A narrative review of tropisetron and palonosetron for the control of chemotherapy-induced nausea and vomiting

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Abstract: Review the clinical evidence of tropisetron or palonosetron, an old- and new-generation serotonin (5-hydroxytryptamine) type 3 (5-HT₃) receptor antagonist (RA), respectively, for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with cancer, and evaluate any difference in efficacy trends. A literature search of the EMBASE and PubMed databases was performed to identify publications of intravenous (IV) tropisetron (generic forms or Navoban®) for the treatment of CINV in patients with various cancers. Data from the pivotal clinical studies evaluating the IV formulation of Aloxi® (palonosetron HCl) were also considered. The effectiveness and safety of each antiemetic was summarized. Sixteen papers for tropisetron fulfilled the inclusion criteria and were extracted for full analysis; publications from six pivotal palonosetron clinical trials were considered. No direct data comparisons could be made between the two drugs, due to the varying definitions of efficacy endpoints between studies. For tropisetron, the rates of no emesis were lower in patients receiving highly emetogenic chemotherapy (HEC) versus moderately emetogenic chemotherapy (MEC). For palonosetron, the rates of complete response (no emesis, no rescue medication) were comparable in the MEC and HEC settings, demonstrating the effectiveness of this agent in patients receiving HEC. Both antiemetics offered some protection against nausea, although lower rates of no nausea were achieved compared with rates of no emesis. Two trials that evaluated the efficacy of palonosetron and tropisetron within the same study reported that palonosetron was more effective than tropisetron in controlling delayed vomiting in the HEC and MEC settings, with significantly higher rates of no emesis observed (P ≤ 0.01). Palonosetron was non-inferior or more efficacious in controlling CINV compared with other older 5-HT₃ RAs, such as dolasetron, ondansetron, and granisetron. Conversely, tropisetron was no more efficacious than ondansetron or granisetron. Both tropisetron and palonosetron were generally well tolerated, with adverse event profiles consistent with drugs of this class (e.g., headache, constipation, and diarrhea). These data suggest that palonosetron is a highly selective prophylactic agent that may have an improved therapeutic profile compared with tropisetron, and is a feasible treatment option for controlling CINV in patients with cancer.

Keywords: Chemotherapy-induced nausea and vomiting (CINV); tropisetron; palonosetron

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Introduction

Chemotherapy-induced nausea and vomiting (CINV), a highly distressing and frequent complication in patients with cancer (1), can negatively impact quality of life and adherence to therapy (2-5), and may be associated with considerable healthcare costs (6).

CINV is a complex and multifactorial process mediated by multiple neurotransmitters, including serotonin, substance P, and dopamine (7). Serotonin (5-hydroxytryptamine) type 3 (5-HT₃) receptor antagonists (RAs) block 5-HT₃ receptors involved in regulating nausea and vomiting in the acute (0–24 hours after chemotherapy) setting. Thought to act via the central nervous system and the vagus and splanchnic nerves in the gastrointestinal tract (8), 5-HT₃/5-HT₄ receptor signaling may also influence delayed (24–120 hours after chemotherapy) nausea and vomiting, possibly by sensitizing the vagus nerve to chemicals such as substance P (9-11).

5-HT₃ RAs, which may be described as old and new generation, form the cornerstone of antiemetic regimens recommended by international guidelines (12-14). Currently used older 5-HT₃ RAs include azasetron (15); dolasetron, granisetron, and ondansetron; tropisetron (16); and ramosetron (17). At the recommended dose, these agents show similar efficacy and safety (8,18-20), with cost being the main differentiator. Despite their effectiveness in controlling CINV in the acute phase, they are not as effective in the delayed phase (21-23), prompting the development of a new 5-HT₃ RA, palonosetron.

Both palonosetron and tropisetron are used as first-line agents to prevent CINV in China, although anecdotal evidence suggests that tropisetron may be favored, despite the lack of evidence to support its superior efficacy. Tropisetron, one of the first 5-HT₃ RAs to be developed (24), has shown promising antiemetic properties in pilot studies (25,26), with acute CINV control rates of approximately 70% (26). Palonosetron is a pharmacologically and clinically distinct new-generation 5-HT₃ RA (27,28) that various meta-analyses have shown to be more effective than older 5-HT₃ RAs (29-32). It exhibits a higher binding affinity for 5-HT₃ receptors and synergistically interacts with the neurokinin 1 (NK₁) receptor signaling pathway (27,33), which may partially account for palonosetron’s effectiveness in the delayed phase. Palonosetron comes in two formulations, oral (0.50 mg) and intravenous (IV; 0.25 mg).

This review aimed to summarize the clinical data on tropisetron IV and Aloxi® (palonosetron HCl) IV, in the first-line setting in patients with CINV, and evaluate the 5-HT₃ RA benefit to patients in terms of preventing nausea and/or vomiting.

Methods

A literature search of EMBASE and PubMed was performed to identify publications reporting the results of tropisetron IV (generic forms or Navoban®) for the treatment of CINV in patients with various cancers. The search strings are detailed in Table 1; no publication date limits were applied. Table 2 details inclusion and exclusion criteria used to screen the publications.

For palonosetron, only pivotal clinical studies evaluating the IV formulation of Aloxi® were included, because of the array of publications that have previously reviewed the use of palonosetron.

The doses considered in this review are tropisetron 5 mg IV and palonosetron 0.25 mg IV, both with and without dexamethasone (at variable doses).

Results

Overall, 193 publications on tropisetron were retrieved (Figure 1), comprising 131 records and two congress abstracts from EMBASE and 60 records from PubMed. After removal of 22 duplicates, 171 records were screened. Of these, 19 records fulfilled the inclusion criteria and were extracted for full analysis: a further four were discounted, and a previously identified study of interest was added (34), making a total of 16 included studies.

For palonosetron, a total of six papers describing pivotal studies on the use of Aloxi® IV in controlling CINV were identified and included; see Table 3 for study designs.

