

2006 Update of the ASCO Recommendations for Antiemetics in Oncology: Guideline Summary

Context

The Antiemetics Update Committee reported ASCO's 2006 practice guideline update for the use of antiemetics in oncology (*J Clin Oncol* 24:2932-2947, 2006). The Committee conducted a literature review and analyzed data from 1998 through February 2006.

Updated 2006 Recommendations

The 2006 update revised the original emetic risk categories for antineoplastic agents and radiation therapy to specify four rather than three categories (available online only). Also added is information on the NK₁ receptor antagonist, aprepitant, and a new 5-HT₃ serotonin receptor antagonist, palonosetron. See Table 1 for a summary of the updated 2006 recommendations; Table 2 groups the antineoplastic agents by specific emetic risk category.

Chemotherapy-Induced Emesis

Antiemetic agents of the highest therapeutic index (3 classes). 5-HT₃ serotonin receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron, and tropisetron); corticosteroids (dexamethasone and methylprednisolone); and the neurokinin 1 (NK₁) receptor antagonist aprepitant. These classes are highly effective, have few significant side effects when used appropriately, and can be given safely in combination. Dexamethasone is the recommended corticosteroid because of the extensive published experience with this agent.

Antiemetic agents of a lower therapeutic index. These agents include metoclopramide, butyrophenones, phenothiazines, and cannabinoids.

Adjunctive drugs for use with antiemetic agents. Benzodiazepines (lorazepam and alprazolam) and antihistamines (diphenhydramine) are considered adjunctive drugs for antiemetic agents.

Radiation-Induced Emesis

The risk of emesis varies with the treatment administered. Using available data and clinical experience, the committee

reached consensus on definitions of four radiotherapy-induced emetic risk groups (see Table 3). This represents a modification from the 1999 guideline, which defined three radiotherapy-induced emesis risk groups.

Discussion

Because published data on drugs that cause emesis are insufficient, the committee considered carefully the guidelines and consensus statements that emerged from the 2004 International Antiemetic Consensus Conference hosted by the Multinational Association of Supportive Care (MASCC). This meeting established a guideline process conducted by representatives from nine international oncology organizations, including ASCO. The MASCC consensus conference classifications were adopted for the 2006 update.

Methodology

The 2006 Update literature review focused on published randomized controlled trials, and systematic reviews and meta-analyses of published phase II and phase III randomized controlled trials. Prepublication copies of two systematic reviews were made available to the committee by the Cancer Care Ontario Program in Evidence-based Care and the Oregon Evidence-based Practice Center.

Additional Resources

The 2006 Update is available in the June 20, 2006, print edition of *JCO* and also at www.jco.org (*J Clin Oncol* 24:2932-2947, 2006). In addition to the full text of the guideline recommendations, available online at <http://www.asco.org/guidelines/antiemetics>, further resources from ASCO include a patient guide, a PowerPoint slide set, and an antiemetics dose and schedule table.

The Antiemetics in Oncology Practice Guideline was developed and written by Mark G. Kris, Paul J. Hesketh, Mark R. Somerfield, Petra Feyer, Rebecca Clark-Snow, James M. Koeller, Gary R. Morrow, Lawrence W. Chinnery, Maurice J. Chesney, Richard J. Gralla, and Steven M. Grunberg.

