Prevention of Emesis from Multiple-Day and High-Dose Chemotherapy Regimens

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Abstract

The prevention of chemotherapy-induced nausea and vomiting (CINV) has improved significantly with the introduction of the 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists combined with dexamethasone. Most studies have reported on patients undergoing single-day highly or moderately emetogenic chemotherapy. There have been fewer studies and much less success in preventing CINV in patients undergoing multiple-day chemotherapy or high-dose chemotherapy with stem cell transplant. Current practice guidelines suggest the use of a first-generation 5-HT3 receptor antagonist and dexamethasone daily for each day of the multiple-day chemotherapy regimens. This practice seems to control acute CINV, but delayed CINV remains poorly controlled with a complete response (e.g., no emesis, no rescue) of less than 50% in most studies. Three new agents—palonosetron, aprepitant, and olanzapine—have shown high efficacy in preventing acute and delayed CINV in patients undergoing single-day chemotherapy. These agents have high potential for preventing CINV in patients undergoing multiple-day chemotherapy. This article proposes recommendations for their use in clinical trials and in practice. (UNCCN 2007;5:51-59)

Chemotherapy-induced nausea and vomiting (CINV) can be a significant problem for patients. Patients consistently report that vomiting and nausea are among the most unpleasant and distressing aspects of chemotherapy.1,2 Even 1 or 2 emetic episodes are associated with a significant deterioration in quality of life and in physical and cognitive functioning, and may cause patients to delay or refuse potentially curative therapy.3,4

The potential for CINV is influenced by the emetogenicity of the chemotherapeutic agents and patient characteristics, such as female gender, younger age, a history of motion sickness, and consumption of minimal amounts of alcohol (less than 1.5 ounces of alcohol per day).5,6 The presence or absence of these risk factors and the emetogenicity of the chemotherapeutic agents being administered determine each patient’s risk for CINV (Table 1).

Introduction of 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists for preventing CINV has resulted in a major improvement in supportive care.7,8 Treatment guidelines for preventing CINV recommended by several international groups9,10 suggest using a 5-HT3 receptor antagonist and dexamethasone prechemotherapy, and using dexamethasone with or without a 5-HT3 receptor antagonist or metoclopramide after chemotherapy to prevent delayed nausea and vomiting. Recently revised guidelines11,12 recommend the addition of aprepitant, a neurokinin-1 (NK-1) receptor antagonist, to a 5-HT3 receptor antagonist and dexamethasone prechemotherapy and to dexamethasone postchemotherapy for patients undergoing highly emetogenic chemotherapy or the combination of cyclophosphamide and doxorubicin.

Table 2 shows the 5-HT3 receptor antagonists currently in use. The first-generation serotonin (5-HT3) receptor antagonists dolasetron, granisetron, ondansetron, tropisetron,13,14 azasetron,15 and ramosetron16 are equivalent in efficacy and toxicities when used in the recommended doses, and compete only on an economic basis.17 They have not been associated with major toxicities, with mild headache and diarrhea the most commonly reported adverse events.18-20 Prolonged cardiac conduction intervals

Key Words

Antiemetics, chemotherapy induced nausea and vomiting, serotonin receptor antagonists, neurokinin-1 receptor antagonists, multiple-day chemotherapy, high-dose chemotherapy
have been reported for this class of compounds, with dolasetron being more extensively studied than granisetron and ondansetron, but no clinical cardiovascular adverse events have been reported.

The first-generation 5-HT3 receptor antagonists have not been as effective against delayed emesis as their efficacy is against acute CINV. Available studies show that for corticosteroids alone, or combined with either metoclopramide or a 5-HT3 receptor antagonist in patients receiving cisplatin, the incidence of delayed emesis has been reduced but remains a significant problem. First-generation 5-HT3 receptor antagonists do not add significant efficacy to that obtained by dexamethasone alone in controlling cisplatin-induced emesis. Hickok et al. reported that the first-generation 5-HT3 receptor antagonists used in the delayed period were no more effective than prochlorperazine in controlling nausea. A recent meta-analysis showed neither clinical evidence nor considerations of cost-effectiveness justified using the first-generation 5-HT3 antagonists beyond 24 hours after chemotherapy for preventing delayed emesis.

