PREVENTION AND TREATMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING AFTER EMETOGENIC CHEMOTHERAPY

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ABSTRACT

Advances in understanding the pathophysiology of emesis have led to the development of new pharmacologic options for the management of chemotherapy-induced nausea and vomiting (CINV). Recently approved antiemetic agents, such as aprepitant and palonosetron, provide a broader range of effective options for patients undergoing chemotherapy. Studies have shown that the newest class of antiemetics—neurokinin-1 (NK1) antagonists—are effective for the control of acute CINV and delayed CINV associated with highly emetogenic chemotherapy and moderately emetogenic chemotherapy. Guidelines developed by the Multinational Association for Supportive Care in Cancer in 2004 include recommendations for the use of aprepitant, an NK1 antagonist; guidelines issued by the National Comprehensive Cancer Network include recommendations for aprepitant and palonosetron, the most recently approved 5-HT3 antagonist. Studies show that institutions often do not adopt evidence-based guidelines in a timely manner. Implementation of management guidelines may be facilitated through educational initiatives. Intervention programs can help to promote the use of agents in a clinically appropriate manner and avoid unnecessary drug costs without compromising the quality of care for patients. Further advances in the prevention and treatment of CINV depend not only upon clinical trials of existing and novel agents but also upon advances in understanding how individual patient characteristics may affect drug disposition. (Adv Stud Nurs. 2005;3(1):22-29)

Evidence suggests that the release of neurotransmitters, such as dopamine, acetylcholine, histamine, opiates, serotonin, and substance P, initiates emesis after chemotherapy.1 The antiemetics that are commonly used to prevent chemotherapy-induced nausea and vomiting (CINV) act by competitively blocking receptors for some of these substances. Although dopamine was once thought to be the neurotransmitter most responsible for CINV, clinical trials now suggest that dopamine antagonists have, at best, modest efficacy. Recent advances in the understanding of the pathophysiology of emesis have shifted attention to the 5-HT3 antagonists and the newest class of antiemetics, neurokinin-1 (NK1) antagonists, as addressed by Dr Grunberg and Ms Ireland earlier in this monograph.

This article examines the pharmacologic options for control of CINV. Evidence-based treatment guidelines are also discussed, along with the genetic influences that may affect drug metabolism and efficacy.
EFFECT OF ANTIEMETIC AGENTS

Ondansetron, granisetron, dolasetron, and palonosetron are the 5-HT₃ antagonists currently available in the United States. These agents prevent the emetic response by binding to the 5-HT₃ receptors of the vagal afferent nerves in the gastrointestinal tract and the chemoreceptor trigger zone. Serotonin antagonists are generally well tolerated, with no significant differences among the rates of adverse effects. In a paper published in 2000, del Giglio et al conducted a meta-analysis to determine if there were any therapeutic differences among the serotonin antagonists. Studies eligible for the meta-analysis were randomized controlled trials including more than 25 patients per trial arm and compared 5HT₃ antagonists for prophylaxis of acute CINV and delayed CINV. The analysis was restricted to ondansetron and granisetron because most of the randomized controlled studies compared these 2 agents. Data from 14 studies with 6467 evaluable patients were grouped into 8 different scenarios: Complete protection from acute vomiting induced by highly emetogenic chemotherapy; acute nausea induced by highly emetogenic chemotherapy; acute vomiting induced by moderately emetogenic chemotherapy; acute nausea induced by moderately emetogenic chemotherapy; delayed vomiting induced by highly emetogenic chemotherapy; delayed nausea induced by highly emetogenic chemotherapy; delayed vomiting induced by moderately emetogenic chemotherapy; and delayed nausea induced by moderately emetogenic chemotherapy. There were no significant differences in the antiemetic effects of ondansetron and granisetron in any of these scenarios. Studies have shown that patients with delayed CINV respond poorly to the 5-HT₃ antagonists ondansetron, granisetron, and dolasetron, indicating that other neurotransmitters may be involved in the pathogenesis of delayed-phase symptoms.

Results from clinical trials of the most recently approved 5-HT₃ antagonist, palonosetron, suggest that not all 5-HT₃ antagonists are equivalent. Several studies have shown that palonosetron is more effective than ondansetron and dolasetron in preventing acute CINV and delayed CINV associated with moderately emetogenic chemotherapy. However, concomitant corticosteroids were not routinely administered in these trials. Palonosetron has also been shown to be effective in preventing acute CINV associated with highly emetogenic chemotherapy.

