Formulary management strategies for type 3 serotonin receptor antagonists

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Abstract: The efficacy of type 3 serotonin (5-hydroxytryptamin) (5-HT₃) receptor antagonists in preventing nausea and vomiting associated with cancer chemotherapy, radiation therapy, and surgery and the role of practice guidelines for the use of these agents in controlling antiemetic drug costs without compromising patient care are described.

Nausea and vomiting caused by cancer chemotherapy, radiation therapy, and surgery can have a negative impact on quality of life and patient outcomes. The 5-HT₃ receptor antagonists are effective for preventing nausea and vomiting from these causes. Oral 5-HT₃ receptor antagonist therapy is as effective as intravenous therapy, while usually costing less. Various factors associated with the patient and the chemotherapy, radiation therapy, or surgery that increase the risk for nausea and vomiting have been identified. Practice guidelines have been developed in which 5-HT₃ receptor antagonist therapy is reserved for patients at high risk for nausea and vomiting based on these various factors. The use of such practice guidelines at Memorial Sloan-Kettering Cancer Center limited antiemetic drug expenditures despite an increase in the number of patients receiving cancer treatment without compromising emetic control or quality of life. The use of special order forms improved compliance with the practice guidelines.

Index terms: Antineoplastic agents; Costs; Economics; Formularies; Nausea; Protocols; Quality of life; Radiation; Serotonin antagonists; Toxicity; Vomiting

The likelihood of vomiting in patients receiving cancer chemotherapy is higher for female patients, patients younger than 50 years of age, and children. On the other hand, a history of chronic, heavy alcohol intake decreases the risk of chemotherapy-induced vomiting compared with occasional alcohol use. The type of chemotherapy used (agents and administration route and schedule) is an important factor.

Failure to prevent or control nau-
sea and vomiting could result in dehydration, electrolyte abnormalities, malnutrition, delay or refusal of potentially curative or beneficial therapy, and poor quality of life. Nausea and vomiting in pediatric patients can have detrimental psychological as well as physiological effects and adversely affect growth and development. The frequency and severity of nausea and vomiting in this patient population are often underestimated. Because chemotherapy-induced vomiting increases the risk of vomiting after subsequent courses of chemotherapy, aggressive antiemetic treatment is recommended during initial cancer chemotherapy courses for adult and pediatric patients at risk.

**5-HT<sub>3</sub> receptor antagonists**

Table 1 lists the commercially available dosage forms of 5-HT<sub>3</sub> receptor antagonists and the dosages that are approved by the Food and Drug Administration (FDA). Cost-effectiveness is optimized if a drug is available in oral and injectable dosage forms for use in patients who are able to take medication orally, especially in ambulatory practice settings. However, clinicians and patients receiving cancer chemotherapy have been reluctant to embrace the use of oral 5-HT<sub>3</sub> receptor antagonists despite evidence that oral and intravenous therapies are equivalent in efficacy.  

**Efficacy.** Oral granisetron was the first 5-HT<sub>3</sub> receptor antagonist approved by FDA in 1991 and is the most studied of the three drugs in this class. A complete response is characterized by no episodes of emesis or need for rescue antiemetic medication. In a study of patients receiving moderately emetogenic cancer chemotherapy (cyclophosphamide or carboplatin), the complete response rates from oral granisetron (2 mg) and intravenous ondansetron (32 mg) were comparable (71% and 73%, respectively). In a separate study, oral granisetron (1 mg twice daily) was at least as effective as oral ondansetron (8 mg twice daily) in preventing nausea and vomiting in patients receiving moderately emetogenic chemotherapy.  

A dose-finding study reported that 1 mg orally twice daily was more effective than smaller dosages, and 2 mg twice daily was no more effective than 1 mg twice daily. There was no significant difference in efficacy between 2 mg orally once daily and 1 mg orally twice daily in another study of patients receiving moderately emetogenic chemotherapy; therefore, both of these regimens are approved by the FDA.  

Another dose-finding study of oral dolasetron in patients receiving moderately emetogenic chemotherapy reported complete response rates of 45%, 71%, 73%, and 83% with single, oral doses of 25, 50, 100, and 200 mg, respectively. The FDA-approved dosage of oral dolasetron is 100 mg despite these findings because another dose-finding study demonstrated no significant difference in complete response rate between a 200- and a 100-mg dose in patients receiving moderately emetogenic chemotherapy.  

