in combination with dexamethasone and aprepitant prevent acute CINV in 60%–80% of patients receiving HEC and a 5-HT₃ receptor antagonist plus dexamethasone prevent acute CINV in 70%–85% of patients receiving MEC.¹⁴,³⁰⁻³³ First generation 5-HT₃ receptor antagonists are less effective for the prevention of delayed CINV,²⁸,³⁴⁻³⁷ for which corticosteroids alone (low risk emetogenic agent) or in combination with other agents (moderate to high risk) are recommended.²¹,²² A meta-analysis in 2005 demonstrated that neither clinical evidence nor considerations of cost-effectiveness justify using the first generation 5-HT₃ receptor antagonist for the prevention of delayed CINV.³⁶

Palonosetron (Aloxi®) is a second generation 5-HT₃ receptor antagonist that was approved by the FDA in 2003 for the prevention of acute CINV for MEC and HEC and the prevention of delayed CINV for MEC.³⁸⁻⁴² Even though previous studies have shown that all 5-HT₃ receptor antagonists are equally effective and safe for the prevention of acute CINV for chemotherapy regimens, NCCN recently updated its practice guidelines by listing palonosetron as the “preferred” 5-HT₃ receptor antagonist for the prevention of CINV associated with HEC.⁴³ For the first time, in comparison to a first generation 5-HT₃ receptor antagonist, palonosetron has demonstrated efficacy in the prevention of delayed CINV associated with HEC.⁴⁴ The use of palonosetron for the prevention of CINV in multi-day chemotherapy regimen is still an issue of debate.

Chemistry, Mechanism of Action, and Pharmacokinetic Profile

Chemistry

Palonosetron hydrochloride is an isoquinoline hydrochloride with an empirical formula of C₁₉H₂₄N₂O•HCL and a molecular weight of 332.87. Palonosetron has a significantly different chemical structure compared to the first generation 5-HT₃ receptor antagonists. Palonosetron is based on a fused tricyclic ring system attached to a quinuclidine moiety, where as the first generation 5-HT₃ receptor antagonists are based on a 3-substituted indole structure that resembles serotonin. Palonosetron exists as a single isomer. Its structural formula is shown in Figure 1. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol. Palonosetron injection is a sterile, clear, colorless, non pyrogenic, isotonic, buffered solution for intravenous administration.⁴²

Mechanism of action

Palonosetron is a highly selective, competitive, high-affinity 5-HT₃ receptor antagonist.⁴⁵ It has

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![Figure 1. Structures of 5-HT₃ antagonists.⁴⁶](image-url)
little or no affinity for other receptors. In addition, palonosetron lacks activity at several ion channels. Palonosetron has demonstrated a binding affinity at 30-fold greater than other 5-HT₃ receptor antagonists; palonosetron (pKi > 10), ondansetron (pKi = 8.39), granisetron (pKi = 8.91), and dolasetron (pKi = 7.60). 5-HT₃ receptors are located on the nerve terminals of the vagus in periphery and centrally in the chemoreceptor zone of the area postrema. There are two proposed mechanisms by which chemotherapy produces nausea and vomiting: 1) through the release of serotonin from the enterochromaffin cells of the small intestine thereby activating 5-HT₃ receptors located on vagal afferents which initiate the vomiting reflex and 2) acting directly upon the 5-HT₃ receptors located in the chemoreceptor trigger zone to initiate the vomiting reflex. Oral and intravenous palonosetron produces dose-dependent inhibition of emetic episodes induced by cisplatin, dacarbazine, dactinomycin, and chlorambucil in animal models, with a potency of 2–93 times higher than that of ondansetron and granisetron. The duration of antiemetic effect of palonosetron (30 µg/kg orally) was 7 hours compared with 4 hours for that of an equieffective dose of ondansetron (300 µg/kg orally) against cisplatin-induced nausea and vomiting.

Recent data has shown that palonosetron exhibits molecular interactions with the 5-HT₃ receptor different from that of other 5-HT₃ receptor antagonists. Diagnostic tests performed by Rojas and colleagues demonstrated that palonosetron acts as an allosteric antagonist with positive cooperativity with 5-HT₃ receptors, causing receptor alteration or internalization resulting in a long-lived inhibition of receptor function. The prolonged inhibition of serotonin-induced calcium-ion reflux also indicates that palonosetron triggers functional effects that persist beyond its immediate binding to 5-HT₃ receptors.

Pharmacokinetic profile

The pharmacokinetic properties of palonosetron have been evaluated in several studies with healthy volunteers and a dose-ranging study in cancer patients.