Corticosteroids such as dexamethasone and prednisolone are commonly used in combination with 5-HT₃ receptor antagonists but may be used as single agents for relatively mild emetogenic chemotherapy (eg, vinorelbine). Although their mechanism of action is not fully understood, these antagonists may have central and peripheral effects. Dexamethasone was one of the first agents to be introduced and is the most commonly used corticosteroid for control of CINV. Ioannidis et al conducted a meta-analysis to evaluate the efficacy of dexamethasone for the prophylaxis of acute CINV and delayed CINV in patients receiving highly or moderately emetogenic cancer chemotherapy. A total of 32 studies (n = 5613) were included in the analysis. Dexamethasone was superior to a placebo or no treatment for complete protection from acute emesis (odds ratio, 2.22; 95% confidence interval [CI], 1.89–2.60) and delayed emesis (odds ratio, 2.04; 95% CI, 1.63–2.56). Similar results were reported for complete protection from nausea. None of the trials addressed the efficacy of dexamethasone in the delayed phase without also having administered dexamethasone for acute-phase protection. Therefore, it is unknown whether the delayed-phase effects of dexamethasone seen in this study were independent of the acute-phase benefit. However, other studies in which patients received dexamethasone for acute-phase and delayed-phase protection have also reported that dexamethasone, alone or in combination with metoclopramide, is significantly better than a placebo in controlling delayed CINV associated with moderately and highly emetogenic chemotherapy. Adrenocorticotropic hormone has also been shown to reduce the incidence and severity of delayed CINV after cisplatin administration.

The antiemetic effects of a 5-HT₃ antagonist and a corticosteroid can increase with the use of both agents in combination. In a study published in 1995, the Italian Group for Antiemetic Research compared the antiemetic effects of a 5-HT₃ antagonist and a corticosteroid in combination (granisetron + dexamethasone) with each agent alone in patients who received moderately emetogenic chemotherapy for the first time. Chemotherapy regimens included the following (alone or in some combination): cyclophosphamide 600 to 1000 mg/m²; 50 mg/m² or more of doxorubicin; 75 mg/m² or more of epirubicin; or 300 mg/m² or more of carboplatin. Among patients who received the combination of granisetron and dexamethasone, complete
protection from vomiting was achieved in 92.6% of patients, and protection from nausea was reported in 71.9% of patients (P < .001). Among patients who received dexamethasone, complete protection from vomiting was achieved in 70.6% of patients and complete protection from nausea was reported in 55.1% of patients. Of the patients who were administered granisetron, 72.3% reported complete protection from vomiting and 48.2% achieved complete protection from nausea (P < .001). In addition, patients who received only granisetron had less protection from delayed vomiting and nausea than those patients who received the 2 drugs combined or dexamethasone alone. The study investigators concluded that granisetron combined with dexamethasone was the most effective regimen for the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy.

Substance P is a neuropeptide that exerts its emetic effects by binding to the NK1 receptor. NK1 antagonists, which are among the newest class of antiemetics, have been shown to improve control of CINV when used in combination with dexamethasone and 5-HT3 antagonists and have also been shown to be more effective in controlling delayed CINV than placebo.17-20 These agents may also be effective in controlling delayed CINV as single agents alone.18 Several compounds selectively block NK1; however, only aprepitant has currently been approved by the US Food and Drug Administration. Aprepitant is approved for use in combination with a corticosteroid and a 5-HT3 antagonist for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy. Substances P (P < .001). Among patients who received the aprepitant regimen, as compared with 42.5% of patients who received the control regimen for the overall, delayed, and acute phases of emesis. Prospective trials in patients receiving only moderately emetogenic chemotherapy are needed to confirm the potential benefits of aprepitant reported in this subgroup analysis.

