

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

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ABSTRACT

Purpose

To update the American Society of Clinical Oncology (ASCO) guideline for antiemetics in oncology.

Methods

A systematic review of the medical literature was completed to inform this update. MEDLINE, the Cochrane Collaboration Library, and meeting materials from ASCO and the Multinational Association for Supportive Care in Cancer were all searched. Primary outcomes of interest were complete response and rates of any vomiting or nausea.

Results

Thirty-seven trials met prespecified inclusion and exclusion criteria for this systematic review. Two systematic reviews from the Cochrane Collaboration were identified; one surveyed the pediatric literature. The other compared the relative efficacy of the 5-hydroxytryptamine-3 (5-HT₃) receptor antagonists.

Recommendations

Combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic. Patients who receive this combination or any highly emetic agents should receive a 5-HT₃ receptor antagonist, dexamethasone, and a neurokinin 1 (NK₁) receptor antagonist. A large trial validated the equivalency of fosaprepitant, a single-day intravenous formulation, with aprepitant; either therapy is appropriate. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. For low-risk agents, patients can be offered dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT₃ receptor antagonist before each fraction and for 24 hours after treatment and may receive a 5-day course of dexamethasone during fractions 1 to 5. The Update Committee noted the importance of continued symptom monitoring throughout therapy. Clinicians underestimate the incidence of nausea, which is not as well controlled as emesis.

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INTRODUCTION

The first American Society of Clinical Oncology (ASCO) guideline for the use of antiemetics was published in 1999¹ and updated once in 2006.² This guideline provides clinicians with recommendations to prevent vomiting and nausea among patients undergoing antineoplastic therapy (chemotherapy-induced nausea and vomiting [CINV]) and/or radiation therapy (radiation-induced nausea and vomiting [RINV]) based on evidence from randomized clinical trials.

METHODS

An Update Committee (Appendix Table A1, online only) met twice to review data published since 2006 and update recommendations as warranted.

Literature Review

Literature search strategy. A systematic review on the effectiveness of newer antiemetics (aprepitant and the 5-hydroxytryptamine-3 [5-HT₃] receptor antagonists), funded by the Agency for Healthcare Research and Quality, was initially reviewed for relevant publications. Two MEDLINE searches (search strategy available in the Data Supplement, <http://www.asco.org/guidelines/antiemetics>) were completed to identify additional randomized controlled trials; a search of the Cochrane Collaboration Library was also conducted. Meeting materials from the ASCO and Multinational Association of Supportive Care in Cancer annual meetings available since the 2006 update were additionally culled. Only full presentations or posters were eligible; material available only in abstract form was not considered.

Inclusion and exclusion criteria. Systematic reviews and reports from randomized controlled trials eligible for inclusion met the following criteria: the intervention was for the treatment of nausea or vomiting secondary

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Editor's note: This is a brief overview of the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update and provides the updated recommendations with brief discussions of the relevant literature for each. The complete guideline, which includes comprehensive discussions of the literature, methodology information, and all cited references, plus a data supplement with evidence tables the Update Committee used to formulate these recommendations are available at www.asco.org/guidelines/antiemetics.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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to cancer therapy; nausea and/or vomiting outcomes were reported; patients were observed for a minimum of 5 days (120 hours) after the intervention; and each trial arm included a minimum of 25 randomly assigned patients. Evidence tables are provided in the Data Supplement.

The guideline was reviewed and approved by the ASCO Clinical Practice Guidelines Committee and the Board of Directors and underwent review and approval for publication in the *Journal of Clinical Oncology*.

THE BOTTOM LINE

American Society of Clinical Oncology Clinical Practice Guideline Update on Antiemetics

Intervention

- Antiemetics for patients receiving cancer therapy.

Target Audience

- Medical Oncologists, Radiation Oncologists, Oncology Nurses.