Tropisetron

Efficacy—tropisetron-only data

Definitions of the extent of nausea/vomiting control differed across publications; therefore, only complete control rates for nausea and/or vomiting were considered in this review. For the majority of papers, complete control of vomiting was described as no vomiting or retching within a 24-hour period, and complete control of nausea was defined as no episodes of nausea within 24 hours, where one episode was any period of 1 hour in which nausea occurred.

Most studies were conducted in Europe, with Navoban®
or generic tropisetron used equally across studies. Nine studies were undertaken in the highly emetogenic chemotherapy (HEC) setting (34,36-38,42,43) [where 93% of the patients received HEC (39,41,45)], two in the moderately emetogenic chemotherapy (MEC) setting (46,47), and three in a mixed HEC/MEC setting (35,40,44). Dexamethasone, at varying doses, was included in six studies (36,38,40,42,45,46), although in the Hulstaert et al. study (40), it was only administered in the second cycle of treatment (data not reported). The comparator arms of each study are detailed in Table 3.

### Complete control of vomiting/emesis (no emesis)

Overall, ten studies report data on the rates of no emesis (35-39,42,43,45-47) (Table 4). In the HEC setting, between 52.0–90.0% of patients in the acute phase (36-39,43), 53.0–75.0% in the delayed setting (36-38), and 22.5–45.0% in the overall phase (36,39,43) reported no emesis. When tropisetron was administered with dexamethasone, the rates of no emesis were 75.0–97.0% in the acute phase (36,38,42,45), 50.0–90.0% in the delayed setting (36,38,42,45), and 42.5–76.0% in the overall phase (36,42).

In the MEC setting, no emesis occurred in 28.3% of patients in the acute phase (46). Adding dexamethasone to tropisetron increased the rate to 41.7–58.8% in the acute phase (46,47), while 52.9% of patients reported no emesis in the delayed phase (47). Neither study reported data for the overall phase.

In the HEC/MEC setting, 45% of patients in the acute phase and 50.0–80.0% of patients in the delayed phase reported no emesis (35).

### Complete control of nausea (no nausea)

In the HEC setting, six studies investigated the effect of tropisetron on controlling nausea, three of which investigated the addition of dexamethasone to tropisetron (Table 4). Tropisetron alone resulted in no-nausea rates of 32–75.0% in the acute phase (36-39,43), 29.0–83.0% in the delayed phase (36-38), and 12.5–34.0% in the overall phase (36,39,43). The addition of dexamethasone to tropisetron increased these rates to 35.0–90.0% in the acute phase (36,38,42,45), 42.0–88.0% in the delayed phase...
Only one study in the MEC setting evaluated nausea. In total, 30% of patients reported no nausea, which increased to 38.3% when dexamethasone was added to tropisetron in the second cycle of treatment (46).

In the HEC/MEC setting, only one study reported data on nausea prevention. Approximately 23% of patients in the acute phase reported no nausea, and while absolute values were reported, a graphical representation of the data indicated that more people in the delayed phase experienced no nausea (35).

Complete control of vomiting and nausea (no emesis and no nausea)
Several studies defined complete control as no emesis and/or nausea in 24 hours. In the HEC setting, 62.5–72.5% of tropisetron-treated patients reported no acute emesis and/or nausea (34,38,41), with 100% control of emesis or nausea observed in 52.5% of patients in the delayed phase (41); 26% of patients reported no nausea and vomiting in the overall phase, increasing to 49.0% when dexamethasone was added (38). In the HEC/MEC setting, 64% of tropisetron-treated patients in the acute phase and 45.0–58.0% in the delayed phase had no emesis or nausea, respectively (44). Another study reported no-emesis or no-nausea rates of 72.0% in the acute phase and 48% over the entire 6-day study period (40).

Efficacy—tropisetron versus other 5-HT3 RAs
Several studies assessed the effectiveness of tropisetron versus other 5-HT3 RAs. Tropisetron was compared with ondansetron and granisetron in the MEC setting (47). The rates of no emesis in the acute phase were 38.8% with ondansetron, 58.8% with tropisetron, and 73.7% with granisetron; in the delayed phase, the rates were 38.8%, 52.9%, and 73.7%, respectively, demonstrating that tropisetron was not significantly better in controlling emesis compared with ondansetron or granisetron. Indeed, granisetron promoted a significantly greater major response rate [defined as the sum of complete and partial (1–4 vomiting episodes/retches in 24 hours)] in the control of delayed emesis (P=0.01), compared with tropisetron (47).