Many clinicians have been skeptical that oral 5-HT<sub>3</sub> receptor antagonist therapy is as effective as 5-HT<sub>3</sub> intravenous therapy in patients receiving chemotherapy with high emetic potential. However, oral granisetron (2 mg) was comparable in efficacy to intravenous ondansetron (32 mg) in preventing nausea and vomiting in patients receiving high-dose, highly emetogenic cisplatin therapy. Intravenous granisetron (10 μg/kg) and oral ondansetron (24 mg) were judged equivalent in efficacy in preventing vomiting in another study of patients receiving highly emetogenic chemotherapy.  

Adding a corticosteroid to the 5-HT<sub>3</sub> receptor antagonist improves the antiemetic response. In patients receiving moderately emetogenic chemotherapy, the use of granisetron (3 mg intravenously before chemotherapy) plus dexamethasone (8 mg intravenously plus 4 mg orally before chemotherapy followed by 4 mg orally every six hours for a total of four doses) was significantly more effective in preventing vomiting than granisetron alone. Vomiting was prevented in 72% of patients receiving granisetron alone and 93% of patients receiving the combination. Similar results were reported when dexamethasone (20 mg intravenously 15 minutes before chemotherapy) used in combination with oral ondansetron (8 mg every four hours for three doses beginning before chemotherapy) in patients receiving highly emetogenic chemotherapy. The complete response rate was 64% with ondansetron alone and 81% with the combination.

**Safety.** The 5-HT<sub>3</sub> receptor antagonists are well tolerated and cause minimal adverse effects. Headache and constipation or diarrhea are among the most common adverse effects. Pretreatment may be given before subsequent chemotherapy cycles to prevent the recurrence of these adverse effects (e.g., acetaminophen for headache and docusate for constipation). Concerns have been raised about the potential for cardiovascular adverse effects from 5-HT<sub>3</sub> receptor antagonists because of electrocardiographic interval changes that were acute, transient, and asymptomatic in patients receiving dolasetron or ondansetron. Dolasetron should be used with caution in patients who have or may develop prolongation of cardiac conduction intervals, especially the QT interval corrected for heart rate.  

**Practice guidelines**

Practice guidelines for the use of 5-HT<sub>3</sub> receptor antagonists in managing acute nausea and vomiting associated with cancer chemotherapy and other causes have been developed by various groups, including the American Society of Health-System Pharmacists, American Society
of Clinical Oncology, Multinational Association of Supportive Care in Cancer, and The National Comprehensive Cancer Network.4,22-24 Practice guidelines help standardize the drug ordering, preparation, and administration processes and reduce the risk of error. They also can be used as an educational tool for physicians, nurses, and pharmacists and to contain costs associated with drug therapy.

Practice guidelines provide antiemetic drug therapy recommendations for specific cancer chemotherapeutic regimens based on the emetic potential of the chemotherapy and the efficacy and cost-effectiveness of antiemetic drug therapies. The emetic potential of a chemotherapeutic agent or regimen may be classified in one of five categories according to

Table 1: FDA-Approved Dosages of 5-HT3 Receptor Antagonists for Adultsa,b,5-10

<table>
<thead>
<tr>
<th>Symptom and Type of Cancer</th>
<th>Dolasetron</th>
<th>Granisetron</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea and vomiting</strong></td>
<td><strong>Intravenous</strong>: 1.8 mg/kg or 100 mg approximately 30 min before chemotherapy</td>
<td><strong>Intravenous</strong>: 10 µg/kg within 30 min before chemotherapy</td>
<td><strong>Intravenous</strong>: 32 mg 30 min before chemotherapy or 0.15 mg/kg every 4 hr for three doses beginning 30 min before chemotherapy</td>
</tr>
<tr>
<td><strong>dosage forms</strong></td>
<td><strong>Oral</strong>: 100 mg within 1 hr before chemotherapy</td>
<td><strong>Oral</strong>: 2 mg up to 1 hr before chemotherapy or 1 mg up to 1 hr before chemotherapy followed by 1 mg 12 hr later</td>
<td><strong>Oral</strong>: 8 mg 30 min before chemotherapy followed by 8 mg 8 hr later and 8 mg every 12 hr for the next 1–2 days</td>
</tr>
<tr>
<td><strong>Moderately emetogenic cancer chemotherapy</strong></td>
<td><strong>Intravenous</strong>: 1.8 mg/kg or 100 mg approximately 30 min before chemotherapy</td>
<td><strong>Intravenous</strong>: 10 µg/kg within 30 min before chemotherapy</td>
<td><strong>Intravenous</strong>: 32 mg 30 min before chemotherapy or 0.15 mg/kg every 4 hr for three doses beginning 30 min before chemotherapy</td>
</tr>
<tr>
<td><strong>Radiation-induced nausea and vomiting</strong></td>
<td><strong>Not approved by FDA for this indication</strong></td>
<td><strong>Oral</strong>: 2 mg up to 1 hr before chemotherapy or 1 mg up to 1 hr before chemotherapy followed by 1 mg 12 hr later</td>
<td><strong>Oral</strong>: 24 mg 30 min before chemotherapy</td>
</tr>
<tr>
<td><strong>Postoperative nausea and vomiting</strong></td>
<td><strong>Intravenous</strong>: 12.5 mg approximately 15 min before cessation of anesthesia or if nausea and vomiting occur</td>
<td><strong>Intravenous</strong>: 1 mg before induction of or immediately before reversal of anesthesia or if postoperative nausea and vomiting occur</td>
<td><strong>Intramuscular</strong>: 5 mg if nausea and vomiting occur</td>
</tr>
<tr>
<td><strong>dosage forms</strong></td>
<td><strong>Oral</strong>: 100 mg within 2 hr before surgery</td>
<td><strong>Oral</strong>: 2 mg 1 hr before induction of anesthesia</td>
<td><strong>Oral</strong>: 16 mg 1 hr before induction of anesthesia</td>
</tr>
</tbody>
</table>