Key Recommendations

- Patients who receive highly emetic chemotherapy regimens should receive the three-drug combination of a neurokinin 1 (NK₁) antagonist, 5-hydroxytryptamine-3 (5-HT₃) antagonist, and dexamethasone.
- The preferred 5-HT₃ antagonist for patients who receive moderate emetic chemotherapy regimens is palonosetron; antiemetic treatment includes that agent combined with a corticosteroid.
- Antiemetic treatment for patients who receive combination chemotherapy should be determined according to the agent with the greatest degree of emetic risk.
- Both dexamethasone and a 5-HT₃ antagonist are recommended for patients undergoing high-dose chemotherapy.
- Pediatric patients receiving either high or moderate emetic risk chemotherapy should be treated with a 5-HT₃ antagonist and corticosteroids; higher weight-based dosing may be required.
- For those treated with high emetic risk radiation therapy, a 5-HT₃ antagonist before each fraction and a 5-day course of dexamethasone are recommended.
- A 5-HT₃ antagonist before each fraction is also recommended before moderate-risk radiation; a 5-day course of dexamethasone is optional.
- For patients who receive combination chemoradiotherapy, antiemetic therapy is dictated by the emetogenicity of chemotherapy, unless the emetic risk of radiation therapy is higher.

Methods

- A systematic review of the literature published since the last update of the guideline.

The data supplement, including evidence tables and clinical tools and resources, can be found at www.asco.org/guidelines/antiemetics.

Guideline Policy

This Executive Summary for physicians is an abridged summary of an ASCO practice guideline. The practice guideline and this summary are not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This summary does not recommend any particular product or course of medical treatment. Use of the practice guideline and this summary is voluntary. The full practice guideline and additional information are available at <http://www.asco.org/guidelines/antiemetics>.

Guideline and Conflict of Interest

The Update Committee was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at <http://www.asco.org/guidelinescoi>). Members of the Update Committee completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

RESULTS

The literature search from 2006 to December 2009 yielded a total of 271 unique citations from MEDLINE and 48 from meetings (QUOROM Diagram available in Data Supplement). Thirty-six reports met inclusion criteria and were selected for data extraction; 11 (30.6%) were reports from meetings.

GUIDELINE RECOMMENDATIONS

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Updated recommendations are listed in Table 1. Table 2 lists intravenous agents organized by emetic risk. Dosing schedules for each risk class are listed in Table 3.

Clinical Question 1

What is the optimal treatment to prevent nausea and vomiting from highly emetogenic antineoplastic agents?

Recommendation 1. The three-drug combination of a neurokinin 1 (NK₁) receptor antagonist (days 1 through 3 for aprepitant; day 1 only for fosaprepitant), a 5-HT₃ receptor antagonist (day 1 only), and dexamethasone (days 1 through 3 or 1 through 4) is recommended for patients receiving highly emetogenic chemotherapy. The Update Committee also recommended reclassification of the combined anthracycline and cyclophosphamide (AC) regimen as highly emetogenic.

Literature update and analysis 1. Five new trials were identified.³⁻⁷ The study by Hoshi et al⁵ provided additional data (Data Supplement) that support use of aprepitant for patients undergoing high-risk chemotherapy.

An equivalency study compared fosaprepitant, a 1-day intravenous formulation of aprepitant, with oral aprepitant.^{3,8} Findings demonstrate equivalence between the agents for complete response and both emesis and nausea control. Fosaprepitant was endorsed by the Update Committee as an acceptable NK₁ receptor antagonist.