Table 1. Summary of Recommendations

Antiemetic Agents and Regimens	
Highest therapeutic index: 5-HT ₃ serotonin receptor antagonists	At equivalent doses for the prevention of acute emesis, 5-HT ₃ serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably. Only established doses of all agents are recommended. Single doses are preferred. At biologically equivalent doses, oral formulations are equally effective and safe as intravenous antiemetics.
Highest therapeutic index: Corticosteroids	At equivalent doses, corticosteroids have equivalent safety and efficacy and can be used interchangeably. Dexamethasone is preferred because of its extensive clinical use and is widely available. Single doses of dexamethasone are recommended.
Highest therapeutic index: NK ₁ receptor antagonist (aprepitant)	Only established dose and schedule of aprepitant should be used.
Lower therapeutic index	For persons receiving chemotherapy of high emetic risk, there is no group of patients for whom agents of lower therapeutic index are appropriate first-choice antiemetics. These agents should be reserved for patients intolerant of, or refractory to, 5-HT ₃ serotonin receptor antagonists, NK ₁ receptor antagonists, or dexamethasone.
Adjunctive drugs	Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs, but are not recommended as single agents.
Combinations of antiemetics	It is recommended that 5-HT ₃ serotonin receptor antagonists be given with dexamethasone and aprepitant in patients receiving chemotherapy of high emetic risk and in patients receiving AC. A 5-HT ₃ serotonin receptor antagonist combined with dexamethasone should be used in patients receiving agents of moderate emetic risk other than AC.
Emetic Risk Categories	
High (> 90%) emetic risk	The three-drug combination of a 5-HT ₃ serotonin receptor antagonist, dexamethasone, and aprepitant is recommended. The Update Committee recommends a 5-HT ₃ serotonin receptor antagonist only before chemotherapy.
Moderate (30%-90%) emetic risk	The three-drug combination of a 5-HT ₃ receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving AC. For patients receiving other chemotherapy of moderate emetic risk, we continue to recommend the two-drug combination of a 5-HT ₃ receptor serotonin antagonist and dexamethasone.
Low (10%-30%) emetic risk	Dexamethasone 8 mg is suggested for patients treated with agents of low emetic risk. No regular preventive use of antiemetics for delayed emesis is suggested.
Minimal (<10%) emetic risk	It is suggested that for patients treated with agents of minimal emetic risk, no antiemetic be routinely administered before chemotherapy. No regular preventive use of antiemetics for delayed emesis is suggested.
Combination chemotherapy	The Update Committee suggests that, when combination chemotherapy is given, the patient should be given antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.
Multiple consecutive days of chemotherapy	It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy and afterward for agents with emetic potential for multiple days (i.e., cisplatin).
Special Emetic Problems	
Anticipatory emesis	The best way to prevent anticipatory emesis is to use the most effective antiemetic regimen appropriate for the chemotherapy at all times. The optimal antiemetic regimen should be used with the initial chemotherapy rather than after assessing the patient's emetic response with less effective treatment. If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and is suggested. Because of their amnesic and anti-anxiety effects, alprazolam and lorazepam have been used to treat and prevent anticipatory symptoms.
Emesis in pediatric oncology 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. Due to variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT ₃ antagonists than those used in adults may be required. Dopamine antagonists given to children, especially over several consecutive days, cause a high incidence of dystonic reactions and are not the first choice for pediatric patients.
High-dose chemotherapy	A 5-HT ₃ serotonin receptor antagonist antiemetic combined with a corticosteroid is suggested. Aprepitant should be considered although evidence is lacking to support its use specifically in these patients.
Vomiting and nausea despite recommended prophylaxis	The Update Committee suggests that clinicians: (1) conduct a careful evaluation of emetic risk, chemotherapy, disease status, concurrent illness, and medications; (2) ascertain that the best regimen is being given for the emetic risk; (3) consider adding lorazepam or alprazolam to the regimen; and (4) consider substituting high-dose intravenous metoclopramide for the 5-HT ₃ antagonist or adding a dopamine antagonist to the regimen.

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Table 1. Summary of Recommendations (continued)

Radiation-Induced Emesis	
High (> 90%) emetic risk	The Update Committee suggests giving a 5-HT ₃ serotonin receptor antagonist with or without a corticosteroid before each fraction and for at least 24 hours after.
Moderate (60%-90%) and low (30%-60%) emetic risk	The Update Committee recommends a 5-HT ₃ serotonin receptor antagonist before each fraction.
Minimal (< 30%) emetic risk	The Update Committee suggests that treatment be given on an as-needed basis only. Dopamine or serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day.

