New options and controversies in the management of chemotherapy-induced nausea and vomiting

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Purpose. An expanding array of options for prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), including regimens containing olanzapine or recently approved neurokinin 1 (NK₁) receptor antagonists, are reviewed.

Summary. Up to 80% of patients receiving chemotherapy have CINV. Current practice guidelines recommend that patients treated with highly emetogenic chemotherapy also receive a 3-drug antiemetic regimen initiated on the day of and continued for 3 days after chemotherapy administration, with the most commonly used 3-drug regimen consisting of an NK₁ receptor antagonist, a 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist, and dexamethasone. Developments in the area of CINV management in recent years include the use of olanzapine in combination with a 5-HT₃ antagonist and dexamethasone; Food and Drug Administration (FDA) approval of the NK₁ receptor antagonist rolapitant, which provides a longer duration of effect than aprepitant; FDA approval of a combination product containing palonosetron and the NK₁ receptor antagonist netupitant; and revisions of U.S. practice guidelines ending palonosetron’s status as the preferred 5-HT₃ antagonist for prevention of CINV associated with moderately or highly emetogenic chemotherapy.

Conclusion. Newer therapeutic options for the management of CINV are equivalent to standard-of-care regimens in terms of efficacy and toxicity. While the NK₁ receptor antagonist rolapitant and a product combining palonosetron and netupitant have potential advantages over standard therapy in terms of convenience or pharmacologic properties, their relatively high costs must be considered.

Keywords: chemotherapy-induced nausea and vomiting, serotonin receptor antagonists, NK receptor antagonists

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Despite advances in the prevention and management of chemotherapy-induced nausea and vomiting (CINV), these adverse effects remain among the most feared and occur in up to 80% of patients receiving chemotherapy. CINV can have a significant impact on patients’ quality of life and are also associated with complications such as electrolyte imbalances, dehydration, and malnutrition. One assessment of a group of 178 patients starting chemotherapy found that of the 61.2% of patients who reported CINV, 37.2% also reported reduced daily functioning. Because of the complications associated with CINV, these adverse effects can also carry an economic burden. In a study evaluating the costs associated with CINV, researchers used a database to identify 19,139 patients whose records indicated a CINV-related diagnosis code. Of these patients, 13.8% had a CINV-related inpatient, outpatient, or emergency room visit, and the mean cost of these visits was $5,299. When averaged across all patients who experienced CINV, the mean CINV-associated cost was $731 per patient. The quality of life
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and economic implications of CINV for both patients and health systems make prevention and management of these adverse effects particularly important.

As understanding of CINV causes and predisposing factors has advanced, so too have the medications used to treat and prevent these adverse effects of chemotherapy. The phenothiazine family, which includes prochlorperazine and promethazine, was the first group of medications demonstrated to provide significant control of CINV, but these medications are largely ineffective in patients receiving highly emetogenic chemotherapy (HEC).4 High-dose metoclopramide (2–3 mg/kg every 2–3 hours starting 30 minutes prior to chemotherapy and continuing for 8–9 hours) was the first agent demonstrated to have a beneficial effect in preventing the severe nausea and vomiting associated with highly emetogenic cisplatin therapy.3 The use of metoclopramide for CINV prophylaxis was supplanted by the use of 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists such as ondansetron, which have proved to be more effective in preventing CINV and have a better toxicity profile.4 The addition of dexamethasone to 5-HT3 antagonist therapy provided additional benefits in preventing CINV, with a 32-study meta-analysis indicating a 16% decrease in the pooled risk for emesis and the need for rescue antiemetics with the use of combination therapy versus 5-HT3 antagonists alone.6 The discovery of neurokinin 1 (NK1) receptor antagonists and the use of these agents in combination with 5-HT3 antagonists and dexamethasone led to further reductions in rates of both acute and delayed CINV (i.e., CINV occurring 0–24 and 25–120 hours after chemotherapy administration, respectively).7,8

The emetogenicity of the anticancer agent is the single most important risk factor for CINV and is the main focus in the selection of a prophylactic antiemetic regimen. Each anticancer agent is classified by emetogenicity, a measure of how likely a patient receiving the agent would be to vomit without antiemetic premedication.14,15 HEC is defined as chemotherapy associated with vomiting in more than 90% of patients, while moderately emetogenic chemotherapy (MEC) describes chemotherapy that induces vomiting in 30–90% of patients. Anticancer agents with low emetogenicity are those associated with vomiting in 10–30% of patients; minimally emetogenic medications induce emesis in less than 10% of patients.14,15 For some agents, such as cyclophosphamide and doxorubicin, emetogenicity depends on the dose administered. The route and frequency of administration can also influence a patient’s risk of experiencing CINV, as can patient-specific factors such as age, sex, and history of alcohol use.16 Younger and female patients both tend to experience more frequent and severe CINV, while patients with a history of chronic alcohol intake tend to be less affected by CINV.17-19