The use of metoclopramide may be somewhat efficacious in relatively high doses (20 mg orally, 3 times a day) in the delayed period, but may result in sedation and extrapyramidal side effects.

Most of the antiemetic studies have been performed with single-day chemotherapy, such as cisplatin or the combination of an anthracycline plus cyclophosphamide. Fewer studies have been performed on the most effective agents and regimens for the prevention of CINV in patients undergoing multiple-day chemotherapy, such as a 5-day cisplatin combination chemotherapy in patients with germ cell tumors or those undergoing high-dose chemotherapy with stem cell transplantation. Multiple-day chemotherapy regimens provide challenges in treating both acute and delayed CINV over multiple days. This article reviews the current recommendations and practices for preventing CINV in multiple-day and high-dose chemotherapy with stem cell transplantation and suggests potential uses in these settings for the new agents palonosetron, aprepitant, and olanzapine.

### Multiple-Day Chemotherapy

Most reported studies on preventing CINV in multiple-day chemotherapy have involved patients with germ cell tumors undergoing 5 days of cisplatin combination chemotherapy. Initial studies with prochlorperazine showed that this agent was essentially ineffective. Introduction of the first-generation 5-HT3 receptor antagonists showed a complete response (no emesis, no rescue) of 30% to 45% over the 5-day cisplatin period when the single-agent 5-HT3 was given daily over the 5-day chemotherapy period. No difference has been seen in the complete response among the various first-generation 5-HT3 receptor antagonists. Based on current knowledge of the mechanism of action of the first-generation 5-HT3 receptor antagonists, using these agents on a daily 5-day regimen prevented acute CINV but was ineffective in preventing delayed CINV.

The complete response rate in preventing CINV over the 5-day cisplatin period increased 50% to 70%

### Table 1 Patient-Related Risk Factors for Emesis After Chemotherapy

<table>
<thead>
<tr>
<th>Major Factors</th>
<th>Minor Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>History of motion sickness</td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
<td>Emesis during past pregnancy</td>
</tr>
<tr>
<td>History of low prior</td>
<td></td>
</tr>
<tr>
<td>chronic alcohol intake</td>
<td></td>
</tr>
<tr>
<td>History of previous</td>
<td></td>
</tr>
<tr>
<td>chemotherapy-induced</td>
<td></td>
</tr>
<tr>
<td>emesis</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 2 Serotonin Antagonists and Dosage Before Chemotherapy

<table>
<thead>
<tr>
<th>Anti-emetic</th>
<th>Route</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azasetron</td>
<td>IV</td>
<td>10 mg</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>IV</td>
<td>100 mg or 1.8 mg/kg</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>100 mg</td>
</tr>
<tr>
<td>Granisetron</td>
<td>IV</td>
<td>10 mcg/kg or 1 mg</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>2 mg (or 1 mg twice daily)</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>IV</td>
<td>8 mg or 0.15 mg/kg</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>24 mg</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>IV</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Ramosetron</td>
<td>IV</td>
<td>0.30 mg</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>IV or PO</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

*The same doses are used for highly and moderately emetic chemotherapy.*

Abbreviations: IV, intravenous; PO, by mouth.
when dexamethasone was added to the first-generation 5-HT3 receptor antagonists on days 1 and 2 or daily for the 5-day period. The addition of dexamethasone most likely increased control of daily acute and delayed CINV.

Some concern exists that the addition of dexamethasone might cause potential side effects if given for all 5 days of the cisplatin regimen. Whether daily versus intermittent dexamethasone during the 5-day cisplatin course provides added benefit is unknown. The current recommendation is to use dexamethasone on days 1 and 2 to control acute and delayed CINV during the days of chemotherapy administration and on days 6 through 8 to control delayed CINV after the chemotherapy is completed. The recommended regimen is based on clinical experience rather than a formal clinical trial.