Table 1. Summary of Recommendations

Clinical Situation	2006 Recommendation	2011 Recommendation
Chemotherapy-induced nausea and vomiting		
Highly emetogenic agents	The three-drug combination of a 5-HT ₃ receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy. In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended. The Update Committee no longer recommends the combination of a 5-HT ₃ serotonin receptor antagonist and dexamethasone on days 2 and 3.	The three-drug combination of an NK ₁ receptor antagonist (days 1-3 for aprepitant; day 1 only for fosaprepitant), a 5-HT ₃ receptor antagonist (day 1 only), and dexamethasone (days 1-3 or 1-4) is recommended for patients receiving highly emetogenic chemotherapy. This recommendation is unchanged since the 2006 update, but reworded for clarification. The Update Committee also recommended reclassification of the combined AC regimen as highly emetogenic.
Moderately emetogenic agents	The three-drug combination of a 5-HT ₃ receptor antagonist, dexamethasone, and aprepitant is recommended for patients receiving AC. For patients receiving chemotherapy of moderate emetic risk other than AC, we recommend the two-drug combination of a 5-HT ₃ receptor antagonist and dexamethasone. In patients receiving AC, aprepitant as a single agent is recommended on days 2 and 3. For all other chemotherapies of moderate emetic risk, single-agent dexamethasone or a 5-HT ₃ receptor antagonist is suggested for the prevention of emesis on days 2 and 3.	The two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1-3) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT ₃ serotonin receptor antagonist, preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT ₃ antagonists is appropriate.
Low emetogenic agents	Dexamethasone 8 mg is suggested. No routine preventive use of antiemetics for delayed emesis is suggested.	A single 8-mg dose of dexamethasone before chemotherapy is suggested. No change since 2006.
Minimally emetogenic agents	No change from the original guideline. No antiemetic should be administered routinely before or after chemotherapy.	No antiemetic should be administered routinely before or after chemotherapy. No change from the original guideline.
Combination chemotherapy	No change from the original guideline. Patients should be administered antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.	Patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk. No change from the original guideline. AC combinations are now classified as highly emetogenic.
Adjunctive drugs	Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single agents.	Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics. No change since 2006.
Complementary therapy	New question for 2011 update.	No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about such therapies.
Pediatric patients	The combination of a 5-HT ₃ antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT ₃ antagonists than those used in adults may be required for antiemetic protection.	The combination of a 5-HT ₃ antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT ₃ antagonists than those used in adults may be required for antiemetic protection. No change since 2006.
High-dose chemotherapy with stem-cell or bone marrow transplantation	No change from original guideline. A 5-HT ₃ receptor antagonist antiemetic combined with dexamethasone is suggested. Aprepitant should be considered, although evidence to support its use specifically in these patients is lacking.	A 5-HT ₃ receptor antagonist combined with dexamethasone is suggested. Aprepitant should be considered, although evidence to support its use is limited.
Multiday chemotherapy	No change from the original guideline. It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined earlier, be administered for each day of the chemotherapy and for 2 days after, if appropriate.	It is suggested that antiemetics appropriate for the emetogenic risk class of the chemotherapy be administered for each day of the chemotherapy and for 2 days after, if appropriate. No change from the original guideline. The Update Committee suggests, based on limited data, that patients receiving 5-day cisplatin regimens be treated with a 5-HT ₃ antagonist in combination with dexamethasone and aprepitant.
Emesis or nausea despite optimal prophylaxis	No change from original guideline. The Update Committee suggests that clinicians conduct a careful re-evaluation of emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider substituting a high-dose intravenous metoclopramide for the 5-HT ₃ antagonist or adding a dopamine antagonist to the regimen.	Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT ₃ antagonist or adding a dopamine antagonist to the regimen.
Anticipatory nausea and vomiting	No change since the original guideline. Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens may be used with the initial chemotherapy, rather than assessing the patient's emetic response with less effective treatment. If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and suggested.	Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens should be used with initial chemotherapy, rather than assessing the patient's emetic response with less effective treatment. If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and suggested. No change since the original guideline.

(continued on following page)

Table 1. Summary of Recommendations (continued)

Clinical Situation	2006 Recommendation	2011 Recommendation
Radiation-induced nausea and vomiting		
High risk	No change from original guideline. The Update Committee suggests administration a 5-HT ₃ antagonist with or without a corticosteroid before each fraction and for at least 24 hours after. There is no change from the original guideline.	On the basis of extrapolation from indirect evidence, the Update Committee recommends that all patients should receive a 5-HT ₃ antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions 1-5.
Moderate risk	The Update Committee recommends a 5-HT ₃ antagonist before each fraction.	The Update Committee recommends that patients receive a 5-HT ₃ antagonist before each fraction for the entire course of radiotherapy. Patients may be offered a short course of dexamethasone during fractions 1-5.
Low risk	No change from original guideline. The Update Committee recommends a 5-HT ₃ antagonist before each fraction.	The Update Committee recommends a 5-HT ₃ antagonist alone as either prophylaxis or rescue. For patients who experience radiation-induced nausea and vomiting while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is complete.
Minimal risk	No change from original guideline. The Update Committee suggests that treatment be administered on an as-needed basis only. Dopamine or serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day.	Patients should receive rescue therapy with either a dopamine receptor antagonist or a 5-HT ₃ antagonist. Prophylactic antiemetics should continue throughout radiation treatment if a patient experiences radiation-induced nausea and vomiting while receiving rescue therapy.
Combined chemotherapy and radiation therapy	Patients should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the planned radiotherapy is higher. No change from the original guideline.	Patients should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the planned radiotherapy is higher. No change from the original guideline.