Both the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend that patients treated with HEC receive a 3-drug antiemetic regimen initiated on the day of chemotherapy administration and continued for 3 days; common regimens consist of an NK1 antagonist, a 5-HT3 antagonist, and dexamethasone.20,21 Rates of complete control (no emesis and no use of rescue medications) in clinical trials ranged from 59% to 89% with various 3-drug combinations versus 40–52% with dexamethasone and a 5-HT3 receptor antagonist alone.8,12,22-24 Both NCCN and ASCO consider all of these 3-drug regimens equivalent in terms of efficacy for patients receiving HEC.20,21 Per NCCN recommendations, an alternative to a regimen consisting of a 5-HT3 antagonist, an NK, antagonist, and dexamethasone is the use of olanzapine in combination with both palonosetron and dexamethasone.25 Similar regimens are also used for patients receiving MEC, with the major difference being that these regimens are continued for only 2 days after MEC administration.

These advances in antiemetic therapy have truly revolutionized the chemotherapy experience for patients with cancer. The purpose of this article is to review the repurposing of olanzapine and the cost and place in therapy of recently approved NK, receptor antagonists in the prevention and management of CINV.

Olanzapine

Olanzapine (a thienobenzodiazepine antipsychotic initially approved for use in treating schizophrenia, bipolar disorder, and depression) is a 5-HT1, 5-HT2, and dopamine antagonist with antiemetic activity. Olanzapine was initially found to be effective in preventing CINV associated with both HEC and MEC in a Phase II trial in which 40 patients received palonosetron, olanzapine, and dexamethasone on day 1 of chemotherapy administration, with olanzapine continued on days 2–4.25 Eight of the 40 patients received HEC, and a complete response (CR), defined as no nausea or vomiting, was seen in 100% of these patients during the
“acute period” (day 1 of treatment; also called the acute phase) and in 75% of patients (6 of 8) during the “delayed period” (treatment days 2–5; also called the delayed phase). Among 32 patients receiving MEC, a CR was seen in 97% of patients (31 of 32) during the acute period and in 75% (24 of 32) during the delayed period.

In 2011, results of a Phase III trial comparing an olanzapine-based regimen with an aprepitant-based regimen in chemotherapy-naive patients receiving HEC were published.26 Of the 241 patients included in the study, 121 received palonosetron 0.25 mg i.v. on day 1 of HEC, dexamethasone phosphate 20 mg i.v. on day 1, and olanzapine 10 mg by mouth on days 1–4. Another 120 patients received identical doses of palonosetron and dexamethasone on day 1 but, in place of olanzapine, received aprepitant 125 mg by mouth on day 1, aprepitant 80 mg by mouth on days 2 and 3, and dexamethasone 4 mg by mouth twice daily on days 2–4. With regard to prevention of acute CINV, a CR was observed in 117 patients (97%) in the olanzapine group and 104 patients (87%) in the apreiptin group (p > 0.05). As for prevention of delayed CINV, a CR was observed in 93 patients (77%) in the olanzapine group and 88 patients (73%) in the aprepitant group (p > 0.05). There was one area in which a significant between-group difference was observed, with a higher percentage of patients in the olanzapine group remaining completely free of delayed nausea (84 patients [69%] in the olanzapine group versus 46 patients [38%] in the apreiptin group, p ≤ 0.01). It appears from these results that olanzapine is comparable to the current standard of care in preventing CINV associated with HEC and may be even more effective in preventing delayed nausea.