Another study compared the effects of tropisetron, ondansetron, and granisetron on complete response (defined as no nausea or vomiting, or only mild nausea in 24 hours) across multiple cycles in cisplatin-treated patients (34). In the first cycle, observed response rates in the acute phase were 72.5% with tropisetron, 82.1% with ondansetron, and 84.2% with granisetron; across multiple cycles, these values were 67.6%, 73.3%, and 72.1%, respectively. Ondansetron resulted in significantly higher numbers of patients with
Table 3 Summary of study designs for the tropisetron IV and palonosetron IV studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients [no. receiving tropisetron]</th>
<th>Tropisetron/palonosetron dose/regimen</th>
<th>Comparator</th>
<th>Steroids</th>
<th>Chemotherapy</th>
<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al., 1994 (35)</td>
<td>102 [51]</td>
<td>Tropisetron 5 mg IV on day 1 and PO on days 2–4</td>
<td>Metoclopramide 2–5 mg/kg on day 1 and 3× 20–40 mg PO on days 2–4</td>
<td>No</td>
<td>HEC/MEC: carboplatin 300 or 140 mg/m² + cyclophosphamide 600 or 300 mg/m² alternating with ifosfamide 5 or 2.5 g/m² + doxorubicin 50 or 25 mg/m², doxorubicin 75 mg/m², carboplatin 300 mg/m² + ifosfamide 5 g/m² + etoposide 120 mg/m² on days 1 and 2 and 240 mg/m² on day 3</td>
<td>Breast, lung, head, and ovarian cancer, and soft tissue sarcoma</td>
</tr>
<tr>
<td>Bruntsch et al., 1994 (36)</td>
<td>87 [87]</td>
<td>Tropisetron monotherapy: 5 mg IV during chemotherapy, followed by 1× 10 mg PO</td>
<td>Tropisetron + D: tropisetron (5 mg IV during chemotherapy, followed by 1× 10 mg PO) + D (1× 20 mg D IV on days 1 and 2 followed by 1× 4 mg PO or IV until the end of chemotherapy); tropisetron + low-dose metoclopramide: tropisetron (5 mg IV during chemotherapy, followed by 1× 10 mg PO) + metoclopramide (1× 20 mg IV, then 2× 10 mg PO on day 1, followed by 3× 10 mg PO)</td>
<td>D 20 mg IV on days 1 and 2 followed by 1× 4 mg PO or IV until the end of chemotherapy</td>
<td>HEC: cisplatin ≥50 mg/m², ifosfamide ≥1.5 g/m², cyclophosphamide ≥750 mg/m², carboplatin ≥300 mg/m² on day 1 of the course</td>
<td>NR</td>
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</table>
| Bruntsch et al., 1993 (37) | 231 [115] | Tropisetron 5 mg/day PO evening before day 1 chemotherapy and mornings for at least 5 days (depending on duration of chemotherapy); IV infusion (15 mins) on day 1 of chemotherapy; investigators discretion whether to continue tropisetron in subsequent chemotherapy courses | Standard antiemetic therapy (investigators discretion, optimized individual patients) | No | 92% HEC | Breast cancer, gynecological cancers, lung cancer, genitourinary cancer, lymphomas, other tumors | (continued)
Table 3 (continued)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients [no. receiving tropisetron]</th>
<th>Tropisetron/palonosetron dose/regimen</th>
<th>Comparator</th>
<th>Steroids</th>
<th>Chemotherapy</th>
<th>Tumor type</th>
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</thead>
<tbody>
<tr>
<td>Drechsler et al., 1997 (38)</td>
<td>193 [193]</td>
<td>Arm A: tropisetron 5 mg IV on days 1 and 2 and then 10 mg PO</td>
<td>Arm B: tropisetron 5 mg IV on days 1 and 2, and then 10 mg PO + D 20 mg IV on days 1 and 2 and then 4 mg PO or IV; Arm C: tropisetron 5 mg IV on days 1 and 2 and then 10 mg PO + metoclopramide 20 mg IV along with 2× 10 mg PO on day 1 and then 3× 10 mg PO</td>
<td>In arm B</td>
<td>HEC: cisplatin ≥50 mg/m² or carboplatin ≥300 mg/m² or cyclophosphamide ≥750 mg/m² or ifosfamide ≥1.5 g/m². Combinations with other chemotherapeutics allowed</td>
<td>Histologically or cytologically verified malignant tumors</td>
</tr>
<tr>
<td>Herrstedt et al., 2007 (39)</td>
<td>81 [81]</td>
<td>Tropisetron 5 mg IV on days 1–5 and PO on day 6 + placebo 30 mg PO tid on day 1 and qid on days 2–6</td>
<td>Tropisetron 5 mg IV on days 1–5 and PO on day 6 + metopimazine 30 mg PO tid on day 1 and qid on days 2–6</td>
<td>No</td>
<td>MEC: cisplatin 20 or 40 mg/m² on days 1–5/21 + etoposide 100 mg/m² on days 1–21/21 + bleomycin 15 mg/ m² on day 2/21 for 4 cycles</td>
<td>Germ cell cancer</td>
</tr>
<tr>
<td>Hulstaert et al., 1994 (40)</td>
<td>460 [460]</td>
<td>Tropisetron 5 mg IV on day 1 and PO on days 2–6</td>
<td>Tropisetron 5 mg IV on day 1 and PO on days 2–6 + D 0.2 mg/kg IV on day 1 and 8 mg on days 2–6; tropisetron 5 mg IV on day 1 and PO on days 2–6 + alizapride 0.2 mg/kg IV on day 1 and 8 mg on days 2–6</td>
<td>D 8 mg in Arm B</td>
<td>HEC/MEC: cisplatin &gt;50 mg/m²/day or &gt;75 mg/m², cyclophosphamide &gt;600 mg/m², cytarabine &gt;500 mg/m², ifosfamide &gt;1,000 mg/m², carboplatin &gt;300 mg/m², epirubicin 70 mg/m², doxorubicin &gt;50 mg/m² or &gt;25 mg/m² in combination, mitoxantrone &gt;10 mg/m² in combination, mitomycin &gt;10 mg/m² in combination, or mustine, carmustine, dactinomycin, or dacarbazine at any dose</td>
<td>Breast cancer, lung cancer, head and neck cancer, ovarian cancer</td>
</tr>
<tr>
<td>Nicolaides et al., 1998 (41)</td>
<td>40 [40]</td>
<td>Tropisetron 5 mg single IV dose as 10-minute infusion before chemotherapy</td>
<td>NR</td>
<td>No</td>
<td>MEC: epirubicin 110 mg/m² IV every 2 or 4 weeks with G-CSF subcutaneous 5 µg/kg days 2–13</td>
<td>Breast cancer</td>
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Table 3 (continued)
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<tr>
<th>Author, year</th>
<th>No. of patients [no. receiving tropisetron]</th>
<th>Tropisetron/palonosetron dose/regimen</th>
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<th>Steroids</th>
<th>Chemotherapy</th>
<th>Tumor type</th>
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<tr>
<td>Ma et al., 2015 (42)</td>
<td>82 [40 tropisetron alone; 42 tropisetron + palonosetron]</td>
<td>Tropisetron 5 mg IV on days 1–3</td>
