Chemotherapy-Induced Nausea and Vomiting: Which Antiemetic for Which Therapy?

By Lee S. Schwartzberg, MD [2]

Chemotherapy-induced nausea and vomiting (CINV) remains an important and common toxicity of cancer treatment. Recent guideline revisions have classified chemotherapeutic agents into four categories of emesis risk without the use of preventive agents: high (> 90%), moderate (30%-90%), low (10%-30%), and minimal (< 10%). Currently available antiemetic agents, including corticosteroids, 5-hydroxytryptamine (HT)3 receptor antagonists, and neurokinin (NK)-1 antagonists are used alone or in combination depending on the level of emetogenic potential as prophylaxis against the development of CINV during the acute period (up to 24 hours after chemotherapy) and the delayed period (up to 5 days after treatment). Newer agents, including the second-generation 5-HT3 receptor antagonist palonosetron (Aloxi) and the NK-1 antagonist aprepitant (Emend), offer additional clinical benefit in highly and moderately emetogenic therapy. However, delayed nausea and vomiting continue to occur frequently in many patients and have an impact on quality of life. Other classes of agents including the benzodiazepines and cannabinoids offer the potential for additional protective benefit. Continued research with new drugs and combinations is necessary to meet this significant unmet need of cancer patients.

Nausea and vomiting caused by the administration of cancer chemotherapy (CINV) is one of the most common and distressing side effects of cancer treatment.[1] Arguably, the development of effective combination chemotherapy regimens capable of prolonging lives and curing patients could not proceed until the parallel development of effective CINV prevention and treatment strategies. Indeed, I vividly remember young testicular cancer patients in the early 1980s who were extremely reluctant to continue curative high-dose cisplatin-based treatments following one cycle delivered without effective antiemetic therapy. Advances in antiemetic development thankfully make such a situation extremely rare today.

This review will focus on the updated classification of the emetogenic potential of available chemotherapeutic agents and current recommendations for the prevention and treatment of CINV based on recent clinical trial evidence.

Physiology of Emesis

Central to the development of modern antiemetic therapy was the understanding of the physiology behind the emetic response. Vomiting is a natural protective mechanism against the ingestion of toxic agents and results from signals triggered by pathways in both the brain and gastrointestinal (GI) tract. A chemoreceptor trigger zone (CTZ) in the brainstem is activated by noxious stimuli and, in turn, stimulates the vomiting center in the medulla. The vomiting center sends signals for salivation, respiratory change, and pharyngeal, GI, and abdominal muscle contractions, which result in vomiting. The enterochromaffin cells of the GI tract contain receptors that can trigger the afferent vagus nerve to stimulate the CTZ and initiate the emesis process.[2] Multiple neurotransmitters are involved in this physiologically complex process. The most important neurotransmitters are the 5-hydroxytryptamine (HT)3 or serotonin receptors, the dopamine receptors, and the neurokinin (NK)-1 receptor, but others include those for histamine, endorphins, acetylcholine, cannabinoids, and gamma-aminobutyric acid (GABA). Typically, multiple receptors are involved in an emesis event.[3] Antagonists to one or more of these receptors form the basis of pharmacologic emesis control.[4]

Classification of CINV

CINV can be classified into four general categories: acute, delayed, anticipatory, and breakthrough. Acute CINV is defined as nausea and/or vomiting occurring in the first 24 hours following chemotherapy administration. Delayed CINV is arbitrarily defined as occurring after the first 24 hours
and up to 120 hours after chemotherapy.[5] Anticipatory CINV is a learned or conditioned response that occurs in patients who have had poorly controlled nausea and vomiting during prior chemotherapy. Anticipatory CINV has been reported in up to 18%-57% of patients[6] and typically responds better to behavioral modification or nonpharmacologic approaches. Primary and secondary prophylaxis against each of these types of CINV reduces the risk of events. However, some patients develop breakthrough CINV, defined as episodes occurring despite appropriate prophylactic use of antiemetics. Breakthrough CINV is generally addressed through the use of antiemetic agents in classes other than those used during the prophylactic phase.