Absorption and distribution

After intravenous dosing of palonosetron in healthy subjects and cancer patients, an initial decline in plasma concentration is followed by a slow elimination from the body. Mean maximum plasma concentration (0.89 to 336 ng/ml) and area under the concentration-time curve (13.8 to 957 ng•h/ml) are generally dose-proportional over the dose range of 0.3–90 µg/kg in healthy subjects and in cancer patients. Palonosetron is extensively distributed to tissues and is moderately bound to plasma proteins (62%) with a volume of distribution of approximately 8.3 L/kg after administration of a single intravenous dose of 10 µg/kg. Area under the plasma concentration-time curve and volume of distribution were similar with a 15-minute compared to a 30-second infusion. This allows flexibility within outpatient infusion clinics; may be given alone as a 30-second infusion thus reducing nursing administration time, or mixed with dexamethasone in the same bag, thereby decreasing the number of items to be compounded and administered separately.

Metabolism and elimination

Approximately 50% of palonosetron is metabolized in the liver through multiple routes to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. Each of these metabolites has less than 1% of the 5-HT₃ receptor antagonist activity of palonosetron. In vitro studies have shown that palonosetron is metabolized primarily by cytochrome P450 (CYP) 2D6 and to a lesser extent by CYP3A4 and CYP1A2. Clinical pharmacokinetic parameters are not significantly different between poor and extensive CYP2D6 metabolizers. In vitro studies have also shown that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1 or CYP3A4/5, nor did it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Stoltz and colleagues demonstrated that the metabolites are not β-glucuronide or sulfate conjugates of the parent drug. The potential drug interactions with palonosetron appear to be low. Controlled clinical trials have demonstrated that palonosetron can safely be administered with corticosteroids (dexamethasone), analgesics, antiemetics (aprepitant, metoclopramide), antispasmodics and anticholinergic agents. Palonosetron did not inhibit the antitumor activity of five chemotherapy agents (cisplatin, cyclophosphamide, cytarabine, doxorubicin, and mitomycin C) in murine tumor models.
After a single intravenous dose of 10 µg/kg palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with 40% as unchanged drug. Total body clearance is 160 ml/h/kg with a renal clearance of 66.5 ml/h/kg, representing 42% of total clearance, indicating a major contribution of the kidney to the clearance of palonosetron. The mean body clearance was approximately 12% of hepatic blood flow, consistent with very low hepatic extraction and elimination. Slow elimination of palonosetron from the body results in a long terminal elimination half-life of approximately 40 hours.

Special populations
Pharmacokinetic profiles between males and females are similar. Population pharmacokinetic analysis did not reveal any differences in palonosetron pharmacokinetics between cancer patients ≥65 years of age compared to younger patients. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by 28% in severe renal impairment relative to healthy patients; however dosage adjustment is not necessary with any degree of renal impairment. Hepatic impairment does not significantly affect total body clearance, therefore dosage adjustment is not recommended.

The pharmacokinetic profile in Japanese patients has shown to be different compared to US patients. Stoltz and colleagues compared the two populations by collecting data from 2 different pharmacokinetic analyses: 1) U.S. patients receiving a 5-minute infusion of palonosetron and 2) Japanese patients receiving IV bolus palonosetron. The study showed higher maximal concentration and greater intersubject variability in the Japanese versus U.S. patients, which may be due to differences in drug delivery methods. The study also showed a 25% increase in total body clearance in Japanese compared to US, which is not clinically significant; therefore dose adjustment is not required.

Clinical studies
Earlier studies
Phase I and II studies demonstrated significant antiemetic properties of palonosetron and identified 3 µg/kg or 10 µg/kg (approximately a fixed dose of 0.25 mg or 0.75 mg) as effective doses to prevent CINV during the acute phase. The clinical efficacy of palonosetron was subsequently compared with that of the first generation 5-HT₃ antagonists in three large randomized trials. All three trials utilized an identical non-inferiority design, with the primary endpoint of a complete response rate (CR; defined as no emetic episode and no use of rescue medication) during the first 24 hours post chemotherapy. A number of secondary endpoints, including complete response during the delayed phase, were also evaluated. Analysis was performed for the intention-to-treat cohort.