<td>Palonosetron 25 mg IV on days 1 and 3 + tropisetron 5 mg IV on days 1–3, both 30 min before chemotherapy</td>
<td>D 10 mg</td>
<td>HEC: docetaxel 60–75 mg/m² on day 1, cisplatin 75 mg/m² on day 1–3/21 per cycle</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>Sorbe et al., 1994 (43)</td>
<td>259 [132]</td>
<td>Tropisetron 5 mg IV on day 1 and PO on days 2–6</td>
<td>Metoclopramide 3 mg IV + D 20 mg IV on day 1 and 10 mg PO or 20 mg suppository on days 2–6</td>
<td>D in comparator arm</td>
<td>HEC: cisplatin 50–89 mg/m²</td>
<td>Gynecological tumors, lung cancer, head and neck cancer, bladder cancer</td>
</tr>
<tr>
<td>Sorbe et al., 1994 (44)</td>
<td>630 [630] of which 619 evaluable</td>
<td>Tropisetron 5 mg IV on day 1 and PO on days 2–6</td>
<td>NA</td>
<td>No</td>
<td>HEC/MEC: common therapies were cisplatin, carboplatin, dacarbazine, anthracyclines, cyclophosphamide, etoposide, fluorouracil</td>
<td>Gynecologic tumors, lung cancer, breast cancer, lymphoma</td>
</tr>
<tr>
<td>Sorbe et al., 1998 (45)</td>
<td>300 [141]</td>
<td>Tropisetron 5 mg IV on day 1 and PO on days 2–6 + D 20 mg IV on day 1 and 3 mg PO on days 2–6</td>
<td>Placebo 5 mg PO on days 2–6 + D 20 mg IV on day 1 and 3 mg PO on days 2–6</td>
<td>D 20 mg IV on day 1 and 3 mg PO on days 2–6</td>
<td>HEC/MEC: cisplatin 50–100 mg/m² or carboplatin (AUC = 7) on day 1. Combination with other cytostatic agents (epidoxorubicin, doxorubicin, cyclophosphamide, paclitaxel, teniposide, etoposide, vincristine, and bleomycin) was allowed</td>
<td>Gynecologic malignancies</td>
</tr>
<tr>
<td>Tsavaris et al., 2008 (46)</td>
<td>60 [60]</td>
<td>Tropisetron 5 mg IV on days 1–3 in cycle 1</td>
<td>Tropisetron 5 mg + D 8 mg IV on days 1–3, before chemotherapy in cycle 2; tropisetron 5 mg IV + 0.25 mg alprazolam tablets on days 1–3, before chemotherapy in cycle 3</td>
<td>D 8 mg</td>
<td>HEC/MEC: carboplatin (AUC = 7) + paclitaxel 225 mg/m² or docetaxel 100 mg/m² on day 1/21 for 3 cycles</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>Yalçın et al., 1999 (47)</td>
<td>54 [17]</td>
<td>Tropisetron 5 mg IV</td>
<td>Ondansetron 8 mg IV or granisetron 3 mg IV</td>
<td>No</td>
<td>MEC: FAC, FEC, or CMF for 1 day</td>
<td>Breast cancer</td>
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<tr>
<td>Author, year</td>
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<td>Qiu et al., 2011 (48)</td>
<td>155 [155]</td>
<td>Tropisetron 5 mg IV</td>
<td>Palonosetron 0.25 mg IV</td>
<td>NR</td>
<td>HEC/MEC: cisplatin ≥60 mg/m² or doxorubicin ≥40 mg/m², pirarubicine ≥40 mg/m², epirubicin ≥60 mg/m²</td>
<td>Malignant solid tumors</td>
</tr>
<tr>
<td>Li et al., 2012 (49)</td>
<td>128 [87]</td>
<td>Tropisetron 5 mg IV</td>
<td>Palonosetron 0.25 mg IV</td>
<td>D 10 mg IV</td>
<td>Cisplatin 75 mg/m²</td>
<td>Malignant solid tumors</td>
</tr>
<tr>
<td>Aapro et al., 2006 (50)</td>
<td>667 [446]</td>
<td>Palonosetron 0.25 mg IV</td>
<td>Palonosetron 0.75 mg IV; ondansetron 32 mg IV</td>
<td>D 20 mg IV (15 min before chemotherapy initiation) was allowed at the physician’s discretion</td>
<td>HEC: cisplatin ≥60 mg/m², cyclophosphamide &gt;1,500 mg/m², camustine [BCNU] &gt; 250 mg/m², dacarbazine [DTIC], or mechlorethamine</td>
<td>Ovarian cancer, lung cancer, Hodgkin’s lymphoma, gastric cancer, breast cancer</td>
</tr>
<tr>
<td>Eisenberg et al., 2003 (51)</td>
<td>569 [378]</td>
<td>Palonosetron 0.25 mg IV</td>
<td>Palonosetron 0.75 mg IV; dolasetron 100 mg IV</td>
<td>A late protocol amendment, and at the discretion of the investigator, a single dose of D 20 mg IV (or, if unavailable, a single dose of D 20 mg PO or methylprednisolone 125 mg IV), administered 15 minutes before chemotherapy, was permitted</td>
<td>MEC: carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, mitoxantrone, methotrexate (≥250 mg/m²), cyclophosphamide (≥1,500 mg/m²), doxorubicin (≥25 mg/m²), or cisplatin (≥50 mg/m²)</td>
<td>Malignant disease (including breast cancer, lung cancer and non-Hodgkin lymphoma)</td>
</tr>
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Table 3 (continued)
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<tr>
<th>Author, year</th>
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<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gralla et al., 2003</td>
<td>563 [378]</td>
<td>Palonosetron 0.25 mg IV</td>
<td>Palonosetron 0.75 mg IV; ondansetron 32 mg IV</td>
<td>No</td>
<td>MEC: any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan or mitoxantrone; methotrexate &gt;250 mg/m²; cyclophosphamide &lt;1,500 mg/m²; doxorubicin &gt;25 mg/m²; or cisplatin &lt;50 mg/m²</td>
<td>Malignant disease including: breast, lung, bladder, colon, rectal, small-cell lung and gastric cancers</td>
</tr>
<tr>
<td>Boccia et al., 2013</td>
<td>651 [639]</td>
<td>Palonosetron 0.25 mg IV</td>
<td>Palonosetron 0.25 mg PO; palonosetron 0.50 mg PO; palonosetron 0.75 mg PO</td>
<td>Randomized 1:1 to D 8 mg IV or placebo on day 1</td>
<td>MEC: any dose of oxaliplatin, carboplatin, epirubicin, idarubicin, doxorubicin, ifosfamide, irinotecan, daunorubicin or cyclophosphamide &lt;1,500 mg/m², or cytarabine &gt;1 g/m²</td>
<td>Malignant disease including breast and colon cancers and lung neoplasms</td>
</tr>
<tr>
<td>Karthaus et al., 2015</td>
<td>743 [743]</td>
<td>Palonosetron 0.25 mg IV</td>
<td>Palonosetron 0.50 mg PO</td>
<td>D 20 mg on day 1 then 8 mg bid on days 2–4</td>
<td>HEC: cisplatin-based regimen</td>
<td>Malignant solid tumors including gastric, head and neck, lung/ respiratory tract/ ovarian and bladder</td>
</tr>
<tr>
<td>Saito et al., 2009</td>
<td>1,143 [555]</td>
<td>Palonosetron 0.75 IV</td>
<td>Granisetron 40 µg/kg</td>
<td>D 16 mg IV on day 1</td>
<td>HEC: cisplatin ≥50 mg/m² or anthracycline and cyclophosphamide regimen</td>
<td>Malignant solid tumors including non-small cell lung cancer, small-cell lung cancer, and breast cancer</td>
</tr>
</tbody>
</table>