Metoclopramide has been used for preventing CINV in patients undergoing single-day chemotherapy. Two studies examining patients receiving 5-day cisplatin showed metoclopramide to be inferior to ondansetron in preventing CINV, and extrapyramidal reactions in the patients receiving metoclopramide resulted in a metoclopramide dose reduction.

It is important to emphasize that CINV from single-day chemotherapy may have a different pattern and mechanism from multiple-day chemotherapy, and results from antiemetic studies in single-day chemotherapy may not be applicable to patients undergoing multiple-day chemotherapy. In addition, CINV may also have a different pattern and mechanism from that of patients with chronic nausea not associated with chemotherapy.

The Multinational Association of Supportive Care in Cancer (MASCC) guidelines and the American Society of Clinical Oncology (ASCO) guidelines suggest that patients receiving multiple-day cisplatin should receive a 5-HT3 receptor antagonist plus dexamethasone for acute CINV and dexamethasone for delayed CINV.

High-Dose Chemotherapy

Nausea and vomiting has several causes in patients undergoing high-dose chemotherapy with stem cell transplant. In addition to the high-dose chemotherapy, many patients undergo total body radiation as part of their conditioning regimen and receive multiple other medications (e.g., antimicrobials, narcotic analgesics, medications for graft-vs.-host disease), all of which can induce nausea and vomiting. Studies evaluating prophylactic antiemetics in patients undergoing high-dose chemotherapy with stem cell transplantation are also difficult to compare because of the many different chemotherapy regimens and patient populations.

Single-agent daily 5-HT3 receptor antagonists given during the period of high-dose chemotherapy to prevent CINV have resulted in a complete response rate of approximately 5% to 15%. Because of the very low response rate, dexamethasone has been added to the 5-HT3 receptor antagonists and each has been given on a daily basis during high-dose chemotherapy. The complete response rate appeared to improve 20% to 50% in various studies with the addition of dexamethasone. The various first-generation 5-HT3 receptor antagonists used with or without dexamethasone seem to show no difference in complete response.

Control of nausea and vomiting in patients undergoing high-dose chemotherapy and stem cell transplantation is a significant challenge, with past studies showing limited success. Current standard therapy seems to be a first-generation 5-HT3 receptor antagonist and dexamethasone, each given daily during the chemotherapy regimen. Clearly, new agents and approaches are needed.

New antiemetic agents developed for single-day chemotherapy have also been effective in both acute and delayed CINV. Three agents—aprepitant, palonosetron, and olanzapine—have been shown to control acute and delayed CINV. The mechanisms of action of these agents suggest that they may have significant efficacy in patients taking multiple-day chemotherapy and those undergoing high-dose chemotherapy with stem cell transplant.

Palonosetron

Palonosetron is a new 5-HT3 receptor antagonist that has antiemetic activity at both central and gastrointestinal sites. In comparison with the older 5-HT3 receptor antagonists, it has a higher binding affinity to the 5-HT3 receptors, a higher potency, a significantly longer half-life (approximately 40 hours, which is 4–5 times longer than that of dolasetron, granisetron, or ondansetron), and an excellent safety profile. A dose-finding phase II study showed that the effective dose was greater than or equal to 0.25 mg. In 2 large randomized phase III clinical studies of patients undergoing moderately emetogenic chemotherapy,
complete response (no emesis, no rescue) was improved in the acute and delayed periods for patients who received 0.25 mg of palonosetron alone compared with either ondansetron alone (570 patients; acute: 81.0% vs. 68.6%; \(P = .008\); delayed: 74.1% vs. 55.1%; \(P < .001\)) or dolasetron alone (392 patients; acute: 63.0% vs. 52.9%; \(P = .049\); delayed: 54.0% vs. 38.7%; \(P = .004\)). Dexamethasone was given with the 5-HT3 receptor antagonists in only a small number of patients (5%) in only 1 of these studies and, therefore, whether the differences in complete response would persist if dexamethasone was used remains to be determined.