Abbreviations: AC, anthracycline and cyclophosphamide; 5-HT₃, 5-hydroxytryptamine-3; NK₁, neurokinin 1.

The pilot study by Herrington et al⁴ compared two dosing schedules of aprepitant (1 day v 3 days). No differences in rates of complete response and emetic episodes for the overall study period were reported. Studies to validate the noninferiority of single-day oral aprepitant are necessary to establish equivalence.

A pilot study compared olanzapine with aprepitant.⁶ Patients randomly assigned to olanzapine experienced similar complete response rates as patients who received aprepitant. Olanzapine was superior for nausea control during the overall study period ($P < .01$). Additional trials are necessary to define the role of olanzapine in this setting.

The AC combination was reclassified based on the high emetic potential of the combined agents. Data from placebo-controlled studies indicate that this combination causes vomiting in 85% of patients not receiving antiemetic prophylaxis.⁹ This borders on the cutoff defined for highly emetogenic agents.⁹

Clinical Question 2

What is the optimal treatment to prevent nausea and vomiting from moderately emetogenic antineoplastic agents?

Recommendation 2. The two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1 through 3) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT₃ receptor antagonist, preferably granisetron or ondansetron.

Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT₃ antagonists is appropriate.

Literature update and analysis 2a: 5-HT₃ receptor antagonist equivalency. The Update Committee evaluated therapeutic equivalence of

the 5-HT₃ receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron, ramosetron, and tropisetron). A Cochrane Review of 5-HT₃ antagonists used to prevent CINV was identified.¹⁰ Most trials compared ondansetron and granisetron. Few trials including dolasetron and tropisetron were identified, and only one study with palonosetron was included,¹¹ which is described in this section. No studies on ramosetron were included. Findings from the review suggest equivalency between ondansetron and granisetron, supported by a meta-analysis (Data Supplement). Another meta-analysis from Jordan et al¹² assessed only first-generation 5-HT₃ receptor antagonists. This study also indicates equivalency of granisetron and ondansetron and superiority of granisetron compared with tropisetron.

A study comparing ramosetron and granisetron was identified.¹³ Findings indicate similar rates of complete response during the first 24 hours after chemotherapy. Research describing the efficacy of ramosetron during the 7-day period after chemotherapy is not available.

Three studies compared palonosetron with first-generation 5-HT₃ antagonists.^{11,14,15} Findings from two larger studies^{11,16} suggested that palonosetron provides superior protection against both nausea and vomiting, particularly during the period from 24 to 120 hours after chemotherapy. However, the third study yielded nonsignificant differences, which might be explained by the fact that it was designed as a noninferiority trial.¹⁵

These studies were conducted in combined emetic risk populations, but not a non-AC moderately emetogenic population, and compared palonosetron with a first-generation 5-HT₃ receptor antagonist in which dexamethasone has also been included. The preference for palonosetron is an extrapolation from the Saito et al¹¹ data; when an NK₁ receptor antagonist is not used in the setting of cisplatin and AC chemotherapy, the combination of palonosetron and dexamethasone is superior to granisetron and dexamethasone. By inference, with non-AC moderately emetogenic chemotherapy, palonosetron

Table 2. Emetic Risk of Intravenous Antineoplastic Agents

Emetic Risk	Agent	
High	Carmustine	
	Cisplatin	
	Cyclophosphamide $\geq 1,500$ mg/m ²	
	Dacarbazine	
	Dactinomycin	
	Mechlorethamine	
	Streptozotocin	
Moderate	Azacitidine	
	Alemtuzumab	
	Bendamustine	
	Carboplatin	
	Clofarabine	
	Cyclophosphamide $< 1,500$ mg/m ²	
	Cytarabine $> 1,000$ mg/m ²	
	Daunorubicin*	
	Doxorubicin*	
	Epirubicin*	
	Idarubicin*	
	Ifosfamide	
	Irinotecan	
	Oxaliplatin	
	Low	Fluorouracil
		Bortezomib
Cabazitaxel		
Catumaxomab		
Cytarabine $\leq 1,000$ mg/m ²		
Docetaxel		
Doxorubicin HCL liposome injection		
Etoposide		
Gemcitabine		
Ixabepilone		
Methotrexate		
Mitomycin		
Mitoxantrone		
Paclitaxel		
Panitumumab		
Pemetrexed		
Temsirolimus		
Topotecan		
Trastuzumab		
Minimal	2-Chlorodeoxyadenosine	
	Bevacizumab	
	Bleomycin	
	Busulfan	
	Cetuximab	
	Fludarabine	
	Pralatrexate	
	Rituximab	
	Vinblastine	
	Vincristine	
	Vinorelbine	

NOTE. This list of agents is not exhaustive.
Abbreviation: HCL, hydrochloride.
*These anthracyclines, when combined with cyclophosphamide, are now designated as high emetic risk.