Two Phase III trials evaluated the efficacy of palonosetron to prevent CINV secondary to MEC. In these randomized, multicenter, double-blind trials (N = 570 and N = 592, respectively), a single dose of intravenous palonosetron (0.25 mg or 0.75 mg) was compared with a single dose of intravenous ondansetron 32 mg or dolasetron 100 mg prior to MEC. Chemotherapy naive or non-naive patients who experienced previous mild nausea were eligible. Most patients did not receive concomitant corticosteroids as pretreatment. During the acute phase, patients receiving palonosetron 0.25 mg had a significantly higher CR rate than those who received ondansetron (81% vs. 69% P < 0.05), and similar to those who received dolasetron (63% vs. 52.9%). During the delayed phase (24–120 hours), the proportion of patients with a CR was significantly higher for palonosetron compare with ondansetron (74% vs. 55.1%, P < 0.05) and dolasetron (54% vs. 38.7%, P = 0.004). Palonosetron 0.25 mg and 0.75 mg were equivalent for all efficacy assessment, suggesting that 0.25 mg may be on the plateau of the efficacy dose-response curve. All treatments were well tolerated without significant differences in toxicities among groups. The results supported the hypothesis that palonosetron is at least effective as the first generation 5-HT₃ receptor antagonists for the prevention of acute CINV. Importantly, these trials provided preliminary evidence that palonosetron is possibly a better agent than its comparators to prevent delayed CINV.

A third phase III, multinational, randomized, double-blind trial (N = 667) evaluated the efficacy of palonosetron to prevent CINV secondary to HEC, including cisplatin ≥60 mg/m² or
cyclophosphamide > 1500 mg/m² and dacarbazine. Each patient was randomized to receive either a single dose of intravenous palonosetron (0.25 mg or 0.75 mg) or a single intravenous ondansetron 32 mg prior to chemotherapy. Two thirds of patients received a concomitant single dose of prophylactic dexamethasone 20 mg. CR rates during the acute and delayed phases were similar between palonosetron 0.25 mg and ondansetron (59.2% vs. 57.0%; 40.8% vs. 33.0%). However, patients pre-treated with a combination of palonosetron and dexamethasone had a significantly high CR rate than those who received ondansetron plus dexamethasone during the delayed phase (42.0% vs. 28.6%, P < 0.05). The authors concluded that palonosetron was as effective as ondansetron in preventing acute CINV following HEC. In the subgroup analysis, the effectiveness of palonosetron in combination with dexamethasone was significantly increased over ondansetron throughout the 5-day post-chemotherapy period.

Based on the results of above trials, intravenous palonosetron 0.25 mg was approved by the FDA in 2003 for the prevention of acute nausea and vomiting associated with initial and repeat courses of MEC and HEC, as well as the prevention of delayed nausea and vomiting associated with MEC.

However, the efficacy of palonosetron during the delayed phase of CINV in all three clinical trials has been questioned for the following reasons. First, dexamethasone is recommended by NCCN, ASCO and MASCC as part of the standard regimen to prevent acute and delayed CINV associated with MEC and HEC, as well as the prevention of delayed nausea and vomiting associated with MEC.

However, palonosetron is as effective as ondansetron in preventing acute CINV following HEC. In the subgroup analysis, the effectiveness of palonosetron in combination with dexamethasone was significantly increased over ondansetron throughout the 5-day post-chemotherapy period.

Further clinical studies are needed to determine whether palonosetron is superior to first generation 5-HT₃ inhibitors to prevent delayed CINV.

Recent studies

CINV secondary to single-day chemotherapy

Since palonosetron was approved by FDA, several more phase II and phase III trials have been published which may help clarify the above issues. These are summarized in Table 2.

Hajdenberg et al designed a phase II study to evaluate the safety and efficacy of intravenous palonosetron 0.25 mg plus intravenous dexamethasone 8 mg for the prevention of CINV in patients receiving MEC. Of 32 patients enrolled, 84% had a complete response during the acute phase and 59% during the delayed phase. In total, 72% of patients had no emetic episodes and 50% had no nausea throughout the overall 5-day period. The combination was well tolerated, and no serious toxicities were reported. The results supported the hypothesis that palonosetron plus a single dose of dexamethasone was effective and safe to prevent both acute and delayed CINV after MEC.

Grote et al evaluated the combination of palonosetron, dexamethasone and aprepitant for the prevention of CINV induced by MEC. Eligible patients received a single intravenous dose of palonosetron 0.25 mg on day 1, aprepitant 125 mg orally on day 1 and 80 mg on days 2–3, and dexamethasone 12 mg orally on day 1, followed by 8 mg orally on days 2 and 3. Fifty-eight patients were evaluated, 52% of patients received cyclophosphamide-based chemotherapy. CR was 88% during the acute phase, 78% during the delayed phase. No unexpected adverse events were reported. This study not only confirmed the findings of Hajdenberg et al that palonosetron can be used with other antiemetics safely and effectively to prevent both acute and delayed CINV, but also suggested that the addition of aprepitant can further extend the benefit.