In another randomized phase III clinical study, 650 patients undergoing highly emetogenic chemotherapy (cisplatin, \(\geq 60 \text{ mg/m}^2\)) received dexamethasone and 1 of 2 doses of palonosetron (0.25 mg or 0.75 mg), or dexamethasone and ondansetron (32 mg) prechemotherapy. The effectiveness of single-dose palonosetron was equivalent to ondansetron in preventing acute CINV and, with dexamethasone pretreatment, was significantly increased over ondansetron throughout the 5-day postchemotherapy period.

In an analysis of the patients in the above studies who underwent repeated cycles of chemotherapy, Cartmel et al. reported that the complete response rates for both acute and delayed CINV were maintained with single intravenous doses of palonosetron without concomitant corticosteroids.

Based on the above studies, palonosetron was approved by the U.S. Food and Drug Administration (FDA) in July 2003 for preventing acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. In addition, palonosetron was approved for preventing delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Because palonosetron seems to be effective in controlling both acute and delayed CINV, it may be very useful for preventing CINV in multiple-day chemotherapy.

Barnes et al. reported a phase II trial on 32 adult men who received 5 days of cisplatin (20 mg/m²) and were treated with palonosetron, 0.25 mg intravenously, on days 1, 3, and 5, and dexamethasone, 20 mg, on days 1 and 2; 8 mg orally on days 6 and 7; and 4 mg orally on day 8. Of these patients, 70% experienced no emetic episodes and 63% experienced no or minimal nausea over the 9-day observation period. The authors concluded that 3 doses of palonosetron and 5 doses of dexamethasone over 8 days effectively prevented both emesis and significant nausea in most patients with germ cell tumors undergoing multiple-day cisplatin-based chemotherapy. Patients receiving this regimen seemed to show an improvement over historical controls. This study suggests that agents that control both acute and delayed CINV have potential as preventative agents in patients undergoing multiple-day chemotherapy.

**Substance P (NK-1) Receptor Antagonists: Aprepitant**

Substance P is a mammalian tachykinin that is found in vagal afferent neurons innervating the brainstem nucleus tractus solitarius (NTS), which sends impulses to a vomiting center. Substance P induces vomiting and binds to NK-1 receptors in the abdominal vagus, the NTS, and the area postrema. Compounds that block NK-1 receptors lessen emesis after cisplatin, ipecac, apomorphine, and radiation therapy. These observations have recently led to the development of NK-1 receptor antagonists and the study of the role they may play in controlling chemotherapy-induced nausea and emesis.

The initial phase II clinical studies using the NK-1 receptor antagonists showed that adding an NK-1 receptor antagonist (CP-122,721, CJ-11,794, or MK-0869) to a 5-HT3 receptor antagonist and dexamethasone before cisplatin chemotherapy improved the control of acute emesis compared with the 5-HT3 and dexamethasone alone, and improved the control of delayed emesis compared with placebo.

In a phase III randomized clinical dosing study of oral MK-869, which was the final capsule formulation of aprepitant and involved 563 chemotherapy-naïve patients receiving cisplatin (\(\geq 70 \text{ mg/m}^2\)), Chawla et al. reported an improvement in the control of acute emesis when MK-869 was added to ondansetron and dexamethasone and an improvement in the control of delayed emesis with the combination of MK-869 and dexamethasone compared with dexamethasone alone.
In both studies, common side effects are in the acute (days 2–4), or standard therapy plus aprepitant given before chemotherapy and aprepitant plus dexamethasone on days 2 and 3 postchemotherapy.\(^6\) In both studies, the patients receiving aprepitant showed a significantly higher complete response (no emesis, no rescue) in the acute period (83\%–89\%), the delayed period (68\%–75\%), and overall (days 1–5, 62.7\%–72.7\%) compared with the acute period (68\%–78\%), the delayed period (47\%–56\%), and overall (days 1–5; 43.3\%–52.3\%) of those undergoing standard therapy. This improved complete response with the addition of aprepitant was maintained over multiple cycles of chemotherapy.\(^6\) Nausea was improved in the aprepitant group only in the delayed period in 1 of the studies.\(^6\)