A recently published meta-analysis evaluated the efficacy of olanzapine and other antiemetic medications in the prevention of CINV.27 The investigators reviewed data from 10 randomized controlled trials (RCTs), including the Phase III trial summarized above,26 that assessed olanzapine for CINV prophylaxis in patients receiving HEC or MEC. These RCTs included a total of 1,082 patients. Only 3 studies compared olanzapine-based regimens with the standard of care (dexamethasone in combination with a 5-HT₁ antagonist and an NK₁ antagonist), while the other studies compared olanzapine with single agents or placebo use; unfortunately, no subgroup analysis comparing olanzapine with a standard-of-care regimen was performed. The majority of the RCTs used an olanzapine dose of 10 mg per day, but 2 trials evaluated a lower dose (5 mg per day). In the acute phase, authors found a significant difference in favor of olanzapine for the endpoint “no emesis” (relative risk [RR], 1.10; 95% confidence interval [CI], 1.03–1.17), but olanzapine was not superior with regard to the second endpoint, “no nausea.” In the delayed phase, olanzapine had demonstrated superiority over comparator agents or regimens in terms of both the no-emesis (RR, 1.31; 95% CI, 1.14–1.52) and no-nausea endpoints (RR = 1.41; 95% CI, 1.18–1.68); data for the overall phase were also favorable, with olanzapine’s superiority established for both endpoints (for no emesis, RR = 1.41 [95% CI, 1.18–1.68]; for no nausea, RR = 1.53 [95% CI, 1.18–1.97]). While this meta-analysis indicated that olanzapine may be superior to standard therapies, the majority of studies evaluated compared olanzapine with single agents or placebo use instead of an NK₁ antagonist. Since monotherapy is not a standard therapy for the prevention of CINV associated with HEC and MEC, this meta-analysis should not be used as evidence that olanzapine-based regimens are superior to aprepitant-based regimens.

With regard to safety, clinical trials found that the most common adverse effects reported with olanzapine-based antiemetic regimens were fatigue, drowsiness, disturbed sleep, and dry mouth. The frequency and severity of these adverse effects did not differ significantly from reported experience with other antiemetic regimens.23,26,28,29 Although not reported during the short courses of olanzapine studied in clinical trials focused on CINV, the adverse effects included in labeled warnings and precautions regarding the use of olanzapine for other indications should also be taken into account when considering this medication for CINV. Olanzapine carries a black-box warning regarding use in elderly patients with dementia-related psychosis due to an increased mortality risk observed with the use of antipsychotic agents in this population.30 Other labeled warnings and precautions pertain to neuroleptic malignant syndrome, metabolic changes, tardive dyskinesia, orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizures, hyperprolactinemia, significant drug interactions, and abnormal laboratory test results.30 Overall, the olanzapine-containing regimens appear to be well tolerated and have efficacy equivalent to that of aprepitant-based regimens. Recent updates to the NCCN guidelines added an olanzapine-containing regimen to the recommendations for prevention of CINV associated with HEC and MEC.20 Day 1 therapy consists of olanzapine 10 mg by mouth, palonosetron 0.25 mg i.v., and dexamethasone phosphate 20 mg i.v., with olanzapine 10 mg by mouth once daily continued on days 2–4 for patients receiving HEC and on days 2 and 3 for those receiving MEC. Although olanzapine was studied in combination with palonosetron, substituting an alternative 5-HT₁ antagonist can be a reasonable and cost-effective option, especially for patients who experience delayed nausea (Tables 1 and 2).

Serotonin receptor antagonists

Four 5-HT₁ antagonists are currently approved for the prevention of CINV associated with HEC and MEC: dolasetron, granisetron, ondansetron, and palonosetron.32–35 Until very recently, NCCN, ASCO, and the Multinational Association of Supportive Care in Cancer all recommended palonosetron as the preferred 5-HT₁ antagonist for prevention of CINV associated with HEC and MEC.36 A recent meta-analysis of
8 clinical trials comparing single-dose therapy with palonosetron (0.25 mg i.v.) versus other 5-HT3 antagonists, however, found that a CR was achieved in 75.2% of patients who received palonosetron and 69.2% of those in comparator groups (overall RR, 1.09; 95% CI, 1.04–1.14). This finding translated to a number needed to treat of 17 patients (95% CI, 8–26 patients). The authors of the meta-analysis, however, noted that many of the included trials compared palonosetron with nonstandard antiemetic regimens and that dosing of 5-HT3 antagonists was suboptimal in some studies. They concluded that there was no evidence demonstrating that palonosetron was more efficacious than other 5-HT3 antagonists. In recent updates to antiemetics practice guidelines, both NCCN and ASCO removed the “preferred” designation from palonosetron 0.25 mg i.v. on day 1 for prevention of CINV associated with HEC, and NCCN also made that change applicable to patients receiving MEC. Consequently, all 5-HT3 antagonists are once again considered equally effective in preventing CINV, leaving costs and patient characteristics to drive prescribing decisions.