Warr et al examined the effects of aprepitant for the prevention of CINV with non–cisplatin-based moderately emetogenic chemotherapy.23 The researchers randomly assigned 866 patients (857 patients were evaluable) with breast cancer who were naïve to emetogenic chemotherapy and treated with cyclophosphamide ± doxorubicin or epirubicin; 99% of these patients were women, all of whom received cyclophosphamide and an anthracycline. Patients were randomly assigned to an aprepitant regimen (day 1: aprepitant 125 mg, ondansetron 8 mg, and dexamethasone 12 mg before chemotherapy, and ondansetron 8 mg 8 hours later; days 2–3: aprepitant 80 mg once daily) or to a standard regimen (day 1: ondansetron 8 mg and dexamethasone 20 mg before chemotherapy, and ondansetron 8 mg 8 hours later; days 2–3: ondansetron 8 mg twice daily). The primary endpoint was the proportion of patients with complete response in the 120 hours after initiation of chemotherapy (ie, defined as no vomiting and no use of rescue therapy) in cycle 1. Complete response was achieved in 50.8% of patients who received the aprepitant regimen, as compared with 42.5% of patients who received the standard regimen (P = .015). In addition, “no vomiting” was reported in more patients taking aprepitant (75.7% vs 58.7%; P < .001).23 The number of patients who did not require rescue therapy was similar for both groups (58.7% vs 56.2%). Patients taking aprepitant achieved a higher complete response during the acute phase (75.7% vs 69.0%; P = .034) and the...
delayed (55.4% vs 49.1%; \( P = .064 \)) phase. Both treatments were generally well tolerated.

**Evidence-Based Treatment Guidelines**

Recommendations for the management of nausea and vomiting are available from a number of organizations, including the American Society of Oncology (ASCO), the American Society of Health-System Pharmacists, and the European Society of Medical Oncology. In 2004, the National Comprehensive Cancer Network (NCCN) also issued guidelines, and the Multinational Association for Supportive Care in Cancer (MASCC) developed guidelines that will be published in 2005.24,25

For the prevention of acute vomiting and nausea after highly emetogenic chemotherapy, the consensus-based MASCC guidelines recommend a 3-drug regimen that includes single doses of a 5-HT\textsubscript{3} antagonist, dexamethasone, and aprepitant administered before chemotherapy.24 In patients receiving cisplatin and a combination of aprepitant, a 5-HT\textsubscript{3} antagonist, and dexamethasone to prevent acute nausea and vomiting, the MASCC recommends a combination of dexamethasone and aprepitant to prevent delayed emesis. The guidelines do not reflect reports from ASCO 2004 or MASCC 2004, and aprepitant currently is not recommended for prevention of acute or delayed nausea and emesis resulting from chemotherapy, other than highly emetogenic chemotherapy. In addition, the MASCC guidelines do not mention the use of the most recently approved 5-HT\textsubscript{3} antagonist palonosetron, which is probably because the published studies did not conform to the recommended standard practice of using dexamethasone for acute emesis. However, the NCCN guidelines recommend aprepitant for the prevention of acute and delayed emesis after highly emetogenic chemotherapy or moderately emetogenic chemotherapy.25 The NCCN guidelines also include palonosetron among the 5-HT\textsubscript{3} antagonists. However, palonosetron requires concomitant dexamethasone or methylprednisolone unless the patient cannot tolerate adjunctive corticosteroids.

Table 1 shows the NCCN recommendations for the prevention of acute and delayed emesis associated with highly emetogenic chemotherapy and moderately emetogenic chemotherapy.

Evidence-based guidelines are meaningless if they are not implemented. A study conducted in Italy found that in the 2 years after the publication of the MASCC guidelines, the recommendations for prevention of acute emesis were prescribed in 56.3% of patients; for delayed emesis, in 45.9% of patients.26 The study included 684 patients who received moderately to highly emetogenic chemotherapy (533 received cyclophosphamide, methotrexate, 5-fluorouracil; 151 received an anthracycline-containing regimen). Most patients received prophylaxis with 5-HT\textsubscript{3} antagonists beyond 24 hours after chemotherapy, a practice that is costly and offers little benefit for the prevention of delayed emesis. The impact of the MASCC guidelines was not as strong or expeditious as was expected. The study’s findings indicate that efforts should be made to accelerate the process of implementing antiemetic guidelines.

In a study published in 2001, Dranitsaris et al examined the effects of a 4-month antiemetic guideline implementation that promoted the use of granisetron within evidence guidelines.27 The guideline implementation process was facilitated using a 6-step multifaceted approach, which consisted of guideline

| Table 1. NCCN Recommendations for Emesis Prevention |
|---|---|
| **Highly Emetogenic Chemotherapy** | **Moderately Emetogenic Chemotherapy** |
| **Acute Emesis** | Before Chemotherapy |
| Aprepitant, dexamethasone, and a 5-HT\textsubscript{3} antagonist with or without lorazepam | Before Chemotherapy |
| Dexamethasone and a 5-HT\textsubscript{3} antagonist with or without lorazepam OR Consider aprepitant in patients receiving carboplatin, cyclophosphamide, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate |

<table>
<thead>
<tr>
<th>Delayed Emesis</th>
<th>Days 2–4</th>
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<tr>
<td>Aprepitant, dexamethasone, and a 5-HT\textsubscript{3} antagonist with or without lorazepam</td>
<td>Days 2–4</td>
</tr>
<tr>
<td>Dexamethasone OR A 5-HT\textsubscript{3} antagonist OR Aprepitant and dexamethasone with or without lorazepam</td>
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dissemination, using opinion leaders, interactive educational workshops, therapeutic reminders in the form of preprinted antiemetic orders, educational outreach using the pharmacist as the vehicle for information, and physician audit and feedback. The study enrolled 195 inpatients over the course of 4 months. Clinical pharmacists evaluated 183 of 195 granisetron orders and compared them with the antiemetic guidelines. In the cases in which prescriptions were identified as being outside of the guidelines, the physician was contacted for therapeutic modification as outlined in the protocol; 39 of 49 orders outside of the protocol were changed to comply with the guidelines. The average length of pharmacist intervention was 10 minutes. Following these interventions, 88.7% of granisetron prescriptions were for an indication, dosage, and duration recommended by the guidelines. Analysis of all outcome data revealed that prescribing within the guidelines did not compromise control of acute and delayed emesis. In addition, patients who received evidence-based antiemetic therapy experienced a significant reduction in the severity of acute nausea (risk ratio, .69; \(P = .03\)). The study investigators concluded that a pharmacist-driven multifaceted intervention program for high-cost agents can promote use of the agents in a clinically appropriate manner and avoid unnecessary drug costs without compromising the quality of care for patients.

**EMERGING ROLE OF GENETICS**

The recently emerged term “pharmacogenomics” describes the field of translating functional genomics to rational therapy.\(^2^8\) Drug metabolism and the potential for drug interactions may, to some extent, be influenced by genetic factors. Ethnicity may also influence drug disposition. There are more than 30 cytochrome P450 (CYP450) enzymes, which are found mainly in the liver and are important in the metabolism of many drugs. Of these enzymes, CYP1A2, CYP2D6, and CYP3A4 account for approximately 85% of total hepatic drug metabolism.\(^2^9\) Polymorphic variations have been identified for CYP2D6 and CYP2C19.\(^2^8\) Ondansetron is metabolized by several enzymes, including CYP2D6, which may account for the wide interpatient and interethnic variability seen with the drug. Granisetron is primarily metabolized by cytochrome CYP3A4. Table 2 shows a range of clinically important compounds whose metabolism is closely associated with CYP2D6 and CYP3A4. Coadministration of these drugs with ondansetron or granisetron may cause a significant reduction in the systemic exposure of the cytotoxic drug.\(^2^8\)

The CYP2D6 enzyme contains 4 levels of metabolic activity: ultrarapid, extensive, intermediate, and poor.\(^2^8\) The prevalence of genetically determined variants varies among ethnic groups. Poor metabolizers are less common in Africans, African Americans, and Asians compared to the white population.\(^2^8\) An ultrarapid metabolizer could experience problems with insufficient drug activity late in the first 24 hours after single dosing. Variations in drug metabolism also have major implications in the coadministration of medications metabolized by the CYP450 enzyme system.\(^2^8\)

Although ondansetron and granisetron have shown equivalent antiemetic activity in randomized trials,\(^3^1\) a study by de Wit et al showed that patients who were switched to granisetron after reporting poor results with ondansetron were significantly more likely to experience complete protection from CINV than patients who continued taking ondansetron.\(^3^0\) The surprising result from this small study may be because of chance alone or perhaps the dose of ondansetron used was suboptimal. An alternative explanation is that some patients respond differently to granisetron than