The studies discussed above formed the basis for the approval of aprepitant by the FDA in March 2003. In combination with other antiemetics, aprepitant is indicated for preventing acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.\(^6,6^5\)

In a follow-up phase III randomized clinical study to the 2 randomized studies described above, the aprepitant regimen was shown to affect a higher complete response in patients receiving cisplatin not only compared with the 1-day ondansetron and 4-day dexamethasone regimen in the previous trials, but also to a 4-day ondansetron and 4-day dexamethasone regimen.\(^6^6\)

The 4-day ondansetron and dexamethasone regimen is similar to what is used to prevent CINV in patients undergoing multiple-day chemotherapy or high-dose chemotherapy with stem cell transplant. Adding aprepitant to the daily first-generation 5-HT3 receptor antagonist and dexamethasone may improve the control of CINV in multiple-day chemotherapy. Current clinical trials are underway to determine the usefulness of aprepitant as an additive therapy.

**Olanzapine**

Olanzapine is an antipsychotic that blocks multiple neurotransmitters: dopamine at D1, D2, D3, D4 brain receptors, serotonin at 5-HT2a, 5-HT2c, 5-HT3, 5-HT6 receptors, catecholamines at α1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors.\(^7^7,7^8\) Common side effects are sedation and weight gain\(^7^9,7^7\) and an association with the onset of diabetes mellitus.\(^7^1\) Olanzapine’s activity at multiple receptors, particularly at the D2 and 5-HT3 receptors, which appear to be involved in nausea and emesis, suggest that it may have significant antiemetic properties.

Based on case reports\(^7^2,7^3\) and phase I data,\(^7^7\) olanzapine appeared to be safe and effective for preventing delayed emesis in chemotherapy-naïve cancer patients receiving cyclophosphamide, doxorubicin, cisplatin, or irinotecan. Using the maximum tolerated dose of olanzapine in the phase I trial, a phase II trial was performed to prevent CINV in patients undergoing their first course of either highly emetogenic or moderately emetogenic chemotherapy. The regimen was 5 mg/d of oral olanzapine on the 2 days before chemotherapy, 10 mg of olanzapine on the day of chemotherapy (day 1; added to intravenous granisetron 10 mcg/kg and dexamethasone 20 mg), and 10 mg/d on days 2 through 4 after chemotherapy (added to dexamethasone, 8 mg orally twice a day on days 2 and 3; 4 mg orally twice a day on day 4). Thirty patients (median age, 58.5 years; range, 25–84; 23 females; Eastern Cooperative Oncology Group Performance Status 0, 1) consented to the protocol and all were evaluable.

Complete response (no emesis, no rescue) was 100\% for the acute period (24 hours postchemotherapy), 80\% for the delayed period (days 2–5 postchemotherapy), and 80\% for the overall period (0–120 hours postchemotherapy) in 10 patients undergoing highly emetogenic chemotherapy (cisplatin ≥70 mg/m\(^2\)). Complete response was also 100\% for the acute period, 85\% for the delayed period, and 85\% for the overall period in 20 patients undergoing moderately emetogenic chemotherapy (doxorubicin ≥50 mg/m\(^2\)). Nausea was very well controlled in the patients undergoing highly emetogenic chemotherapy with no patient having nausea (0 on scale of 0–10, M. D. Anderson Symptom Inventory)\(^7^9\) in the acute or delayed periods. Nausea was also well controlled in patients undergoing moderately emetogenic chemotherapy with no nausea in 85\% of patients in the acute period and 65\% in the delayed and overall periods.