Table 3. Antiemetic Dosing by Chemotherapy Risk Category

Risk Category	Dosing on Day of Chemotherapy	Dosing on Subsequent Days	
High emetic risk*			
NK ₁ antagonist	Aprepitant	125 mg oral	
	Fosaprepitant	150 mg IV	
5-HT ₃ antagonist	Granisetron	2 mg oral; 1 mg or 0.01 mg/kg IV	
	Ondansetron	8 mg oral twice daily; 8 mg or 0.15 mg/kg IV	
Corticosteroid†	Palonosetron	0.50 mg oral; 0.25 mg IV	
	Dexamethasone	12 mg oral or IV	
Moderate emetic risk‡	Corticosteroid	Palonosetron	0.50 mg oral; 0.25 mg IV
		Dexamethasone	8 mg oral or IV
Low emetic risk			
Corticosteroid			
Dexamethasone			
	8 mg oral or IV	8 mg; days 2 and 3	

NOTE. For patients receiving multiday chemotherapy, clinicians must first determine the emetic risk of the agent(s) included in the regimen. Patients should receive the agent of the highest therapeutic index daily during chemotherapy and for 2 days thereafter. Patients can also be offered the granisetron transdermal patch that delivers therapy over multiple days rather than taking a serotonin antagonist daily.
Abbreviations: 5-HT₃, 5-hydroxytryptamine-3; IV, intravenous; NK₁, neurokinin 1.
*Includes combination of an anthracycline and cyclophosphamide.
†The dexamethasone dose is for patients who are receiving the recommended three-drug regimen for highly emetic chemotherapy. If patients do not receive aprepitant, the dexamethasone dose should be adjusted to 20 mg on day 1 and 16 mg on days 2 to 4.
‡Clinicians who choose to use an NK₁ antagonist should follow high emetic risk chemotherapy dosing. Importantly, corticosteroid is only given on day 1; dexamethasone dose is 12 mg.

of aprepitant in patients undergoing moderately emetogenic chemotherapy.¹⁷ Improved CINV protection with aprepitant was noted. An advantage of using aprepitant with moderate-risk agents is abbreviated dexamethasone dosing.

Literature update and analysis 2c: Dexamethasone dosing. Two trials^{16,18} evaluated dexamethasone dosing, comparing 1- and 3-day dexamethasone dosing combined with palonosetron. Findings from these trials suggest similar outcomes with the two regimens. Additional trials that validate these findings may warrant a change to the current recommendation.

Clinical Question 3

What is the optimal treatment to prevent nausea and vomiting from low emetogenic antineoplastic agents?

Recommendation 3. A single 8-mg dose of dexamethasone before chemotherapy is suggested.

Literature update and analysis 3. No new evidence was identified.

and dexamethasone are also likely to be superior to a first-generation 5-HT₃ receptor antagonist and dexamethasone.

Literature update and analysis 2b: NK₁ receptor antagonist for moderately emetogenic chemotherapy. One trial evaluated the utility

Clinical Question 4

What is the optimal treatment to prevent nausea and vomiting from minimally emetogenic antineoplastic agents?

Recommendation 4. No antiemetic should be administered routinely before or after chemotherapy.

Literature update and analysis 4. No new evidence was identified.

Clinical Question 5

What is the optimal treatment to prevent nausea and vomiting from combination chemotherapy?

Recommendation 5. Patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk. AC combinations are now classified as highly emetogenic.

Literature update and analysis 5. No new evidence was identified.

Clinical Question 6

What is the role of adjunctive drugs for nausea and vomiting induced by cancer treatments?

Recommendation 6. Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics.

Literature update and analysis 6. One new trial evaluated the impact of including olanzapine in antiemetic regimens.¹⁹ Benefits of olanzapine were most evident during the days after chemotherapy.