AUC, area under the curve; bid, twice a day; CMF, cyclophosphamide, methotrexate, fluorouracil; D, dexamethasone; FAC, fluorouracil, adriamycin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; HEC, highly emetogenic chemotherapy; IV, intravenous; MEC, moderately emetogenic chemotherapy; NR, not reported; PO, orally; qid, four times a day; tid, three times a day.
**Table 4** Summary of efficacy parameters for tropisetron

<table>
<thead>
<tr>
<th>Trial</th>
<th>Emetogenic potential</th>
<th>Patient number, total [number receiving tropisetron 5 mg]</th>
<th>D dose in tropisetron arm</th>
<th>No emesis, %</th>
<th>No nausea, %</th>
<th>No emesis and/or no vomiting, %</th>
<th>TRAEs incidence in tropisetron arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruntsch et al., 1993 (37)</td>
<td>93% HEC</td>
<td>231 [115]</td>
<td>N</td>
<td>52</td>
<td>32</td>
<td>NR</td>
<td>71/115</td>
</tr>
<tr>
<td>Bruntsch et al., 1994 (36)</td>
<td>HEC</td>
<td>87 [30 for tropisetron alone; 30 for tropisetron + D]</td>
<td>Y in cycle 2 (20 mg IV on days 1 and 2; then 4 mg PO or IV until end of treatment)</td>
<td>−D: 69; +D: 81</td>
<td>−D: 63–83; −D: 34</td>
<td>NR</td>
<td>−D: 7/30; +D: 9/30</td>
</tr>
<tr>
<td>Drechsler et al., 1997 (38)</td>
<td>HEC</td>
<td>193 [65 tropisetron alone; 60 for tropisetron + D]</td>
<td>Y (in comparator arm; 20 mg IV on days 1 and 2, then 4 mg IV/PO thereafter)</td>
<td>−D: 80; +D: 97</td>
<td>−D: 75; +D: 58</td>
<td>NR</td>
<td>−D: 26; −D: 26/65; +D: 49 +D: 37/60</td>
</tr>
<tr>
<td>Ma et al., 2015 (42)</td>
<td>HEC</td>
<td>82 [40 tropisetron alone]</td>
<td>10 mg</td>
<td>75.0</td>
<td>35.0</td>
<td>NR</td>
<td>64.3</td>
</tr>
<tr>
<td>Mantovani et al., 1996 (34)</td>
<td>HEC</td>
<td>117 [40]</td>
<td>N</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Total AEs NR but none severe and incidence of headache was &lt;10%</td>
</tr>
<tr>
<td>Sorbe et al., 1994 (43)</td>
<td>HEC</td>
<td>259 [131]</td>
<td>N</td>
<td>63</td>
<td>40</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Herrstedt et al., 2007 (39)</td>
<td>HEC</td>
<td>82 [40]</td>
<td>N</td>
<td>90</td>
<td>62.5</td>
<td>NR</td>
<td>No absolute figures given</td>
</tr>
<tr>
<td>Nicolaides et al., 1998 (41)</td>
<td>HEC</td>
<td>40 [40]</td>
<td>N</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sorbe et al., 1998 (45)</td>
<td>HEC</td>
<td>300 [141]</td>
<td>Y (20 mg IV on day 1; 3 mg PO on days 2–6)</td>
<td>87</td>
<td>77</td>
<td>NR</td>
<td>75%</td>
</tr>
<tr>
<td>Tsavaris et al., 2008 (46)</td>
<td>MEC</td>
<td>60 [60]</td>
<td>Y (tropisetron 8 mg in + D in the second cycle)</td>
<td>−D: 28.3; +D: 41.7</td>
<td>−D: 30; +D: 38.3</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Table 4 (continued)*
Table 4 (continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Emetogenic potential</th>
<th>Patient number, total</th>
<th>Dose in tropisetron arm</th>
<th>No emesis, %</th>
<th>No nausea, %</th>
<th>No emesis and/or no vomiting, %</th>
<th>TRAEs incidence in tropisetron arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yalçin et al., 1999 (47)</td>
<td>MEC</td>
<td>54 [17]</td>
<td>N</td>
<td>58.8</td>
<td>52.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hulstaert et al., 1994 (40)</td>
<td>HEC/MEC</td>
<td>1,072 [1,072]</td>
<td>N in first cycle (data reported)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>25 [50–85]</td>
</tr>
<tr>
<td>Sorbe et al., 1994 (44)</td>
<td>HEC/MEC</td>
<td>630 [630]</td>
<td>N</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>72 [NR]</td>
</tr>
<tr>
<td>Anderson et al., 1994 (35)</td>
<td>HEC/MEC</td>
<td>120 [51]</td>
<td>N</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>64 [45–58]</td>
</tr>
</tbody>
</table>