Saito et al conducted a double-blind, double dummy, randomized, phase III trial in Japanese patients with cancer. Patients were randomized to receive either a single dose of palonosetron 0.75 mg or granisetron 40 µg/kg 30 minutes before HEC (cisplatin ≥ 50 mg/m² or a combination of doxorubicin/epirubicin and cyclophosphamide).
Table 2. Recent clinical studies of palonosetron (2006–2009) in CINV.

<table>
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<tr>
<th>Study design</th>
<th>Types of chemotherapy</th>
<th>Sample size</th>
<th>Premedication on Day 1</th>
<th>Premedication on Days 2–4</th>
<th>Results</th>
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<tr>
<td>Phase II, single arm</td>
<td>MEC</td>
<td>32</td>
<td>Palonosetron 0.25 mg IV + dexamethasone 8 mg IV</td>
<td>None</td>
<td>84% CR during the acute phase, 59% CR during the delayed phase</td>
<td>58</td>
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<tr>
<td>Phase II, single arm</td>
<td>MEC</td>
<td>58</td>
<td>Palonosetron 0.25 mg IV + dexamethasone 12 mg po + aprepitant 125 mg po</td>
<td>Dexamethasone 8 mg po on Days 2–3 + aprepitant 80 mg po on day 2–3</td>
<td>88% CR during the acute phase, 78% had a CR during the delayed phase</td>
<td>59</td>
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<tr>
<td>Phase II, single arm</td>
<td>MEC</td>
<td>41</td>
<td>Palonosetron 0.25 mg IV + dexamethasone 20 mg po + aprepitant 285 mg po</td>
<td>None</td>
<td>76% CR during the acute phase, 66% CR during the delayed phase</td>
<td>60</td>
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<tr>
<td>Phase II, single arm</td>
<td>MEC and HEC</td>
<td>40</td>
<td>Palonosetron 0.25 mg IV + dexamethasone 8 mg po/IV (MEC) or 20 mg po/IV (HEC) + olanzapine 10 mg</td>
<td>Olanzapine 10 mg on Days 2–4</td>
<td>100% CR during the acute phase, 75% CR during the delayed phase</td>
<td>61</td>
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<tr>
<td>Phase II, randomized, double-blind</td>
<td>HEC</td>
<td>208</td>
<td>Palonosetron 0.25 mg IV vs. granisetron 3 mg IV</td>
<td>None</td>
<td>82.69% (palonosetron) vs. 72.12% (granisetron) CR during the acute phase (P &gt; 0.05); non-inferiority of palonosetron during the delayed phase (P &gt; 0.05)</td>
<td>62</td>
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<tr>
<td>Phase II, randomized, double-blind</td>
<td>HEC</td>
<td>233</td>
<td>Palonosetron 0.075, 0.25 or 0.75 mg IV + dexamethasone 12–16 mg IV</td>
<td>Dexamethasone 8 mg IV on Day 2 and 4–8 mg on Day 3</td>
<td>77.6%, 81.8%, and 79.5% CR for 0.075, 0.25, and 0.75 mg groups during the acute phase (P &gt; 0.05)</td>
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<td>Phase II, randomized, double-blind, placebo controlled</td>
<td>HEC</td>
<td>75</td>
<td>Palonosetron 0.25 mg IV + dexamethasone 12 mg po + aprepitant 125 mg po (Arm A and Arm B)</td>
<td>Aprepitant 80 mg (Arm A) or placebo (Arm B) on Days 2–3</td>
<td>96.4% (Arm A) vs. 100% (Arm B) no emesis during the acute phase, 92.9% (Arm A) vs. 92.6% (Arm B) had a CR during the delayed phase (P &gt; 0.05)</td>
<td>64</td>
</tr>
<tr>
<td>Phase III, randomized, double-blind</td>
<td>HEC</td>
<td>1143</td>
<td>Palonosetron 0.75 mg IV or granisetron 40 µg/kg IV + dexamethasone 12 mg IV</td>
<td>Dexamethasone 8 mg for cisplatin or 4 mg po for AC/EC on Days 2–3</td>
<td>75.3% (palonosetron) vs. 73.3% (granisetron) CR during the acute phase (P &gt; 0.05); 56.8% (palonosetron) vs. 44.5% (granisetron) CR during the delayed phase (P &lt; 0.05)</td>
<td>44</td>
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Both groups received dexamethasone 16 mg intravenously on day 1 followed by either 8 mg intravenously (for patients receiving cisplatin) or 4 mg orally (patients receiving AC/EC) on days 2 and 3. Patients were stratified based on nausea/vomiting risk factors, including age, sex and type of HEC. The primary endpoints were the proportion of patients with CR during the acute phase (non-inferiority comparison with granisetron) and the proportion of patients with CR during the delayed phase (superiority comparison with granisetron). Secondary endpoints included CR during the overall phase (0–120 hours), the number of emetic episodes, time to treatment failure and severity of nausea. The study was designed to have 80% power with two-sided \( P = 0.05 \). The results were analyzed on the intention-to-treat principle.