Classification of Chemotherapeutic Agents by Emetogenic Risk

A major advance in determining risk for CINV by agent was achieved in 1997, when Hesketh et al devised a classification schema dividing chemotherapeutic agents into five levels according to the percentage of patients experiencing acute emesis without prophylactic antiemetic therapy in clinical trials: level 1 (< 10%), level 2 (10%-30%), level 3 (30%-60%), level 4 (60%-90%), and level 5 (> 90%).[7] This system was updated by Grunberg and colleagues in 2005 by collapsing the levels into four categories of risk: > 90%, 30%-90%, 10%-30%, and < 10%.[8] In patients receiving combination chemotherapy, the highest-level drug defines the risk. In addition, a separate classification for oral agents was provided.

### TABLE 1

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<thead>
<tr>
<th>Emetogenic Risk Associated With Intravenously Administered Antineoplastic Agents</th>
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<td>In 2006, the American Society of Clinical Oncology (ASCO) published a revision of their evidence-based antiemetic guidelines—the first update of their recommendation since 1999.[9] National Comprehensive Cancer Network (NCCN) guidelines, updated yearly by consensus standards, classify agents very similarly to the ASCO guidelines.[10] The 2006 revised emetogenic risks for antineoplastic agents are presented in Table 1. Agents in the highest-risk group include many drugs no longer regularly employed in current chemotherapy regimens but do contain cisplatin and dacarbazine. The moderate-risk group (&gt; 30%-90% emesis risk) contains many of the commonly used drugs to treat cancer including carboplatin, oxaliplatin (Eloxatin), cyclophosphamide, doxorubicin, epirubicin (Ellence), and irinotecan (Camptosar). Drugs considered to have low emetogenic risk (10%-30%) include the taxanes, etoposide, and biologics such as trastuzumab (Herceptin) and cetuximab (Erbitux). Some antineoplastic agents such as the vinca alkaloids as a class or bevacizumab (Avastin) are associated with minimal risk of emesis without prophylaxis (&lt; 10%). Clinicians should be aware of recent changes in the 2006 ASCO guidelines—for example, paclitaxel and gemcitabine (Gemzar) being reclassified as low-risk rather than minimal-risk drugs while others (eg, vincristine, fludarabine) have changed from low to minimal risk. In addition to the type of chemotherapeutic agent, patient-specific risk factors are known to increase the likelihood of developing CINV. These include age &lt; 50 years, history of light alcohol use, history of vomiting associated with previous chemotherapy, nausea or vomiting during pregnancy, history of motion sickness, and extreme anxiety.[11] Gender also plays a role, as women are more likely to experience CINV than men. A complete patient history aids in identifying historical risk factors that can affect the level of emetogenic risk and alter the antiemetic therapy prescribed.</td>
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Dopamine antagonists, corticosteroids, serotonin antagonists, neurokinin antagonists, and cannabinoids. Early trials evaluated antidopaminergic agents such as phenothiazines and high-dose metoclopramide, which proved to be of limited efficacy or high toxicity. Current guidelines recommend that patients be treated with antiemetic regimens offering the highest therapeutic index. In practice, this means a combination of a 5-HT3 receptor antagonist, corticosteroids, and an NK-1 antagonist.

5-HT3 Receptor Antagonists

The first-generation 5-HT3 receptor antagonists include ondansetron (Zofran), dolasetron (Anzemet), granisetron (Kytril), and tropisetron (not available in the United States). While chemical structure and pharmacologic characteristics vary among these drugs, they have equivalent efficacy and safety profiles and can be used interchangeably—conclusions supported by category 1 evidence and three sets of treatment guidelines, from ASCO, NCCN, and the Multinational Association of Supportive Care in Cancer (MASCC).[9,10,13]