A, acute; AE, adverse event; Del, delayed; HEC, highly emetogenic chemotherapy; IV, intravenous; MEC, moderately emetogenic chemotherapy; N, no; NR, not reported; O, overall; PO, orally; TRAE, treatment-related adverse event; Y, yes.

major efficacy [complete response plus major response (single vomiting or no vomiting but moderate to severe nausea in 24 hours)] versus tropisetron (P=0.021) (34).

**Safety**

The two most commonly reported adverse events (AEs) were headache (incidence range 5–41.7%) (34,35,37-47), and constipation (incidence range 2.5–58%) (35-47). Other AEs that were reported were: abdominal distention (42); effects on appetite and activity (46); sedation (45,46); asthenia (43,46); dizziness (39,40,43-45); tiredness (35,36,38-40,44); mild “mouth dryness” (41); diarrhea (36,38,40,43,47); other gastrointestinal symptoms (38) and sleep disturbances (38,47); paresis, anxiety, and somnolence (43); abdominal pain (40,43,45); epigastric pain (40,44); allergy and heart symptoms (44); pyrosis, hiccups, and fever (40); depression, migraine, and confusion (35); anorexia and fatigue (36); and edema (45).

**Palonosetron**

**Efficacy—palonosetron only**

Six pivotal trials evaluated the efficacy of palonosetron (Aloxi® IV in CINV prevention (50-55) (Table 5). Three studies evaluated the 0.25- and 0.75-mg doses of palonosetron IV, and included a third arm that featured an older-generation 5-HT_3 RA (50-52), while two trials compared the efficacy of the oral and IV formulations of palonosetron in the MEC (53) and HEC (54) settings. The final study evaluated the efficacy of 0.75 mg palonosetron versus granisetron in patients from Japan (where the standard dose is 0.75 mg IV) (55). Studies used the same definitions for complete response (no emesis and no rescue medication use) and complete control (no emesis, no rescue medication use, and no more than mild nausea).

In the MEC setting, 63.0–81.0% of patients had a complete response during the acute phase (51-53). For the delayed and overall phases, the complete response rates were 54.0–74.1% (51-53) and 46.0–69.3% (51-53), respectively. Moreover, the Gralla study (52) reported that >70% of patients had no emetic episodes in any phase. In the Boccia study (53), the rates of no emesis and no nausea were also reported. In the acute, delayed, and overall phases, the proportion of patients with no emesis was 77.2%, 74.7%, and 67.3%, respectively, and the rates of no nausea were 57.4%, 47.5%, and 42.6%, respectively (53). This study also reported complete response rates in patients who received dexamethasone versus those who did not; these were
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82.9% vs. 57.5%, 68.3% vs. 62.5%, and 65.9% vs. 52.5% in the acute, delayed, and overall phases, respectively (53).

In the HEC setting, the rates of complete response during acute, delayed, and overall phases were 59.2%, 45.3%, and 40.8%, respectively (50). The proportion of patients with no emesis was 68.5%, 56.5%, and 46.6% in the acute, delayed, and overall phases, respectively. In another study where dexamethasone was administered to all patients, 86.2% achieved a complete response in the acute phase, 74.8% in the delayed phase, and 70.2% in the overall phase. In the delayed and overall phases, 77.5% and 73.2% of patients reported no vomiting, and rates of no nausea were 75.6%, 53.4%, and 47.4%, in the acute, delayed, and overall phases, respectively (54).

Finally, a Japanese study (55) evaluated the effect of 0.75 mg palonosetron plus dexamethasone. The rates of complete response during the acute, delayed, and overall phases were 75.3%, 56.8%, and 51.5%, respectively. Complete control was observed in 73.7% of patients in the acute phase, 53.0% in the delayed phase, and 47.9% in the overall phase. Rates of no nausea were 58.7%, 37.8%, and 31.9%, in the acute, delayed, and overall phases, respectively, and for no emesis these values were 77.5%, 63.2%, and 57.5%, respectively.

### Efficacy—palonosetron versus older-generation 5-HT₃ RAs

Four studies featured a comparator arm containing an older-generation 5-HT₃ RA. Two compared the antiemetic activity of 0.25 mg palonosetron, 0.75 mg palonosetron, and 32 mg ondansetron, with one study in the MEC setting (52), and the other in the HEC setting (50). The other studies compared palonosetron with dolasetron in patients receiving MEC (51), and with granisetron in patients receiving HEC (55).

In the MEC setting, 0.25 mg palonosetron was significantly superior to ondansetron in preventing acute vomiting (lower bound of the 97.5% CI >0; P=0.009), and non-inferiority was demonstrated for both the 0.25- and 0.75-mg doses of palonosetron (52). The 0.25-mg palonosetron dose was also significantly better than ondansetron at controlling complete response in the delayed (74.1% vs. 55.1%; P<0.001) and overall (69.3% vs. 50.3%; P<0.001) phases. Significantly higher rates of patients with no emesis, no rescue medication use, and no more than mild nausea were observed with palonosetron 0.25 and 0.75 mg, compared with ondansetron during the delayed (66.7% vs. 50.3%; P=0.001) and overall (63.0% vs. 44.9%; P=0.001) phases. Palonosetron 0.25 mg was also...
superior to ondansetron in terms of the number of patients who experienced no emesis, used no rescue medication, and experienced no more than mild nausea on days 2, 3, and 4 (P=0.001, P=0.001, and P=0.003, respectively). At no point was palonosetron inferior to ondansetron (52).