A total of 1143 patients were enrolled into the study, with 1114 patients eligible for efficacy analysis. The most common types of cancer were non-small cell lung cancer (44.6%) and breast cancer (42.6%). The majority of patients were chemotherapy naïve. Distribution of emetic risk factors was similar between the two groups. The percentage of patients with a CR during the acute phase (0–24 h) was 75.3% in the palonosetron group, which was similar to 73.3% in the granisetron group (mean difference 95% CI 2.70%–7.27%). However, the percentage of patients with CR during the delayed phase (24–120 h) in the palonosetron group was significantly higher than in the granisetron group (56.8% vs. 44.5%, \( P < 0.001 \)). Secondary endpoint analysis demonstrated proportions of patients in the palonosetron group with no nausea (37.8%) or emetic episodes (63.2%) during the delayed phase were significantly greater than patients in the granisetron group (27.2% and 54.2%, respectively, both \( P < 0.05 \)). Time to treatment failure was also longer in the palonosetron group. Patient’s overall satisfaction measured by visual analog scale (VAS) score in the palonosetron group was equal to or higher than those of the patients in the granisetron group. Both palonosetron and granisetron were well tolerated.

This clinical trial demonstrated that a single dose of palonosetron was superior to a single dose of a first generation 5-HT\(_3\) receptor antagonist in the prevention of delayed CINV following HEC. It is noteworthy that the efficacy of palonosetron during the delayed phase of CINV was the primary endpoint, which differed from earlier studies. This ensured enough power to detect possible superiority of palonosetron, not just limiting the conclusion to “as effective as other first generations of 5-\( HT_3\) receptor antagonists”.

At the same time, there are several limitations of this study. Like earlier Phase III trials, aprepitant was not included in this trial (aprepitant was not available in Japan). The dose of dexamethasone was lower than the recommended dose, although patients did receive dexamethasone on days 1, 2 and 3. In addition, the dose of palonosetron 0.75 mg used in this trial is higher than the approved dose in North America and Europe. In the Caucasian population, palonosetron 0.25 mg has been shown as effective as 0.75 mg from earlier large clinical trials.© Theoretically, palonosetron 0.25 mg (FDA-approved dose) in combination with dexamethasone and aprepitant may be superior to the first generation 5-\( HT_3\) receptor antagonists against delayed CINV associated with HEC, but only further prospectively randomized trials can provide the definitive answer. These trials should be designed to demonstrate the superiority of palonosetron when used according to evidence-based guidelines incorporating other appropriate classes of antiemetics administered at the recommended dose.

CINV secondary to multiple-day chemotherapy

All previously discussed palonosetron data has focused on the prevention of acute and delayed CINV associated with a single day of chemotherapy; many chemotherapy regimens, however, are administered on multiple days. Instead of distinct acute and delayed phases, multiple-day chemotherapy regimens involve the overlap of acute and delayed CINV phases which may confound antiemetic prophylaxis. ASCO, NCCN and MASCC have recommended administration of a 5-\( HT_3\) receptor antagonist and dexamethasone on each day.© Several studies have been published recently to explore the use of palonosetron to prevent multiple-day regimen induced CINV.

A phase II, multicenter study evaluated the safety and efficacy of multiple-day dosing of palonosetron plus dexamethasone in patients receiving highly emetogenic 5-day cisplatin-based chemotherapy for germ cell carcinoma.© A total of 41 men were given intravenous palonosetron 0.25 mg 30 minutes before chemotherapy on days 1, 3, and 5 plus intravenous dexamethasone 20 mg 30 minutes before
chemotherapy on day 1 and 2, then 8 mg bid on days 6 and 7, and 4 mg bid on day 8. Efficacy was assessed daily for a total of 9 days. End points included emesis, CR, intensity of nausea and interference with patient functioning. The intention-to-treat cohort consisted of all patients. The majority of patients had no emesis at any time throughout days 1–5 (51%) or days 6–9 (83%). Proportions of patients with no or mild nausea were 42% on days 1–5 and 63% on days 6–9. A CR was also seen in 34.1% of patients on days 1–5 and 61% on days 6–9. The regimen was safe and well tolerated, with mild headache and constipation as the most common adverse effects.