Multiple clinical trials support these recommendations. For instance, a double-blind randomized study compared IV dolasetron to IV ondansetron to prevent CINV after cisplatin-based chemotherapy. This study demonstrated the comparable efficacy and safety of a single dose of dolasetron compared to a single 32-mg dose of ondansetron after highly emetogenic chemotherapy. Similarly, a single dose of IV granisetron showed similar efficacy to three doses of ondansetron in chemotherapy-naive patients receiving high-dose cisplatin at doses > 60 mg/m².[14] The first-generation 5-HT3 receptor antagonists have been shown to undergo very good GI absorption, which led to the testing of oral formulations for efficacy. A multicenter, randomized, double-blind study of over 1,000 patients scheduled to receive highly emetogenic cisplatinum-based chemotherapy received either 2 mg of oral granisetron or 32 mg of IV ondansetron prior to chemotherapy administration. Activity was comparable between the two groups, with 54.7% of granisetron-treated patients and 58.3% of ondansetron-treated patients achieving total control of emesis.[15] Similarly, single-dose oral granisetron was shown in another large trial of moderately emetogenic chemotherapy to be equivalent to IV ondansetron in this setting. Complete response, defined as no emesis or no need for any breakthrough medication, was achieved by 59.4% of granisetron-treated patients vs 58% of ondansetron-treated patients.[16]

The toxicity profile of 5-HT3 receptor antagonists is modest. The most commonly reported toxicity includes headache in 10% to 15% of patients and constipation in 10% to 15%. Rare adverse reactions include anxiety, dizziness, diarrhea, and fatigue. Individual reactions can vary from one agent to another. Thus, if a patient experiences headache with one 5-HT3 receptor antagonist, switching to a different agent often abrogates this toxicity while maintaining efficacy. Recently, potential differences in the metabolism of these agents based on pharmacogenetic variations in the cytochrome P450 system have been described. CYP2D6 is involved in the metabolism of all 5-HT3 receptor antagonists except granisetron.[17] In an intriguing trial that included genotyping for CYP2D6 in patients receiving either ondansetron or tropisetron, investigators were able to sort patients into three clinical groups: poor metabolizers of CYP2D6 with the lowest incidence of CINV, extensive metabolizers with an intermediate incidence of CINV, and ultrafast metabolizers with the highest incidence of CINV after emetogenic chemotherapy.[18] Of the available 5-HT3 receptor antagonists, granisetron exclusively is not metabolized through CYP2D6. Instead, this drug is metabolized by CYP3A subtypes and the CYP1A1 enzyme. While not yet standard clinical practice, determination of a patient's pharmacokinetic profile may be of use in selecting antiemetic agents.

Although first-generation 5-HT3 receptor antagonists were a major clinical advance in prophylaxis against CINV, nausea and vomiting remain significant issues for many patients receiving antiemetic therapy.[20,21] Palonosetron (Aloxi), a novel 5-HT3 receptor antagonist with pharmacokinetic properties that differ from other agents in its class was approved by the US Food and Drug Administration (FDA) in 2003, making it the first new drug for CINV in a decade. Palonosetron has a 100-fold greater binding affinity for the type 3 serotonin receptor, and its half-life of approximately 40 hours is significantly longer than that of other 5-HT3 receptor antagonists.
Palonosetron vs 5-HT3 Receptor Antagonists

Palonosetron was compared in head-to-head trials against either 32 mg of ondansetron or 100 mg of dolasetron.[22,23] A single dose of palonosetron at 0.25 mg IV provided a statistically significant improvement in complete response compared with either of the other two agents. Palonosetron maintained its superiority through the period of delayed CINV for 120 hours from chemotherapy administration. Overall complete response over the 5-day period was observed in 57.7% of patients receiving palonosetron compared to 42.0% for ondansetron/dolasetron (Figure 1).[24]

Another phase III trial compared palonosetron to ondansetron with dexamethasone after highly emetogenic chemotherapy.[25] Palonosetron plus dexamethasone produced a complete response rate of 40.7% vs 25.2% for ondansetron plus dexamethasone throughout the 5-day postchemotherapy period. Palonosetron is approved for the prevention of acute and delayed CINV following moderately emetogenic chemotherapy and for the prevention of acute CINV associated with highly emetogenic chemotherapy. Because of its long half-life, palonosetron is not indicated for multiple-day usage in multiple-day chemotherapy regimens.