The efficacy of 0.25 mg palonosetron, 0.75 mg palonosetron, and 100 mg dolasetron was compared in patients receiving MEC (51). Both the 0.25- and 0.75-mg doses of palonosetron were non-inferior to dolasetron in terms of complete response in the acute phase, with numerically higher rates of complete response achieved with 0.25 mg (63.0% vs. 52.9%; P=0.049) and 0.75 mg palonosetron (57.1% vs. 52.9%; P=0.412), compared with dolasetron. In the delayed and overall phases, significantly higher complete response rates were observed for 0.25 mg palonosetron compared with dolasetron (54.0% vs. 38.7%; P=0.004, and 46.0% vs. 34.0%; P=0.21, respectively) and for 0.75 mg palonosetron (56.6% vs. 38.7%; P=0.001, and 47.1% vs. 34.0%; P=0.012, respectively). There were a significantly higher proportion of patients who experienced no emesis, used no rescue medication, and experienced no more than mild nausea for 0.25 mg palonosetron and 0.75 mg palonosetron, compared with dolasetron, during the delayed phase (48.1% and 51.9% vs. 36.1%, respectively; P=0.018 and P=0.002 for palonosetron 0.25 and 0.75 mg vs. dolasetron, respectively) and overall phases (41.8% and 42.9% versus 30.9%; P=0.027 and P=0.016, respectively).

The lower dose of 0.25 mg palonosetron led to significantly fewer emetic episodes during the acute, delayed, and overall phases compared with dolasetron (P=0.0135, P=0.0183, and P=0.0036, respectively), with more patients reporting no emetic episodes during the delayed and overall phases (P=0.028 and P=0.014, respectively) (51).

Non-inferiority of palonosetron compared with ondansetron in terms of acute complete response was also demonstrated in the HEC setting (50). Numerically higher increases in the complete response rates for palonosetron 0.25 mg during the delayed (45.3% vs. 38.9%) and overall (40.8% vs. 33.0%) phases were reported. The percentage of patients who experienced no emesis, used no rescue medication, and experienced no more than mild nausea was slightly higher for palonosetron 0.25 mg compared with ondansetron in the acute phase (56.5% vs. 51.6%, respectively), although the rates were comparable in the delayed and overall phases (50).

Finally, in Japanese patients receiving HEC, 0.75 mg palonosetron was non-inferior to granisetron in terms of acute-phase complete response (75.3% vs. 73.3%, respectively; mean difference 2.9% (95% CI, −2.70% to 7.27%)). In the delayed phase, palonosetron resulted in significantly higher complete response rates compared with granisetron (56.8% vs. 44.5%; P<0.0001) (55).

Safety
Palonosetron was well tolerated. Most AEs were mild in intensity, and the majority were assessed as not related, or unlikely to be related to the study medication (50-53). The most frequently reported were: headache (incidence range 1.6–26.4%) (50-54); constipation (incidence range 1.6–17.4%) (50-55); fatigue (10.9%) (51); dizziness (0.5%) (52); diarrhea (1.3%) (50); gastrointestinal disorders (3.0%); and nervous system disorders (1.6%) (54). No significant changes related to study drug were observed with respect to laboratory parameters, vital sign measurements, and electrocardiogram recordings (50-54).

Palonosetron vs. tropisetron
Two Chinese studies evaluated the efficacy of tropisetron and palonosetron (48,49). One study determined the effectiveness of these drugs in preventing emesis and nausea in the MEC (an anthracycline-based regimen) and HEC (a cisplatin-based regimen) settings (48). In patients receiving MEC, the rates of no emesis in the acute phase were 61.8% for palonosetron and 55.3% for tropisetron; in patients receiving HEC, the rates were 44.6% and 46.4%, respectively. In the delayed phase, the rates of no emesis were 63.2% for palonosetron and 47.4% for tropisetron in the MEC setting, and 39.3% and 26.8%, respectively, in the HEC setting. Considering data from the MEC and HEC settings together, no significant difference (P>0.05) was observed between the two drugs in preventing acute vomiting. This contrasted with the data observed in the delayed setting, where significantly higher rates of no emesis were observed for palonosetron versus tropisetron (53.0% vs. 38.6%; P=0.01). The overall incidence of AEs between the two drugs was similar [4.9% (palonosetron) vs. 7.4% (tropisetron); P>0.05]; the majority were mild, and there was no incidence of severe AEs. The most common were headache (2.7% vs. 2.1% for palonosetron versus tropisetron, respectively) and dizziness (2.7% vs. 2.1%, respectively).

The second study evaluated the effectiveness of palonosetron and tropisetron in the HEC setting (49). There was no significant difference in the rates of no emesis in the acute phase between palonosetron and tropisetron.
(79.7% vs. 75.8%, respectively; P=0.45). However, palonosetron appeared significantly more effective in controlling delayed emesis (no emesis rates: 70.3% vs. 50.8%, respectively; P<0.01). AEs were generally mild to moderate in severity and the incidence was similar for both drugs. The most commonly observed AEs were constipation (palonosetron versus tropisetron: 14.8% vs. 17.2%), distention (3.9% vs. 7.8%), headache (1.6% vs. 2.3%), fatigue (7.8% vs. 10.9%), and increased aminotransferase (2.3% each).

Discussion

In our review of the clinical evidence supporting the use of 0.5 mg tropisetron IV and 0.25 mg palonosetron IV as antiemetic agents in the HEC and MEC settings, we have discussed data from 16 publications on tropisetron and data from 6 pivotal trials of palonosetron IV. Most papers that investigated the efficacy of tropisetron measured the rates of no emesis or no nausea (both reported as no episodes within a 24-hour period), with only a few reporting on rates of no nausea and/or no vomiting. Rescue medication use was varied, with four studies not specifying whether it was used. This contrasted with palonosetron IV, where the primary efficacy parameter in each study was complete response, defined as no emetic episodes and no rescue medication. Consequently, a direct comparison of the data was not possible, so overall trends were instead considered, where sample sizes permitted.