Clinical Question 7

What is the role of complementary and alternative medicine therapies to prevent or control nausea and vomiting induced by chemotherapy?

Recommendation 7. No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about such therapies.

Literature update and analysis 7. A phase III trial of ginger was presented at an ASCO meeting in 2009.²⁰ No significant differences in the prevalence of vomiting and nausea between patients who received ginger and placebo were reported.

A Cochrane Systematic Review of acupuncture-point stimulation for CINV was published.²¹ However, this effort did not meet prespecified inclusion and exclusion criteria for this systematic review.

SPECIAL POPULATIONS**Clinical Question 8**

What is the optimal treatment to prevent nausea and vomiting associated with cancer therapy for pediatric patients?

Recommendation 8. The combination of a 5-HT₃ antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of the variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT₃ antagonists than those used in adults may be required for antiemetic protection. There is no change in this recommendation from 2006.

Literature update and analysis 8. A systematic review of available therapies for CINV in children was published by the Cochrane Collaboration.²² Few trials identified had similarities in intervention characteristics, so the review was primarily qualitative. A pooled analysis indicates that the addition of dexamethasone to the newer 5-HT₃ antagonists provides benefits in the high emetic risk setting.

Two trials were also identified. One assessed the use of aprepitant in this population.²³ The second evaluated the efficacy and safety of palonosetron in pediatric patients.²⁴

Clinical Question 9

What is the optimal treatment to prevent nausea and vomiting in patients who are undergoing high-dose chemotherapy with stem-cell or bone marrow transplantation?

Recommendation 9. A 5-HT₃ receptor antagonist combined with dexamethasone is recommended. Aprepitant should be considered, although evidence to support its use is limited.

Literature update and analysis 9. Two new studies were identified.^{25,26} One report detailed superior emetic control with palonosetron. Data suggest that 2 days of palonosetron therapy will decrease the likelihood of CINV. The other trial evaluated use of aprepitant during chemotherapy conditioning. Patients who received aprepitant experienced markedly improved vomiting control.

Clinical Question 10

What is the optimal treatment to prevent nausea and vomiting for patients receiving multiday chemotherapy?

Recommendation 10. It is suggested that antiemetics appropriate for the emetogenic risk class of the chemotherapy be administered for each day of the chemotherapy and for 2 days after, if appropriate. There is no change from the original guideline.

The Update Committee suggests, based on limited data, that patients receiving 5-day cisplatin regimens be treated with a 5-HT₃ antagonist in combination with dexamethasone and aprepitant.

Literature update and analysis 10. One trial of patients receiving 5-day cisplatin evaluated incorporation of metopimazine with tropisetron.²⁷ Findings suggested improved nausea and vomiting.

Noninferiority of the new granisetron transdermal system compared with the oral formulation was validated in a trial of patients who received multiday chemotherapy.²⁸ The patch is indicated for use in patients receiving high- or moderate-risk chemotherapy.

Clinical Question 11

What is the optimal antiemetic regimen for patients who experience nausea and vomiting secondary to cancer therapy despite optimal prophylaxis?

Recommendation 11. Language from the 2006 guideline was reformatted for clarity. Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT₃ antagonist or adding a dopamine antagonist to the regimen.

Literature update and analysis 11. No new evidence was identified.

Clinical Question 12

What treatment options are available for patients who experience anticipatory nausea and vomiting?

Recommendation 12. Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens should be used with initial chemotherapy, rather than assessing the patient's emetic response with less effective treatment. If anticipatory emesis

Table 4. Emetic Risk by Site of Radiation Therapy

Emetic Risk	Site of Radiation Therapy
High	Total-body irradiation
	Total nodal irradiation
Moderate	Upper abdomen
	Upper body irradiation
	Half-body irradiation
Low	Cranium
	Craniospinal
	Head and neck
	Lower thorax region
	Pelvis
Minimal	Extremities
	Breast

Data adapted.²⁹

occurs, behavioral therapy with systematic desensitization is effective and suggested. No change since the original guideline.

Literature update and analysis 12. No new evidence was identified.

RADIATION-INDUCED NAUSEA AND VOMITING

An updated risk stratification table according to site of radiation treatment is provided in Table 4.²⁹ Dosing schedules according to risk are listed in Table 5.

Clinical Question 13

What is the optimal prophylaxis for nausea and vomiting caused by high emetic risk radiation therapy?