a,5-HT3 = type 3 serotonin, FDA = Food and Drug Administration.

The frequency of emesis (Table 2).25,26 This classification scheme is widely accepted, although some clinicians prefer simpler schemes with fewer categories for ease of use and FDA characterizes the emetic potential of chemotherapy in one of two categories (moderate or high) in expressing the indications for antiemetic agents. The various groups' practice guidelines for managing cancer chemotherapy-induced nausea and vomiting are fairly consistent in their recommendations for 5-HT3 receptor antagonist use. A 5-HT3 receptor antagonist plus a corticosteroid should be used to prevent emesis from chemotherapeutic regimens with a level 3, 4, or 5 emetic potential.4 A corticosteroid or prochlorperazine alone is recommended for chemotherapy with a level 2 emetic potential, and no prophylaxis is required for chemotherapy with a level 1 emetic potential.4 Because the efficacy and safety of the three 5-HT3 receptor antagonists are comparable, the choice among these agents should be based on convenience, availability, and cost.22 The oral route of administration is preferred over the intravenous route when feasible (i.e., when the patient is able to take medication orally) because it is more convenient for outpatients and usually is less costly.4 The oral 5-HT3 receptor antagonist dosages recommended in various practice guidelines are relatively consistent with FDA-approved dosages, except for the larger oral dolasetron dosages (100 to 200 mg) and smaller ondansetron dosages (e.g., 12 to 16 mg for patients receiving chemotherapy with a moderate...
SYMPOSIUM Serotonin receptor antagonists

Table 2.
Classification of Cancer Chemotherapeutic Agents by Emetic Potential

<table>
<thead>
<tr>
<th>Level</th>
<th>Emetic Potential</th>
<th>Frequency of Emesis (%)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>High</td>
<td>&gt;90</td>
<td>Cisplatin (≥250 mg/m²), cyclophosphamide (&gt;1500 mg/m²), dacarbazine (≥2500 mg/m²), streptozocin</td>
</tr>
<tr>
<td>4</td>
<td>Moderately high</td>
<td>60–90</td>
<td>Carboplatin, cisplatin (&lt;50 mg/m²), cyclophosphamide (&gt;750 to ≤1500 mg/m²), doxorubicin (&gt;60 mg/m²)</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>30–60</td>
<td>Cyclophosphamide (≤750 mg/m²), doxorubicin (20–60 mg/m²), epirubicin (≤90 mg/m²), ifosfamide</td>
</tr>
<tr>
<td>2</td>
<td>Moderately low</td>
<td>10–30</td>
<td>Docetaxel, etoposide, mitomycin, paclitaxel</td>
</tr>
<tr>
<td>1</td>
<td>Low</td>
<td>&lt;10</td>
<td>Bleomycin, busulfan (oral, &lt;4 mg/kg/day), fludarabine, vincristine</td>
</tr>
</tbody>
</table>

emetic potential) recommended in some guidelines.4,22,23

As in adults, a combination of a 5-HT₃ receptor antagonist and a corticosteroid should be used to prevent acute nausea and vomiting in pediatric patients receiving chemotherapy with a level 3, 4, or 5 emetic potential.4 The safety and efficacy of 5-HT₃ receptor antagonists have been demonstrated in children as young as two years of age.6,8,10 Antiemetic therapy in children should be administered orally when feasible, and convenience (e.g., availability of an oral liquid dosage form) may influence the choice of a 5-HT₃ receptor antagonist. Education of the parent or caregiver is vital to the success of interventions to manage nausea and vomiting in pediatric patients receiving cancer chemotherapy.