A phase II trial evaluated the combination of palonosetron (0.25 mg IV) and dexamethasone (8 mg po) on day 1 prior to receiving moderately emetogenic chemotherapy. In this small study, the complete response rate for the first 24 hours was 84.4%; over the entire 120-hour period of evaluation, 59% had a complete response, 77% had no emetic episodes, and 66% required no rescue medication.[26]

Neurokinin-1 Antagonists

A new class of agents for CINV was introduced with aprepitant (Emend), a novel NK-1 antagonist approved in 2003. This agent blocks the neurokinin receptor and thus enhances the activity of 5-HT3 receptor antagonists with a complementary mechanism of action.[27,28] Aprepitant added to ondansetron and dexamethasone provided a greater degree of protection against acute and delayed CINV than ondansetron and dexamethasone alone after high-dose cisplatin chemotherapy, with complete response rates of 72.7% vs 52.3% on days 1 to 5.[29] FIGURE 2

Addition of Aprepitant to 5-HT3 Receptor Antagonist/Dexamethasone

A randomized double-blind placebo controlled study in breast cancer patients receiving an anthracycline and cyclophosphamide evaluated the use of ondansetron (8 mg po bid) and dexamethasone (20 mg bid) on day 1, compared to the same combination of ondansetron and dexamethasone plus aprepitant (125 mg on day 1) followed on days 2 and 3 by additional doses of aprepitant (80 mg).[30] Overall, the complete response rate during days 1 through 5 was superior for the aprepitant-containing arm—51% vs 42% (P = .015, see Figure 2). A recent combined analysis reviewing over 1,000 patients receiving high-dose cisplatin-containing regimens suggested aprepitant improves control of CINV differentially in women, and therefore may negate the adverse prognostic effect of female gender.[31]

Aprepitant alone or in combination with dexamethasone does not control acute emesis as well as 5-HT3 receptor antagonists and dexamethasone.[32] However, aprepitant does appear to retain its
benefit when used in multiple cycles of cisplatinum-based chemotherapy. Aprepitant is metabolized through the CYP3A4 enzyme, and dose adjustments of other common medications using this pathway, particularly dexamethasone and warfarin, should be considered. The availability of newer antiemetics led to a phase II trial of the combination of palonosetron, dexamethasone, and aprepitant in patients receiving moderately to highly emetogenic chemotherapy. Patients received aprepitant (125 mg po) 1 hour before chemotherapy on day 1 followed by palonosetron (0.25 mg IV) and dexamethasone (12 mg po) a half-hour before chemotherapy. On days 2 and 3, patients received aprepitant (80 mg po) and dexamethasone (8 mg po). Intent-to-treat analysis demonstrated an 88% complete response rate during the first 24 hours and an overall complete response rate of 78% over 5 days. These encouraging results will hopefully be confirmed in other trials.