In another European study, Musso and colleagues evaluated the efficacy of palonosetron with dexamethasone in the prevention of acute and delayed CINV in patients with hematological malignancies receiving multiple-day chemotherapy. The efficacy of a second dose of palonosetron for the treatment of breakthrough emesis was also evaluated.\(^{66}\) Regimens included DHAP (dexamethasone, cisplatin, cytarabine), Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), Flu-Cy (fludarabine, cyclophosphamide), and ICE (idarubicin, vinorelbine, prednisone, filgrastim) with the duration of chemotherapy varying between 2–7 days per cycle. Forty-six patients received palonosetron 0.25 mg on the first day of chemotherapy and intravenous dexamethasone 8 mg or 4 mg bid every day throughout the treatment. If breakthrough emesis occurred during the treatment, a second dose of palonosetron was administered if 72 hours had elapsed following the first dose. The primary endpoint was complete control (CC; defined as no emetic episode, no need for rescue medication and no more than mild nausea) during chemotherapy and within 5 days after the end of chemotherapy. The results were compared retrospectively with similar patients using ondansetron. In total, 80% of patients treated with palonosetron achieved CC without emesis during the overall period versus 60% patients on ondansetron using historical data (P < 0.05). Among 9 patients who required rescue medications, six patients (67%) were emesis-free after the second dose of palonosetron, significantly higher than 22% in the ondansetron group after metoclopramide treatment (P < 0.04).

Considering the overlap of acute and delayed CINV involved with multiple-day chemotherapy, the approach to CINV prevention becomes more challenging as data are limited. It appears that a single dose of palonosetron, in combination with dexamethasone, is effective for the prevention of CINV associated with the treatment of hematological malignancies. Repeat-dose palonosetron demonstrated efficacy for the prevention of CINV associated with a multiple-day cisplatin regimen used to treat germ cell cancer. Larger, prospective trials are needed to confirm these findings and to further explore optimal palonosetron dosing in comparison with other 5-HT\(_3\) receptor antagonists in the setting of multiple-day chemotherapy.

CINV in geriatric populations

Although the risk of experiencing CINV generally decreases with age, the elderly may experience delayed CINV for a longer duration of time and find it more difficult to tolerate these symptoms.\(^{67}\) Because of the promising palonosetron data found in adult patients, several studies explored its use in geriatric populations.

In one clinical study, 30 elderly breast cancer patients were treated with palonosetron 0.25 mg plus intravenous dexamethasone 8 mg prior to receiving liposomal doxorubicin and cyclophosphamide on day 1.\(^{67}\) Another group of 37 patients with breast cancer previously treated with intravenous ondansetron 8 mg plus intravenous dexamethasone 8 mg prior to AC regimen was used as a control. All patients received additional dexamethasone 4 mg bid for 3 days following chemotherapy. The control rate of delayed CINV in the palonosetron group was 71.4%, numerically higher than patients in the ondansetron group 42.3%. The quality of life (QOL) score was also higher in the palonosetron group than in the ondansetron group (+12.3 vs. 6.4). However, no statistical analysis was mentioned in the abstract, and the definition of “elderly” was not stated clearly.

Massa and colleagues compared palonosetron plus dexamethasone in the prevention of CINV in patients ≥65 years of age with patients <65 years of age who received either HEC or MEC.\(^{68}\) All patients failed a first-generation of 5-HT\(_3\) antagonist during the first cycle. End points included CR and CC. Of 47 patients involved, 23 patients were ≥65 years of age, and 24 patients were <65 years of age. CR rates in elderly patients and non-elderly patients
were 74% and 78% respectively during the acute phase, without statistically significant difference. CR rates were 78% in the elderly patients, and 83% in the nonelderly patients during the delayed phase. The differences were not statistically significant. The author concluded that palonosetron showed similar efficacy and safety in elderly patients ≥65 years of age as in patients <65 years of age.

Based on the results from the above mentioned trials, palonosetron has similar safety and efficacy in controlling acute and delayed CINV in elderly patients ≥65 years of age as compared to patients <65 years of age. More data are needed to further confirm the current results, especially during the delayed phase with the concurrent use of dexamethasone.

Safety
Clinical studies have demonstrated that palonosetron is well tolerated. In phase III trials, the incidence of palonosetron-associated adverse effects was 16% to 30.5%.38,39,41,44 No significant differences in adverse effects (frequency or severity) were seen between palonosetron and all three US-approved first generation 5-HT3 receptor antagonists. Table 3 summarizes the adverse events which occurred in ≥2% of patients in any phase III trial with palonosetron, ondansetron and dolasetron.38,39,41 The most common side effects of palonosetron were headache and constipation. Elevated AST and ALT were reported in ≥2% of patients in the most recent Japanese trial, higher than data reported in other phase III trials held in the US or Europe.44 It is unclear if this finding is related to the genetic differences seen in Japanese patients.