Formulary management efforts

Memorial Sloan-Kettering Cancer Center (MSKCC) is a major cancer treatment center. More than 350 cancer chemotherapy treatments are administered every day at MSKCC. Before FDA approval of ondansetron in 1991, the annual budget at MSKCC for antiemetic drugs (e.g., metoclopramide, prochlorperazine, diphenhydramine, dexamethasone) was about $75,000.11 MSKCC was skeptical that oral antiemetic drug therapy would be as effective an intervention as intravenous ondansetron. Outcomes with granisetron were similar to outcomes previously reported with intravenous ondansetron. However, outcomes with oral granisetron were comparable to outcomes with intravenous granisetron and intravenous ondansetron.

In 1993, clinicians at MSKCC had access to preliminary results of a study in which the emetic potential of chemotherapy was evaluated in prescribing intravenous ondansetron, with full doses reserved for patients receiving highly emetogenic chemotherapy and smaller doses used in patients receiving less emetogenic chemotherapy.27 Because the preliminary results of this study were favorable (i.e., efficacy in preventing emesis was not compromised by the use of smaller ondansetron doses in selected patients), this approach was considered as a possible solution to the antiemetic drug budget crisis at MSKCC.

A multidisciplinary team comprised of a medical oncologist, nurses, and pharmacists was formed to categorize chemotherapy regimens at MSKCC according to emetic potential and to establish antiemetic guidelines.11 The antiemetic drug regimens that had been used in the study with favorable preliminary results were used in the 1993 antiemetic guidelines at MSKCC (Table 3). After guideline implementation, patient surveys revealed that the percentages of patients receiving chemotherapy with a mild, moderate, or high emetic potential and a complete response to antiemetic drug therapy were 74%, 83%, and 73%, respectively.11 The corresponding percentages of patients who reported that quality of life was not affected by chemotherapy-induced nausea and vomiting were 80%, 80%, and 69%, respectively. The projected annual cost saving from using the 1993 guidelines was $756,000.

The introduction of granisetron in the United States in 1994 led to a revision of the guidelines at MSKCC. Patients receiving chemotherapy with a moderate or high emetic potential were given intravenous granisetron instead of intravenous ondansetron. Outcomes with granisetron were comparable to outcomes previously reported with ondansetron (Figures 1 and 2). The MSKCC guidelines were revised in 1995. A considerable amount of time was required to educate the nursing staff and patients, who were skeptical that oral antiemetic drug therapy would be as effective an intervention as intravenous ondansetron. The outcomes with oral granisetron were similar to those previously reported with intravenous granisetron and intravenous ondansetron. Use of the oral route instead of the intravenous route resulted in additional cost savings. The projected 1996 annual budget for antiemetic drugs was $1.3 million. This is less than half of what had been projected in 1993 before implementation of the practice guidelines despite the fact that the number of patients receiving treatment increased nearly twofold during this period.11

Current guidelines. The antiemetic guidelines currently used at MSKCC recommend the use of granisetron 2 mg orally (or 10 µg/kg in-
Table 3. Practice Guidelines Used for Prophylaxis of Acute Emesis Associated with Cancer Chemotherapy at MSKCC\textsuperscript{a,b,11}

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>High</td>
<td>Ondansetron 32 mg i.v.</td>
<td>Granisetron 10 µg/kg i.v.</td>
<td>Granisetron 2 mg orally</td>
</tr>
<tr>
<td>Moderate</td>
<td>Ondansetron 24 mg i.v.</td>
<td>Granisetron 10 µg/kg i.v.</td>
<td>Granisetron 2 mg orally</td>
</tr>
<tr>
<td>Mild</td>
<td>Ondansetron 8 mg i.v.</td>
<td>Ondansetron 8 mg i.v.</td>
<td>Ondansetron 16 mg orally</td>
</tr>
<tr>
<td>Low</td>
<td>Dexamethasone 20 mg i.v.</td>
<td>Dexamethasone 20 mg i.v.</td>
<td>Dexamethasone 20 mg orally</td>
</tr>
<tr>
<td>Minimal</td>
<td>As-needed antiemetics only</td>
<td>As-needed antiemetics only</td>
<td>As-needed antiemetics only</td>
</tr>
</tbody>
</table>

\textsuperscript{a}MSKCC = Memorial Sloan-Kettering Cancer Center.
\textsuperscript{b}Dexamethasone 20 mg was given with all type 3 serotonin (5-HT\textsubscript{3}) receptor antagonists using whatever route of administration was used for the 5-HT\textsubscript{3} receptor antagonist. As-needed antiemetics (oral lorazepam, prochlorperazine plus diphenhydramine, or metoclopramide plus diphenhydramine) also were available.