Cannabinoids and Other Antiemetics

Other classes of agents appear to have activity in preventing CINV. Olanzapine (Zyprexa), an antipsychotic thienobenzodiazepine, was evaluated in sequential phase I/II studies. A regimen of oral olanzapine at 5 mg on days -2 and -1, olanzapine at 10 mg added to IV granisetron and dexamethasone on day 1, followed by dexamethasone and olanzapine at 10 mg po on days 2 to 4 was evaluated. The complete response rate in 30 patients receiving moderately to highly emetogenic chemotherapy was 100% in the acute period and 80% during the delayed period. No severe toxicities were noted, and this combination appeared effective over multiple cycles. There is a resurgent interest in the use of cannabinoids in CINV. In part, this is due to an enhancement of knowledge concerning endogenous cannabinoids and their receptors. The CB-1 receptor, a member of a large family of receptors coupled to G-proteins, is found in high quantities in the basal ganglia, cerebellum, brainstem, and hypothalamus. The second receptor subtype, the CB-2, has been identified predominantly in cells of the immune system. Both CB-1 and CB-2 receptors are activated by THC, the constituent most responsible for marijuana's pharmacologic activity. Natural endogenous ligands for both cannabinoid receptors have been identified, as have signaling pathways and synthetic and metabolic pathways for these ligand-receptor complexes. Animal models support a role for the endocannabinoids in controlling emesis. Two pharmaceutical cannabinoids have been approved in the United States for the prevention and treatment of CINV—dronabinol (Marinol) and nabilone (Cesamet). The pharmacokinetics of both drugs are similar, although nabilone has fewer metabolites and a longer duration of action, allowing less frequent twice-daily dosing. Clinical trials evaluating dronabinol and nabilone were predominantly performed in the era before 5-HT3 receptor antagonists were available. A systematic review of available trials evaluating the use of cannabinoids for control of CINV was published in 2001. Most of these trials compared dronabinol and nabilone to prochlorperazine, metoclopramide, domperidone, or placebo in moderately to highly emetogenic chemotherapy during the first 24 hours after treatment. Across all trials, cannabinoids were more effective than active comparators and placebo with a number needed to treat of 6.4 to 8.0 to achieve complete control of nausea and vomiting compared to an active comparator. Interestingly, patients highly prefered the cannabinoid over active comparators or placebo. However, significant psychotropic side effects were identified with the cannabinoids. Some of these side effects were potentially beneficial, such as a feeling of euphoria, high sensation, drowsiness, or sedation, while some were distressing or harmful, such as dizziness, dysphoria, or even hallucinations or paranoia in a small fraction of patients. It should be noted that these studies employed relatively high doses of dronabinol. Surprisingly, there have been no well-controlled studies of cannabinoids in the era of combination antiemetic therapy with 5-HT3 receptor antagonists plus dexamethasone. Given the significant number of patients with delayed CINV and the unmet need for additional effective agents in this setting, the opportunity for further study is clear.

Prevention and Treatment of Delayed CINV

REFERENCE GUIDE

Therapeutic Agents

Mentioned in This Article
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The perception among health-care providers persists that patients are achieving good control of CINV during both the acute and delayed periods following emetogenic chemotherapy. Patient surveys suggest a disparity between the provider’s belief and reality.[39]

In a prospective trial focusing on delayed CINV recently reported by Hickock et al,[21] 704 chemotherapy-naive patients receiving an anthracycline-based chemotherapy regimen were treated with an oral 5-HT3 receptor antagonist plus dexamethasone on day 1 followed by dexamethasone on day 2. They were then randomized to receive an oral 5-HT3 receptor antagonist on days 2 to 5 vs...
prochlorperazine on days 2 to 5 on a fixed schedule vs prochlorperazine as needed after
breakthrough nausea and vomiting. 5-HT3 receptor antagonists proved no better than
prochlorperazine in reducing delayed CINV, and in fact, more patients receiving 5-HT3 receptor
antagonists required rescue medication (45%) than those on the prochlorperazine arms (27%-30%; \( P = 0.002 \)). More emetic events occurred during the delayed period (34%) than the acute period (19%;
\( P < 0.01 \)). Overall, 75% of patients experienced nausea during the delayed period.
A recent study addressed patient quality of life (QOL) as prospectively reported using a validated
tool—the Functional Living Index-Emesis (FLIE) questionnaire—before and on day 6 following
moderately emetogenic chemotherapy or highly emetogenic chemotherapy.[40] Almost all patients
were treated in accordance with standardized guidelines, including a 5-HT3 receptor antagonist
and dexamethasone. Despite prophylactic treatment, delayed nausea occurred in 54.3% of patients and
delayed emesis, in 32.5%. The investigators found little difference in delayed nausea between the
levels of emetogenic risk. Patients reported more impact on daily living in QOL from nausea than
from vomiting. Overall, nearly one in two patients suffered an impact on QOL during the delayed
period. A substantial fraction of patients not experiencing acute nausea or vomiting felt an impact on
their quality of life during the delayed period. These results are consistent with the observation that
5-HT3 receptor antagonists[41] and NK-1 antagonists[30] are less effective in preventing nausea
than vomiting.
Another recent study addressed the effect of CINV and QOL across 10 community oncology
practices.[42] During cycle 1, only 33% had neither acute nor delayed CINV; 59% of patients
reported delayed CINV, with approximately half having acute and delayed symptoms and half had
delayed CINV only. Both acute and delayed CINV had a significant impact on QOL and daily
functioning, with patients experiencing symptoms during both periods showing a greater impairment
of their daily functioning. Moreover, daily functioning levels were significantly lower when the patient
had acute or delayed CINV in the previous cycle, even when acute/delayed CINV was controlled in
the current cycle. These results suggest that the impact of CINV on a patient’s functioning and
quality of life is cumulative and persistent.
A recent meta-analysis addressed the benefit of 5-HT3 receptor antagonists in preventing delayed
emetesis from chemotherapy.[43] Five trials compared 5-HT3 receptor antagonist monotherapy with
placebo, and another five studies involving 2,240 patients compared 5-HT3 receptor antagonist plus
dexamethasone to dexamethasone alone. The absolute risk reduction for 5-HT3 receptor antagonists
was 8.2%, with a number needed to treat of 74 doses to protect one patient from delayed emesis.
For dexamethasone plus a 5-HT3 receptor antagonist, the absolute risk reduction was only 2.6%
(95% confidence interval = -0.6% to 5.8%), and 423 doses of a 5-HT3 receptor antagonist would be
required to protect one patient.
The abundance of evidence suggests that 5-HT3 receptor antagonists appear to offer little protective
benefit in the delayed CINV setting and certainly add little to dexamethasone. An oral 5-HT3 receptor
antagonist should not be prescribed after palonosetron, given the long half-life of palonosetron and
the potential added toxicity with no evidence of any incremental activity for combined 5-HT3
receptor antagonists.