Serious side effects are rare; one case of severe hepatitis was found to be treatment related in the Japanese trial.44 Seizure was recently reported in a patient with breast cancer after receiving palonosetron and dexamethasone prior to the 4th cycle of CEF (cyclophosphamide, 5-FU and epirubicin) chemotherapy; one hour after palonosetron and dexamethasone administration, the patient developed generalized tonic and clonic seizures. Other causes of seizure were excluded; however, no adverse drug reaction (ADR) score was reported.69 Changes in liver enzymes occurs predominantly in patients receiving HEC.42

No significant treatment-related EKG results were observed in palonosetron studies. The mean post-dose changes in QTc interval from baseline was reported less than 4 ms (1–3.4 ms) in patients receiving palonosetron, similar to those receiving ondansetron, dolasetron or granisetron.38,39 In a double-blind, randomized, placebo-control trial recently completed in Europe, a dose of palonosetron up to 2.25 mg did not cause a significant effect on QTc interval.70 As a result, QTc prolongation seen in clinical trials may be attributed to other causes.

Palonosetron can be safely administered over repeated cycles of chemotherapy. In a Phase III study, palonosetron 0.75 mg was given to patients over repeated chemotherapy cycles 1 to 3.71 There was no significant difference in the incidence of adverse effects from cycle 1 to 3.

Palonosetron seems safe when used in both pediatric and geriatric populations. In one pediatric study, mild pyrexia and pruritis occurred in 2 of

| Table 3. Adverse events occurring ≥2% in any treatment groups from phase III trials evaluating chemotherapy-induced nausea and vomiting. |
|-----------------|-------------------|-----------------|
| **Adverse events** | **Palonosetron 0.25 mg I.V. (N = 633)** | **Ondansetron 32 mg I.V. (N = 410)** | **Dolasetron 100 mg I.V. (N = 194)** |
| Headache | 9% | 8% | 16% |
| Constipation | 5% | 2% | 6% |
| Diarrhea | 1% | 2% | 2% |
| Dizziness | 1% | 2% | 2% |
| Fatigue | <1% | 1% | 2% |
| Abdominal pain | <1% | <1% | 2% |
| Insomnia | <1% | 1% | 2% |

**Note:** Modified from39
60 patients. In another pediatric study, no adverse effects were observed. Due to the age of patients, the incidence of adverse events may be under-estimated. In patients ≥65 years of age, one non-randomized trial found no statistical significant difference in adverse effects between elderly and non-elderly patients. No patients withdrew from the study due to the toxicity.

Palonosetron is a pregnancy Category B agent. There are no well controlled trials evaluating palonosetron in pregnant females. Oral doses up to 60 mg/kg/day of palonosetron in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus. Because animal studies are not always predictive of human response, palonosetron should be used cautiously during pregnancy.

**Patient Preference**

Patient preference may be impacted by quality of life, cost, and convenience. Quality of life was evaluated by Aapro and colleagues in a phase III, double-blind, randomized trial. This study compared palonosetron with ondansetron in preventing CINV following HEC. The effect of CINV on daily activities was measured using the Functional Living Index-Emesis (FLIE). No impact of CINV on daily life (NIDL) was defined by a score >6 on the seven-point FLIE scale. In the acute phase, 78% of palonosetron patients and 68% of ondansetron patients reported NIDL for combined nausea and vomiting domain. During the delayed phase, 59% of palonosetron patients and 52% of ondansetron patients reported NIDL for the combined nausea and vomiting. Even though the rates of NIDL were higher in the palonosetron-treated patients, statistics were not performed with this data therefore statistical significance cannot be determined. Healthcare professionals understand that quality of life data has potential for bias and that further studies are needed to validate the results; however, patients may find this data significant. This study also demonstrated less impact from CINV on daily functioning in all patients receiving dexamethasone compared to those who were not pre-treated. Adverse effects would not be expected to impact patient preference given the similar side effects profiles of all 5-HT\textsubscript{3} antagonists.

A 2005 economic evaluation analysis was performed in 5 European countries (Italy, Germany, Russia, Netherlands, and UK) comparing palonosetron-based antiemetic therapy versus ondansetron-based antiemetic treatment. This analysis suggests that palonosetron, because of its clinical efficacy in controlling emesis, offered lower or equal net treatment costs for the hospital. Unfortunately, it is difficult to extrapolate this data to patient cost, especially in the United States given the complex healthcare structure. It is important to point out that all patients with solid tumors in this economic analysis were admitted to the hospital for treatment despite the type of chemotherapy regimen. Today, the majority of these patients are treated as outpatients; therefore this economic analysis may not be widely applicable.