**New NK1 receptor antagonists**

Although multiple interchangeable 5-HT3 antagonists have been available for more than a decade, until recently the only NK1 receptor antagonist available was aprepitant (and the i.v. formulation, fosaprepitant). Two new NK1 antagonists, however, were approved in recent years, giving patients and providers more options for the prevention of CINV. Akynzeo (Eisai), a combination product containing the new NK1 antagonist netupitant (300 mg) and palonosetron 0.5 mg, was approved in late 2014 for use in patients receiving HEC or MEC; it is given as a single oral dose 1–2 hours prior to chemotherapy administration on day 1 of each chemotherapy cycle. A recommended rolapitant-based regimen also calls for administration of a 5-HT3 antagonist and dexamethasone on the day of chemotherapy administration, with the latter continued for 2 or 3 days after. After its approval in 2014, Akynzeo (used in combination with dexamethasone) was added to both the NCCN and ASCO guidelines as an option for prevention of CINV associated with HEC or MEC. In a dose-ranging study conducted outside the United States, 694 chemotherapy-naive patients who were to receive cisplatin-based chemotherapy received an antiemetic regimen of palonosetron 0.5 mg on day 1 and dexamethasone by mouth on days 1–4. They were also randomly assigned to placebo use (136 patients) or to receive netupitant 100 mg (135 patients), 200 mg (137 patients), or 300 mg (135 patients) on day 1. The primary aim of the study was to compare the 3 doses of netupitant with placebo use in terms of CR (no emesis and no use of rescue medication) over 0–120 hours. The trial also evaluated an “exploratory arm,” in which 136 patients received a standard 3-day course of aprepitant with ondansetron 32 mg i.v. on day 1 and dexamethasone on days 1–4. Notably, in the United States, the maximum recommended i.v. dose of ondansetron is 16 mg due to concerns about Q-T interval prolongation, and the standard duration of therapy is 4 days instead of 1 day. The CR rates for the overall period (i.e., the acute and delayed periods combined) were 76.5% (104 of 136 patients) in the placebo group, 87.4% (118 of 135 patients) in the 100-mg group (p = 0.018 for comparison with placebo use), 87.6% (120 of 137 patients) in the 200-mg group (p = 0.017 for compar-
The toxicity profile of the netupitant–palonosetron combination did not differ significantly from that of palonosetron monotherapy; the most common adverse events in both study groups were headache and constipation.

Another Phase III trial evaluated the same netupitant–palonosetron formulation in 413 chemotherapy-naïve patients receiving HEC or MEC.24 Patients were randomly assigned to receive netupitant–palonosetron and dexamethasone on day 1 of chemotherapy or a standard 3-day regimen of aprepitant with palonosetron and dexamethasone; dexamethasone was continued on days 2–4 in patients receiving HEC. The primary objective of this study was to assess the safety of palonosetron and netupitant over 6 cycles of therapy, and the authors did not plan a statistical comparison of the netupitant- and aprepitant-treated groups. Over the course of all cycles of therapy, treatment-related adverse effects occurred in 10.1% of patients (31 of 308) in the netupitant group, as compared with 5.8% of patients (6 of 104) in the aprepitant group. In the netupitant group, there were 2 serious treatment-related adverse effects (ventricular systole and psychosis) and 1 severe (unspecified) effect, and 1 patient discontinued treatment. There were no serious or severe adverse reactions in the aprepitant group, and no patients discontinued treatment. A CR (no emesis and no use of rescue medications) in the overall period (0–120 hours after chemotherapy) of cycle 1 was observed in 250 of 309 patients (81%) in the netupitant group, versus 78 of 103 patients (76%) in the aprepitant group. Patients completed a total of 1,961 cycles of chemotherapy (76% with MEC and 24% with HEC), and CR rates in the 2 groups (and the between-group difference in CR rates) were maintained throughout repeated cycles. The investigators concluded that the combination of netupitant–palonosetron with dexamethasone was both safe and effective.

Rolapitant was approved by the Food and Drug Administration (FDA)
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on September 2, 2015, and subsequently received a category 1 recommendation from NCCN for use in combination with a 5-HT\textsubscript{3} antagonist and steroid therapy in the context of HEC and MEC.\textsuperscript{2,33} One publication that supported FDA approval of this agent for prevention of CINV associated with HEC reported on an analysis of pooled data from 2 Phase III trials comparing rolapitant use (180 mg by mouth on day 1 of chemotherapy) with placebo use.\textsuperscript{39} In addition, all patients received granisetron 10 μg/kg i.v. and dexamethasone 20 mg by mouth on day 1 and dexamethasone 8 mg by mouth twice daily on days 2–4. The pooled analysis included data on 535 patients who received rolapitant and 535 placebo users. The researchers found that patients in the rolapitant group had a better CR rate in the delayed period than placebo recipients (71% [\(n = 382\)] versus 60% [\(n = 322\)], \(p = 0.0001\)). Adverse effects were similar in the 2 groups, with the most frequently reported events being headache, hiccups, constipation, and dyspepsia (all occurred at a rate of <1% in both groups).