Current Guidelines

TABLE 2

| Drug Regimens for Preventing Chemotherapy-Induced Emesis by Emetogenic-Risk Category |
| Prophylactic antiemetic regimens are guided by the maximal emetogenic potential of
chemotherapeutic regimens and are separated into prevention regimens and breakthrough
| treatment. These preventive strategies have recently been updated by both ASCO and NCCN (Table
| 2). An important revision in the classification is the classification of combination anthracyclines and
cyclophosphamide regimens into the highly emetogenic risk category. Highly emetogenic
Chemotherapy should be accompanied by a three-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant followed by dexamethasone and aprepitant on days 2 and 3.

TABLE 3

Outpatient Breakthrough Treatment for CINV

For moderately emetogenic chemotherapy, patients should receive a two-drug regimen of a 5-HT3 receptor antagonist plus dexamethasone on day 1 followed by dexamethasone alone or 5-HT3 receptor antagonist for delayed CINV. For regimens with low emetogenic potential, dexamethasone alone is recommended, whereas minimal emetic risks should not prompt routine preventive therapy. Treatment strategies for breakthrough CINV are outlined in Table 3.

Practice Guidelines

The current era of evidence-based medicine has emphasized the need for practice-based guidelines that standardize, simplify, and make more efficient the approach to common clinical scenarios. Indeed, the Centers for Medicare and Medicaid Services (CMS) demonstration projects for 2005 and 2006 included items evaluating the extent to which nausea and vomiting were evaluated with each treatment and the extent to which guidelines were followed in prescribing chemotherapy. Despite increased awareness, assessment and management of symptomatology has not been commonly standardized in most settings. Compliance with antiemetic treatment guidelines can significantly increase treatment outcomes. In one study, after adjusting for prognostic variables for delayed CINV, compliance with guidelines resulted in a decrease in the proportion of patients reporting these symptoms (55% vs 75%; \( P = .02 \)).[44] However, even when guidelines were followed, half of all patients treated with a first-generation 5-HT3 receptor antagonist still experienced delayed CINV. Similar results were observed in a European population: Compliance with guidelines reduced CINV and emesis; however, symptoms were still present in half of all cycles of therapy even when guidelines were carefully applied.[45] These results point out the ongoing need for more effective treatment of CINV. A great deal of progress has been made over the past 2 decades in preventing this common adverse effect, and hopefully, new clinical trials will focus on strategies to further reduce the morbidity associated with chemotherapy-induced nausea and vomiting.

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References:


37. Davis M, Maida V, Daeninck P, et al: The emerging role of cannabinoid neuromodulators in...


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