In the U.S. the wholesale price of oral generic ondansetron is approximately $5.00 (16 mg) to $7.50 (24 mg) compared to approximately $200 for one injection of 0.25 mg palonosetron (brand name only). The significant higher cost associated with palonosetron may impact accessibility of the drug for patients with limited insurance coverage or no coverage.

**Place in Therapy**

Antiemetic guidelines for the prevention of CINV have been published by NCCN, ASCO and MASCC. Before the Saito study was published, previous clinical trials had focused directly on the comparison of ondansetron, dolasetron, and granisetron to palonosetron in the prevention of CINV. Although these trials had different doses, routes and schedules of administration of 5-HT\textsubscript{3} receptor antagonists, and different concomitant medications, they consistently demonstrated that all 5-HT\textsubscript{3} receptor antagonists were equivalent. As a result, antiemetic guidelines reflected equivalent safety and efficacy of 5-HT\textsubscript{3} receptor antagonist in MEC and HEC. NCCN, ASCO and MASCC all recommended the use of a 5-HT\textsubscript{3} receptor antagonist, dexamethasone and aprepitant for the preventing of acute CINV in patients receiving HEC.

Although palonosetron performed better than dolasetron and ondansetron in several subgroup and secondary endpoints analysis, including the control of delayed nausea and vomiting in all three registration trials, the primary end point was noninferiority during the acute phase after chemotherapy. Palonosetron exhibits 100 times higher binding affinity and much longer half-life (40 hours) than all first generation 5-HT\textsubscript{3} receptor antagonists. These findings, however,
could not completely explain the mechanisms of better control of delayed CINV of using palonosetron as a pure receptor antagonist. A previous study found multiple times of administration of a first generation 5-HT\textsubscript{3} receptor antagonist was not clearly better than single-dose to control delayed CINV.\textsuperscript{36}

The recent Phase III trial (Saito) demonstrated that palonosetron is as effective as granisetron during the acute phase of CINV, but superior to granisetron for delayed CINV.\textsuperscript{44} Different from previous trials, this trial was powered to evaluate the CR rate during the delayed phase as a primary end point. Based in part on the findings of this trial, NCCN has updated its antiemetic guidelines and now recommends palonosetron as the preferred 5-HT\textsubscript{3} receptor antagonist, in combination with dexamethasone and aprepitant/fosaprepitant as prophylaxis in patients receiving HEC (2009, v3 version, category 2B recommendation).\textsuperscript{43} None of the antiemetic guidelines have recommended palonosetron as the preferred 5-HT\textsubscript{3} receptor antagonist in patients receiving MEC. The use of palonosetron in the setting of multiple day chemotherapy has not been well established and is therefore not recommended at this time. ASCO and MASCC have not updated their guidelines since the Saito study was published, but the new data regarding the efficacy of palonosetron in the prevention of delayed CINV may impact these two evidence-based guidelines in the future.

Conclusions
Chemotherapy-induced nausea and vomiting is one of the most problematic experiences reported by cancer patients. While the first generation 5-HT\textsubscript{3} receptor antagonists have significantly decreased the incidence of CINV during the acute phase, control of CINV during the delayed phase remains more problematic. Palonosetron is a second generation 5-HT\textsubscript{3} receptor antagonist with high potency, selectivity, and prolonged half life. Earlier phase III trials demonstrated equivalence with other first generation 5-HT\textsubscript{3} receptor antagonist in the prevention of acute CINV following MEC and HEC. Although several subset analysis and secondary endpoints suggested palonosetron superiority, this was questioned due to the lack of concomitant dexamethasone and apreptitant, and lack of repeated dosing of the comparators. The recent phase III randomized trial (Saito) demonstrated that a single dose of palonosetron, when used in combination with dexamethasone, is indeed superior to a single dose of granisetron in the prevention of delayed CINV; CR during the delayed phase was measured as one of two primary endpoints. This clinical outcome is consistent with the newest laboratory findings that palonosetron exhibits allosteric binding and positive cooperativity when binding to 5-HT\textsubscript{3} receptors to increase calcium influx. This unique mechanism has not been seen in other 5-HT\textsubscript{3} receptor antagonists. NCCN has now recognized palonosetron as the preferred 5-HT\textsubscript{3} receptor antagonist in the prevention of CINV associated with HEC. Palonosetron has demonstrated efficacy and safety in geriatric population, and preliminary data looks encouraging in the setting of multiple-day chemotherapy, although more studies are needed. Like other 5-HT\textsubscript{3} receptor antagonists, palonosetron is well-tolerated with minimal serious side effects. With improved efficacy, a comparable safety profile and less frequent administration, palonosetron may surpass its comparators as part of a new, standard combination for the prevention of CINV.

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