For tropisetron, the rates of no emesis were lower in patients receiving HEC vs. MEC. For palonosetron, the rates of complete response were comparable between both settings, thus demonstrating the effectiveness of this agent in patients receiving HEC. Tropisetron was less effective at controlling nausea than emesis regardless of the phase or emetogenic potential of the chemotherapy. Lower rates of no nausea, versus rates of no emesis, were also observed with palonosetron, although the effect was not as pronounced (rates of no nausea were 57.4–75.6% in the acute phase).

These data could indirectly suggest that palonosetron may be more effective than tropisetron in controlling CINV in patients with cancer. The results of two studies examining the effectiveness of palonosetron and tropisetron (48,49) within the same trial provided direct data to support this supposition. Palonosetron was seen to be more effective than tropisetron in controlling delayed vomiting in both the MEC and HEC settings. In both studies, significantly higher rates of no emesis were seen with palonosetron in the delayed phase, compared with tropisetron, and comparable efficacy was observed in the acute phase (48,49). The results of a subgroup analysis within a recent meta-analysis of palonosetron versus the older 5-HT3 RAs, tropisetron appears less effective in controlling CINV, regardless of the phase. One study reported that granisetron was significantly better in controlling emesis in the delayed phase, compared with tropisetron (P=0.01) (47). Another study reported significantly higher complete (no emesis or nausea) and major responses (single emetic episode or no emesis but moderate to severe nausea) in the acute phase across multiple cycles for ondansetron compared with tropisetron (P=0.021) (34).

Conversely, palonosetron had significantly higher rates of complete response compared with ondansetron in the acute, delayed, and overall phases, and was significantly superior to ondansetron in preventing acute emesis (lower bound of the 97.5% CI >0; P=0.009) (52). Palonosetron was non-inferior to dolasetron in the prevention of acute emesis (51), with significantly higher response rates observed in the delayed (P=0.004) and overall (P=0.021) phases, significantly higher numbers of patients with no emesis, no rescue medication use, and no more than mild nausea in the delayed (P=0.0018) and overall phases (P=0.027), significantly fewer emetic episodes in the acute (P=0.0135), delayed (P=0.0183), and overall (P=0.0036) phases, as well as a greater proportion of patients with no emetic episodes in the delayed and overall phases for palonosetron, compared with dolasetron (51). Finally, one pivotal Japanese study reported the non-inferiority of palonosetron to granisetron in controlling acute emesis, with significantly more patients reporting no emesis in the delayed phase (55). While this study used 0.75 mg of palonosetron, data from a subgroup analysis of a larger meta-analysis of palonosetron in CINV have shown that the doses appear to be equivalent in terms of efficacy (57). No statistical difference was seen between the 0.25- and 0.75-mg doses of palonosetron in controlling CINV in the acute (P=0.50), delayed (P=0.68), and overall (P=0.38) phases.

Both tropisetron and palonosetron were generally well tolerated, with AE profiles consistent with drugs of this class (19). In line with other 5-HT3 RAs, tropisetron appears less effective in controlling CINV, regardless of the phase.
It is worth noting that today multinational guidelines (12,13) recommend the use of 5-HT\textsubscript{3} RAs in combination with an NK\textsubscript{1} RA (such as aprepitant) and dexamethasone for preventing HEC- (and MEC-) mediated CINV. The inclusion of this class of drugs reflects their purported ability to inhibit emesis by blocking the binding of substance P to the NK\textsubscript{1} receptor in the brain stem emetic center (58).

Aprepitant was the first European Medicines Agency (EMA)- and US Food and Drug Administration (FDA)-approved NK\textsubscript{1} RA for the prevention of CINV in the HEC setting [2003], and in the MEC setting [2005] (59-61); it was followed by fosaprepitant, its water-soluble prodrug. Various studies have demonstrated the safety and efficacy of both agents in the prevention of HEC- or MEC-mediated CINV (62-65). Two other NK\textsubscript{1} RAs have since become commercially available: rolapitant was approved for delayed CINV prevention (66), and netupitant (administered as a convenient fixed combination with palonosetron, known as NEPA) was approved for the prevention of acute and delayed nausea and vomiting in the HEC and MEC settings (67). In addition, in August 2019, oral NEPA was approved by the Chinese National Medical Products Administration (NMPA) for the prevention of acute and delayed CINV associated with HEC or MEC settings. This approval was granted on the basis of the outcomes of a phase III study in adult Asian patients, in which a single dose of NEPA demonstrated comparable efficacy to a standard 3-day regimen of aprepitant plus granisetron (68). The IV formulation of NEPA was recently approved by FDA and is under evaluation by EMA. While the addition of rolapitant to a standard antiemetic regimen has proven effective [reviewed in Heo and Deeks, 2017 (69)], evidence suggests there is no consistent improvement in nausea protection (70,71). In contrast, the administration of oral NEPA and dexamethasone results in significant improvement in delayed and overall nausea control compared with oral palonosetron alone and dexamethasone in patients receiving cisplatin or anthracycline-cyclophosphamide (72,73). Finally, the addition of an NK\textsubscript{1} RA has proven to be more effective in controlling CINV in HEC and MEC settings, compared to the standard 5-HT\textsubscript{3} RA plus dexamethasone combination.

In conclusion, this review has shown that the newer 5-HT\textsubscript{3} RA, palonosetron, is an effective first-line agent in preventing CINV in patients receiving MEC or HEC, and its efficacy can be further increased in combination with an NK\textsubscript{1} RA. The high levels of emetic control observed in the acute, delayed, and overall phases twinned with its safety profile suggest that palonosetron is a very feasible prophylactic agent with a potentially improved therapeutic profile compared with tropisetron for controlling CINV in acute and delayed phases.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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