Another Phase III trial of rolapitant focused on chemotherapy-naïve patients receiving MEC.\textsuperscript{40} Patients were randomly assigned to receive rolapitant 180 mg by mouth (684 patients) or a placebo (685 patients) on day 1. All patients also received granisetron 2 mg by mouth and dexamethasone 20 mg by mouth on day 1, with granisetron continued on days 2 and 3. This study, too, found a better CR rate in the delayed period among patients receiving rolapitant versus placebo users (71% [\(n = 475\)] versus 62% [\(n = 410\)], odds ratio, 1.6; \(p = 0.0002\)). The frequencies of adverse effects were similar in the 2 treatment groups, with fatigue, constipation, and headache most frequently reported.

It appears that a key advantage of rolapitant over other agents for CINV control is its long elimination half-life (169–183 hours),\textsuperscript{38} which is longer than that of aprepitant (9–13 hours).\textsuperscript{41} Still, the clinical significance of rolapitant’s long half-life for the majority of patients is unclear. Patients receiving cisplatin, for example, usually experience the onset of delayed CINV within 24–72 hours after chemotherapy administration, and the rolapitant clinical trials evaluated CR during the delayed period in terms of the standard definition of that period (i.e., 25–120 hours after chemotherapy administration).\textsuperscript{39,40}

Roplatin has an average wholesale price of $636 per dose,\textsuperscript{11} so, with such a high cost of therapy (relative to the cost of other NK\textsubscript{1} inhibitors such as fosaprepitant), it is important to consider whether or not the theoretically prolonged therapeutic coverage is worth the additional cost to the patient and the health system. While rolapitant may have a place in therapy for patients who experience very delayed CINV while using more established agents, it is difficult to recommend this medication as first-line therapy.

It is important to note that the clinical trials evaluating the efficacy and safety of rolapitant and some trials assessing netupitant involved comparisons with placebo use rather than use of another NK\textsubscript{1} antagonist. In the context of HEC especially, the standard of care is a combination regimen containing 3 antiemetic medications with unique mechanisms of action. The NK\textsubscript{1} antagonist aprepitant has been included in the NCCN guidelines since 2004, and aprepitant-containing regimens offer a degree of benefit similar to that provided by rolapitant-based regimens—an improvement of about 10–20% in CR rates—relative to regimens consisting of only a 5-HT\textsubscript{3} antagonist and a steroid.\textsuperscript{12,42}

**Place in therapy**

Advances in the prevention and management of CINV over the past couple of decades have gone a long way to improve patients’ experiences with adverse effects of chemotherapy, and patients and clinicians now have a number of options for the prevention of CINV. Given that the regimens described here are considered equivalent in terms of efficacy and adverse effects, the choice of a regimen may be based on cost (Tables 1 and 2).

For most patients, a regimen consisting of fosaprepitant, ondansetron, and dexamethasone will not only be effective but will cost hundreds of dollars less per administration. It is also important to remember that these antiemetic regimens are not given just once; rather, the patient must receive these medications with each administration of HEC or MEC.

Many of the newer medications may have advantages over older agents used for CINV control in terms of frequency and ease of administration or duration of activity, but pursuit of these benefits must be balanced with recognition of the associated high costs. There is a place in therapy for these newer agents; their greatest utility likely lies in improving outcomes in patients who are refractory to or who experience adverse effects with the more established regimens for CINV prevention and treatment. If high-quality cancer care is to be sustainable, healthcare providers will increasingly need the ability to delineate statistical significance from clinical significance when evaluating clinical trial data and to make judgments regarding cost-effectiveness.

**Conclusion**

Newer therapeutic options for the management of CINV are equivalent to standard-of-care regimens in terms of efficacy and toxicity. While the NK\textsubscript{1} receptor antagonist rolapitant and a product combining palonosetron and netupitant have potential advantages over standard therapy in terms of convenience or pharmacologic properties, their relatively high costs must be considered.

**Disclosures**

The authors have declared no potential conflicts of interest.

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