<table>
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<th>Table 2. Potential CYP450 Interactions with Clinically Important Compounds</th>
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<tr>
<td><strong>Oncology drugs</strong></td>
</tr>
<tr>
<td>CYP2D6</td>
</tr>
<tr>
<td>Doxorubicin, lomustine, tamoxifen, vinorelbine</td>
</tr>
<tr>
<td>CYP3A4</td>
</tr>
<tr>
<td>Cyclophosphamide, docetaxel, etoposide, irinotecan, paclitaxel, vinorelbine, vinristine</td>
</tr>
<tr>
<td><strong>Cardiovascular drugs</strong></td>
</tr>
<tr>
<td>Amiodarone, flecainide, mexiletine, quinidine</td>
</tr>
<tr>
<td>Amiodarone, diltiazem, nifedipine, phenytoin, quinidine, sildenafil, simvastatin, verapamil</td>
</tr>
<tr>
<td><strong>Psychoactive drugs</strong></td>
</tr>
<tr>
<td>Chlorpromazine, tricyclic antidepressants</td>
</tr>
<tr>
<td>Sertraline, St John’s wort, trazodone</td>
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<tr>
<td><strong>Gastrointestinal drugs</strong></td>
</tr>
<tr>
<td>Cimetidine, ranitidine</td>
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<tr>
<td>Cimetidine, finasteride</td>
</tr>
<tr>
<td><strong>Others</strong></td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Immune modulators, protease inhibitors, cisapride, erythromycin, ketoconazole, lignocaine, methadone, quinine</td>
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</tbody>
</table>

Adapted with permission from Blower. Cancer J. 2002;8:405-414.\(^3^4\)
ondansetron, despite the fact that both drugs are highly selective for the same receptor. Similarly, some patients with cancer who experience inadequate pain relief and intolerable side effects with one opioid find that switching to an alternative opioid improves pain control and reduces opioid-related adverse effects.31

Apart from differences in patient metabolism, some variability in response to different 5-HT3 receptors could occur if there were differences in the structure of 5-HT3 receptors in humans. Tremblay et al hypothesized that polymorphism in the 5-HT3B receptor gene may result in differential responses to antiemetic treatment with a 5-HT3 antagonist.32 The study included 242 patients with cancer who were undergoing chemotherapy for the first time or undergoing the first course of chemotherapy after relapse. All patients received antiemetic treatment with a 5-HT3 antagonist. Approximately 30% of all patients experienced nausea or vomiting. After the entire 5-HT3B receptor gene was sequenced, 13 polymorphisms were found. Three patients with one particular variant experienced more vomiting than the other patients. Although a hypothesis relating receptor variants to antiemetic response is intriguing, the difference may be because of chance association. In addition, the very low frequency of the putative responsible variant means that this polymorphism would, at best, be a rare explanation for antiemetic failure.

**NEW ANTIEMETIC AGENTS IN CLINICAL TRIALS**

Although there are several effective management options for CINV and the choices have been broadened by the emergence of newer antiemetic protocols, nausea and vomiting remain significant problems for patients receiving chemotherapy. Additional clinical trials of existing agents and novel agents are critical for further progress in the prevention and treatment of CINV. There are several NK1 antagonists, other than aprepitant, being used in clinical trials. In addition, the activity of the psychotropic agent olanzapine at multiple dopaminergic, serotonergic, muscarinic, and histaminic receptor sites suggests it may have antiemetic effects. Olanzapine is currently indicated for the treatment of schizophrenia, bipolar disorder, and agitation associated with schizophrenia and bipolar I mania.33 Results from a recent phase 2 study conducted by Navari et al suggest that olanzapine is safe and effective in controlling acute CINV and delayed CINV in patients receiving highly emetogenic chemotherapy or moderately emetogenic chemotherapy.34

**CONCLUSIONS**

Progress is being made in the understanding and management of CINV, and the number of treatment options has increased. Implementation of evidence-based guidelines can help to ensure that antiemetics are used in a clinically appropriate manner to optimize control while avoiding unnecessary drug costs and adverse effects. The combination of a 5-HT3 receptor antagonist and a corticosteroid in the first 24 hours of chemotherapy administration results in better control of acute CINV than either agent alone. Despite their frequent use for more than 24 hours beyond chemotherapy, randomized trials suggest that 5-HT3 receptor antagonists have little impact on delayed CINV. In contrast, corticosteroid administration beyond 24 hours appears to reduce delayed CINV resulting from highly emetogenic chemotherapy or moderately emetogenic chemotherapy. NK1 antagonists, the newest class of antiemetics, represent a substantial advance in the control of acute emesis and delayed emesis and have demonstrated activity in the setting of highly and moderately emetogenic chemotherapy. Thus far, pharmacogenomics and differences in receptor subtype have not been proven to have important roles in clinical management.

Despite much progress, a substantial minority of patients will still experience troublesome nausea and vomiting. Additional research is needed to discover which drugs can help patients achieve optimal control and maintain their functional status during chemotherapy.

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