Abbreviations: NK₁, neurokinin 1; AC, anthracycline in combination with cyclophosphamide.

Table 2. Emetic Risk of Intravenously Administered Antineoplastic Agents

High (> 90%)	Moderate (30%-90%)	Low (10%-30%)	Minimal (< 10%)
Carmustine	Carboplatin	Fluorouracil	2-Chlorodeoxyadenosine
Cisplatin	Cyclophosphamide < 1,500 mg/m ²	Bortezomib	Bevacizumab
Cyclophosphamide ≥ 1,500 mg/m ²	Cytarabine > 1 g/m ²	Cetuximab	Bleomycin
Dacarbazine	Daunorubicin	Cytarabine ≤ 1,000 mg/m ²	Busulfan
Dactinomycin	Doxorubicin	Docetaxel	Fludarabine
Mechlorethamine	Epirubicin	Etoposide	Rituximab
Streptozotocin	Idarubicin	Gemcitabine	Vinblastine
	Ifosfamide	Methotrexate	Vincristine
	Irinotecan	Mitomycin	Vinorelbine
	Oxaliplatin	Mitoxantrone	
		Paclitaxel	
		Pemetrexed	
		Topotecan	
		Trastuzumab	

Table 3. Emetic Risk of Radiation Regimens

Radiation Emetic Risk	Irradiated Area
High (> 90%)	Total body
Moderate (60%-90%)	Upper abdomen, hemibody irradiation, abdominal-pelvic, mantle, craniospinal irradiation, and cranial radiosurgery
Low (30%-60%)	Lower thorax, cranium (radiosurgery), and craniospinal
Minimal (< 30%)	Radiation of breast, head and neck, cranium, and extremities

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.

Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

References

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In Reply

Dr Morris offers some helpful and provocative observations on my article on oncologists and malpractice.

Regarding the required elements of informed consent for chemotherapy, it may be difficult not to be ambiguous. This is an area in which accepted practices varies widely, in part for the practical reasons mentioned in the article (eg, trying to communicate risks truthfully while avoiding frightening the patient away from a treatment that, despite toxicity, may extend his or her life). Dr Morris worries that one could find an expert witness who would disagree with a particular physician's approach to this matter. Nevertheless, I suspect that one could also find a counterbalancing expert for the defense.

Dr Morris wonders whether ASCO could generate template consent forms for various chemotherapy regimens. While these might be convenient, I would worry that they might be hard to keep complete and updated. One might alternately offer some of the various patient information sheets on drugs that are published online by other reliable sources, such as the American Cancer Society or People Living With Cancer (www.plwc.org). Then one might refer to them in the documentation of consent, whether this is in a progress note or in a formal signed consent form. As I am not a lawyer,

I don't know what the legal ramifications of this process would be.

In addition to my concerns about the impact of second opinions on patient trust and understanding, Dr Morris alludes to several other aspects, both positive and negative, of second opinions. These include physician collegiality, medical expense, and treatment delay. This is a complex subject that deserves a fuller, more candid assessment than I believe is currently available, and should be considered as a future topic for the *Journal of Oncology Practice* to address.

Finally, I agree entirely with Dr Morris' last point, that it is often the family member who has been least involved in the patient's care who becomes a later malpractice risk. In oncology circles, we recognize this "California syndrome," in which the family member who appears late on the scene then, perhaps for reasons of guilt and/or grief, finds fault with the local caregivers, both family members and physicians. It may just be an unavoidable risk of our profession, including for those who practice in California (who tell me it is known as the "New York syndrome").

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In the July 2006 *Journal of Oncology Practice*, the online supplementary material for pages 193-195 of What's New in JCO? contained errors in the table on drug dose and schedule recommendations for antiemetic regimens.

For high emetic risk, dexamethasone was recommended on days 1, 2, and 3 only, but it should have continued on day 4 at 8 mg. Also, the dosage for dexamethasone on day 1 was given as 20 mg/12 mg with aprepitant, but it should have been 12 mg only.

These corrections have been made online.

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