Recommendation 13. On the basis of extrapolation from indirect evidence, the Update Committee recommends that all patients should receive a 5-HT₃ antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions 1 to 5.

Literature update and analysis 13. No new evidence was identified; the modification was based on evidence from the moderate-risk category.³⁰

Clinical Question 14

What is the optimal prophylaxis for nausea and vomiting caused by moderate emetic risk radiation therapy?

Recommendation 14. The Update Committee recommends that patients receive a 5-HT₃ antagonist before each fraction for the entire course of radiotherapy. Patients may be offered a short course of dexamethasone during fractions 1 to 5.

Literature update and analysis 14. A new trial that evaluated the efficacy of adding 5 days of dexamethasone during radiation to the upper abdomen was identified.³⁰ The addition of dexamethasone provided superior vomiting protection and lower average nausea, both secondary end points.

Clinical Question 15

What is the optimal treatment to manage nausea and vomiting associated with low emetic risk radiation therapy?

Recommendation 15. The Update Committee recommends a 5-HT₃ antagonist alone as either prophylaxis or rescue. For patients

Table 5. Antiemetic Dosing by Radiation Risk Category

Risk Category	Dose	Schedule
High emetic risk		
5-HT ₃ antagonist		5-HT ₃ antagonist before each fraction throughout XRT; continue for at least 24 hours after completion of XRT
Granisetron*	2 mg oral; 1 mg or 0.01 mg/kg IV	
Ondansetron*	8 mg oral twice daily; 8 mg or 0.15 mg/kg IV	
Palonosetron†	0.50 mg oral; 0.25 mg IV	
Dolasetron	100 mg oral only	
Tropisetron	5 mg oral or IV	
Corticosteroid		
Dexamethasone	4 mg oral or IV	During fractions 1-5
Moderate emetic risk		
5-HT ₃ antagonist	Any of the above listed agents are acceptable; note preferred options†	5-HT ₃ antagonist before each fraction throughout XRT
Corticosteroid		
Dexamethasone	4 mg IV or oral	During fractions 1-5
Low emetic risk		
5-HT ₃ antagonist	Any of the above listed agents are acceptable; note preferred options	5-HT ₃ either as rescue or prophylaxis; if rescue is used, then prophylactic therapy should be given until the end of XRT
Minimal emetic risk		
5-HT ₃ antagonist	Any of the above listed agents are acceptable; note preferred options	Patients should be offered either class as rescue therapy; if rescue is used, then prophylactic therapy should be given until the end of XRT
Dopamine receptor antagonist		
Metoclopramide	20 mg oral	
Prochlorperazine	10 oral or IV	

Abbreviations: 5-HT₃, 5-hydroxytryptamine-3; IV, intravenous; XRT, radiation therapy.
 *Preferred agents.
 †No data are currently available on the appropriate dosing frequency with palonosetron in this setting. The Update Committee suggests that dosing every second or third day may be appropriate for this agent.

who experience RINV while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is complete.

Literature update and analysis 15. The recommendation was modified to include rescue therapy.

Clinical Question 16

What is the optimal treatment to manage nausea and vomiting associated with minimal emetic risk radiation therapy?

Recommendation 16. Patients should receive rescue therapy with either a dopamine receptor antagonist or a 5-HT₃ antagonist. Prophylactic antiemetics should continue throughout radiation treatment if a patient experiences RINV while receiving rescue therapy.

Literature update and analysis 16. No new evidence was identified.

Clinical Question 17

What is the optimal treatment to manage nausea and vomiting during concurrent radiation and chemotherapy?

Recommendation 17. Patients should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the planned radiotherapy is higher. There is no change from the original guideline.

Literature update and analysis 17. No new evidence was identified.

Drug Formulations and Agent Dosing

Since the last update, an orally disintegrating ondansetron tablet became available.³¹ The orally disintegrating form is equivalent with respect to both emesis and nausea control. This is an acceptable alternative to the standard tablet.

Two other antiemetic agents received regulatory approval. As discussed, the granisetron transdermal patch is an option for patients who receive high-risk, multiday chemotherapy. The Update Committee suggests that this agent can also be considered for high- or moderate-risk radiation.