The patients experienced no grade 3 or 4 toxicities and no significant pain, fatigue, disturbed sleep, memory changes, dyspnea, lack of appetite, drowsiness, dry mouth, mood changes, or restlessness. Complete response and control of nausea in subsequent cycles of chemotherapy (25 patients in cycle 2; 25 patients in cycle 3; 21 patients in cycle 4) were equal to or greater than cycle 1. The study
concluded that olanzapine was safe and highly effective in controlling acute and delayed CINV in patients undergoing highly and moderately emetogenic chemotherapy.

**Conclusions and Treatment Recommendations**

Although significant improvements have occurred in preventing CINV in patients undergoing single-day highly and moderately emetogenic chemotherapy, limited progress has been made in preventing CINV in patients undergoing multiple-day chemotherapy or high-dose chemotherapy with stem cell transplant. The current recommendation is to give a first-generation 5-HT3 receptor antagonist and dexamethasone daily during each day of chemotherapy in patients undergoing multiple-day chemotherapy or high-dose chemotherapy with stem cell transplant. This regimen seems to be at least partially effective in controlling acute CINV but is not very effective in controlling delayed CINV. The complete response in most studies of 5 days of cisplatin and in various high-dose chemotherapy regimens is 30% to 70%, with most studies reporting a complete response of 50% or less.

The new antiemetic agents, palonosetron, aprepitant, and olanzapine, have shown effectiveness in controlling both acute and delayed CINV in patients undergoing single-day moderately and highly emetogenic chemotherapy. With the exception of one report using palonosetron in patients receiving 5 days of cisplatin, these agents have not been studied in patients undergoing multiple-day or high-dose chemotherapy.

Palonosetron is the only 5-HT3 receptor antagonist indicated to control delayed CINV, suggesting that it may be more effective than first-generation 5-HT3 receptor antagonists in patients undergoing multiple-day and high-dose chemotherapy. Using palonosetron on an every-other-day or daily dosing schedule during the period of daily chemotherapy may be a reasonable approach in patients undergoing multiple-day or high-dose chemotherapy. The use of palonosetron may treat both acute and delayed CINV, and in combination with dexamethasone may result in a relatively high complete response. A specific dosing schedule requires future studies.

Aprepitant is approved as an additive agent to a 5-HT3 receptor antagonist and dexamethasone in controlling acute and delayed CINV in patients undergoing single-day chemotherapy. It is given for 3 days, beginning on the day of chemotherapy. For patients undergoing multiple-day or high-dose chemotherapy, a consideration for clinical implementation and for a potential clinical trial would be to add aprepitant to a 5-HT3 receptor antagonist and dexamethasone for the first 3 days of chemotherapy and then repeat the 3-day aprepitant regimen on the final day of chemotherapy. This approach may improve both the acute and delayed CINV during and after the multiple-day chemotherapy regimen.

Olanzapine has been shown to be an effective agent in controlling CINV in patients undergoing single-day chemotherapy when added to a 5-HT3 receptor antagonist and dexamethasone. The addition of olanzapine to a 5-HT3 receptor antagonist and dexamethasone during each day of multiple-day chemotherapy and for 3 days after the completion of chemotherapy may significantly improve complete response. This would be a consideration for clinical implementation and for a potential clinical trial.

A clinical trial is being prepared within the Hoosier Oncology Group to compare the addition of either aprepitant or olanzapine to palonosetron and dexamethasone with a first-generation 5-HT3 receptor antagonist and dexamethasone in patients undergoing multiple-day chemotherapy. Additional trials (Hoosier Oncology Group) using the new agents are planned for patients undergoing high-dose chemotherapy with stem cell transplant. The new agents are anticipated to significantly improve the complete response in patients undergoing multiple-day chemotherapy or high-dose chemotherapy with stem cell transplant primarily because of the demonstrated effectiveness of these agents in controlling delayed CINV.

**References**

Emesis Prevention


Emesis Prevention