Figure 1. Percentage of patients who received moderately emetogenic chemotherapy (i.e., cyclophosphamide, doxorubicin, and vincristine) with no emesis or up to two emetic episodes and who stated their quality of life was unaffected by emesis for each of the three versions of the antiemetic guidelines. Reprinted with permission.

As-needed antiemetics
- **Dexamethasone 20 mg orally** or intravenously (two doses daily for two days)
- **Ondansetron 8 mg orally** twice daily
- **Granisetron 10 mg orally** twice daily

Intravenous therapy in pediatric patients at MSKCC:
- High: Dexamethasone 20 mg was used.
- Moderate: Ondansetron 8 mg was used.
- Mild: Dexamethasone 20 mg was used.
- Low: Dexamethasone 20 mg was used.
- Minimal: As-needed antiemetics were used.

When granisetron must be given intravenously, a single 2-mg dose is used in children because the risk of vomiting is greater in children. Oral granisetron is given as two 1-mg doses 12 hours apart instead of one 2-mg dose. The response is better with that approach. When granisetron must be given intravenously to pediatric patients receiving chemotherapy with a high or moderate emetic potential at MSKCC, a 20-µg/kg dose is used because the response is better than with the FDA-approved 10-µg/kg dose.

**Order form.** The use of a special cancer chemotherapy order form has played a key role in formulary management and cost containment ef-
The American Society of Clinical Oncology ranked the outcomes on the basis of how frequently the outcome occurs and the extent to which patients wish to avoid the outcome. Postoperative nausea and vomiting were ranked as the second and third most undesirable outcomes, respectively, after pain from the incision.

Thus, postoperative nausea and vomiting remain dreaded consequences of surgery for patients, despite the availability of effective antiemetic agents.

A variety of factors increase the risk of postoperative nausea and vomiting. Patient-specific factors...
include female sex, obesity, and delayed gastric emptying from various conditions (e.g., neuromuscular disorders, gastroesophageal reflux disease). Nausea and vomiting are associated with certain types of surgical procedures (e.g., intraabdominal, gynecologic, breast, ear–nose–throat, adenotonsillectomy, surgery for strabismus) and surgical procedures that are lengthy. Certain types of anesthesia (e.g., ether) and a long duration of anesthesia also increase the risk for postoperative nausea and vomiting, although the risk is reduced by propofol. Unrelieved visceral or pelvic pain increases the risk of nausea and vomiting in the postoperative period, although opioid use is a more important factor.

The risk for postoperative nausea and vomiting increases as the number of risk factors increases. The incidence of postoperative nausea and vomiting in patients with many risk factors is as high as 70%.

Patients who are at high risk for postoperative nausea and vomiting should receive antiemetic therapy as prophylaxis, according to the ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. These guidelines recommend droperidol or a 5-HT₃ receptor antagonist for prophylaxis or treatment of postoperative nausea and vomiting in adults and pediatric patients. However, these guidelines were published in 1999 before a black box warning about the risk of potentially fatal prolongation of the QT interval was added to the FDA-approved product labeling for droperidol. Droperidol is no longer used at MSKCC and many other institutions because of the need to monitor for cardiac arrhythmias after surgery. The 5-HT₃ receptor antagonists are effective for preventing and treating postoperative nausea and vomiting.

Other guidelines have been developed in which the risk for postoperative nausea and vomiting is classified as mild to moderate, moderate to high, or very high based on the number of risk factors that are present (Figure 3). Different approaches to antiemetic drug therapy are recommended for each of these three categories, with single agents for patients at mild to moderate risk and combinations of agents that act at different receptors (e.g., 5-HT₃ and dopamine receptors) for patients at higher risk. This strategy for the use of antiemetic agents may help control costs.

References
4. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health-Syst Pharm. 1999; 56:729-64.

Figure 3. Risk factors for postoperative nausea and vomiting (PONV) and guidelines for prophylactic antiemetic therapy. Reprinted with permission.