Palonosetron is now available orally.³² A noninferiority trial documented similarity between the oral and intravenous formulations and validated the dose for the agents when taken orally.³³

PATIENT AND CLINICIAN COMMUNICATION

The purpose of this section is to address aspects of patient-provider communication that are relevant to decision making regarding selection of antiemetic therapy. Clinicians are encouraged to provide patients with a prescription for a rescue antiemetic therapy before the patient leaves on the first day of treatment.

Data suggest that physicians frequently underestimate rates of nausea and vomiting secondary to radiation therapy and chemotherapy.³⁴ To ensure optimal symptom management, clinicians should assess symptoms throughout therapy. Patient response to antiemetic treatment may change over time, requiring ongoing assessments and modification to antiemetic strategies, as warranted.

Checklists can facilitate collection of direct patient reporting of symptom presence and severity. For example, the National Cancer Institute is developing a Patient-Reported Outcomes version of its Common Terminology Criteria for Adverse Events, which includes two items to assess nausea.³⁵ These items are as follows: "In the last 7 days, how OFTEN did you have NAUSEA?" (Never/Rarely/Occasionally/Frequently/Al-

Table 6. Antiemetic Estimated Cost Table

Agent	Price per Dose (USD)	Total Cost per Treatment Cycle (USD)*
NK₁ antagonists		
Aprepitant, 125 mg oral	150.45	343.03
Aprepitant, 80 mg oral	96.29	
Fosaprepitant, 150 mg IV	262.65	262.65
5-HT₃ antagonists		
Granisetron, 2 mg oral	0.68	0.68
Granisetron, 1 mg IV	17.92	17.92
Ondansetron, 8 mg oral	1.04	2.08
Ondansetron, 8 mg IV	1.19	2.38
Palonosetron, 0.25 mg IV	188.70	188.70
Dolasetron, 100 mg oral	65.21	65.21
Ramosetron	Pricing not available	Pricing not available

NOTE. Drug prices were estimated from a third-party payer perspective, based on reimbursement rates from the Centers for Medicare and Medicaid Services as of the first quarter of 2011, computed at the manufacturer's average sales price plus 6%. Other treatment-related direct and indirect costs or discounts were not considered. Actual treatment costs and reimbursement vary considerably across regions, payers, institutions, and practices, as well as over time, and the reader should consult current local cost information specific to his or her specific context.

Abbreviations: 5-HT₃, 5-hydroxytryptamine-3; IV, intravenous; NK₁, neurokinin 1; USD, US dollars.

*Treatment cycle assumed for single-day agents.

most constantly) and "In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?" (None/Mild/Moderate/Severe/Very severe).

Clinicians and patients are also encouraged to discuss cost of treatment (Table 6) to assess whether cost is prohibitive, a hardship to patients, or may impact treatment compliance.

HEALTH DISPARITIES

ASCO clinical practice guidelines represent evidence-based expert recommendations on best practices to provide the highest level of cancer care. However, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Racial/ethnic minority patients with cancer suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured or underinsured, and are at greater risk of receiving care of poor quality compared with other Americans.³⁶⁻³⁹ Other patients lack access to care because of geography and, specifically, distance from appropriate treatment facilities. Other factors associated with disparities include advanced age, low educational attainment, and low socioeconomic status. Awareness of these disparities should be considered. Health care providers should strive to consider the factors faced by vulnerable populations to ensure that all patients receive the highest level of cancer care.

FUTURE DIRECTIONS

For most patients, antiemetic regimens prevent emesis and lessen nausea while patients are undergoing cancer therapy. However, some patients continue to report nausea.⁴⁰ Identification of new approaches to decrease nausea is required. Limited research on nausea and vomiting control in special populations is available, particularly pediatric patients. Similarly, few randomized controlled trials have investigated the role of antiemetics

in patients undergoing radiation therapy. Research to improve symptom control in these patients is necessary.

The Update Committee recommends that studies that include nausea as an outcome include patient-reported measures of nausea, consistent with recommendations of the US Food and Drug Administration.⁴¹ Standardized approaches to assess nausea should be used across trials, which will allow for improved ability to compare regimens and trial data.

ADDITIONAL RESOURCES

The full guideline, comprehensive literature discussion, complete methodology, full reference list, evidence tables, and clinical tools and resources can be found at <http://www.asco.org/guidelines/antiemetics>. Patient information is available there as well as at <http://www.cancer.net>.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

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Appendix

Table A1. Update Committee Members, 2011

Member	Affiliation
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