ASCO SPECIAL ARTICLE

Recommendations for the Use of Antiemetics: Evidence-Based, Clinical Practice Guidelines

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THE GOAL OF ANTIEMETIC therapy is to prevent nausea and vomiting completely. This goal is achieved for many patients receiving chemotherapy or radiation therapy, and is based on clinical and basic research that has steadily improved the control of emesis over the last 20 years. As therapy has become more effective, it has also become safer, with few side effects associated with the most commonly used regimens. These regimens are convenient for patients to receive and for health care professionals to administer. However, despite improvements, a significant number of patients still experience emesis, and efforts to reduce this side effect of treatment must continue.

As antiemetic usage has grown, the classes of agents available for antiemetic treatment, the number of agents, and the indications for antiemetics have all increased as well. The prevention of delayed emesis and anticipatory emesis is equal in importance to the need to prevent acute chemotherapy- and radiation-induced emesis. Additionally, managing special and difficult emetic problems and selecting the proper antiemetic approach necessitate identification of the patient's emetic risk.

Although the neuropharmacologic basis of emesis is still incompletely understood, the selection of an appropriate antiemetic regimen is possible and can have an impact on several aspects of clinical care. Goals related to the complete control of emesis, ie, no vomiting, include providing care that is convenient for the patient, treatment that reduces hospitalization and time in the ambulatory setting, and therapy that enhances the patient's quality of life. Additionally, practitioners need to be mindful of reducing costs of treatment while achieving these goals.[1-3]

The American Society of Clinical Oncology (ASCO) appreciates these issues and their applicability to the management of patients with cancer. Accordingly, ASCO convened an Expert Panel under the auspices of its Health Services Research Committee to develop recommendations regarding antiemetic therapy (Table 1). This report describes the aims, methods, and results of this Panel's deliberations.

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements to assist the practitioner and patient decisions about appropriate health care for specific clinical circumstances.[4] Good clinical guidelines include considerations of validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation.[4]

In formulating recommendations for antiemetic usage, ASCO considered these tenets of guideline development, emphasizing the review of data from controlled clinical trials. The level and grade of evidence can differ; such evidence is rated according to the criteria outlined in Table 2. It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. They cannot be considered to be inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.

It is also important to note that not all relevant questions regarding emesis in cancer care have been addressed by clinical trials. The antiemetic methods listed in this article have been shown to be beneficial (or not), but additional research in the prevention of emesis is strongly encouraged. In some instances, specific areas of research need are indicated in this article. As ongoing research is completed, helpful results from these trials will be incorporated into updates of these guidelines.

Accordingly, ASCO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative and novel therapies for this symptom in

From the American Society of Clinical Oncology, Alexandria, VA.

Adopted on February 18, 1999, by the American Society of Clinical Oncology.

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0732-183X/99/1709-2971

Table 1. Summary of Guidelines

I. Chemotherapy-Induced Emesis
  A. Acute Emesis (vomiting occurring 0 to 24 hours after chemotherapy)
    1. Antiemetic Agents: Highest Therapeutic Index
      a. Serotonin Receptor Antagonists
        i. Agent equivalence
          At equivalent doses, serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably based on convenience, availability, and cost.
        ii. Drug dosage
          Established, proven doses of all agents are recommended.
        iii. Drug schedule
          Single doses of antiemetics are effective and preferred for convenience and cost.
        iv. Route of administration
          At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are less costly and more convenient; for these reasons, they are recommended over intravenous therapy.
      b. Corticosteroids
        i. Agent equivalence and route of administration
          At equivalent doses, corticosteroids have equivalent safety and efficacy and can be used interchangeably.
        ii. Drug dose and schedule
          Single doses of corticosteroids are recommended.
    2. Antiemetic Agents: Lower Therapeutic Index—Dopamine Antagonists, Butyrophenones, Phenothiazines, and Cannabinoids
      For chemotherapy with a high risk of emesis, selective serotonin antagonists (with dexamethosone) are recommended.
    3. Antiemetic Agents: Adjunctive Drugs—Benzodiazepines and Antihistamines
      Benzodiazepines and antihistamines are useful adjuncts to antiemetic drugs but are not recommended as single agents.
    4. Antiemetic Agents: Combinations of Antiemetics
      It is recommended that serotonin antagonists be given with corticosteroids.
    5. Risk Factors for Acute Emesis
      a. Patient Characteristics
      b. Chemotherapeutic Agents
      c. Guidelines
        i(a). High risk: Cisplatin
          The combination of a 5-HT_3 antagonist plus a corticosteroid is recommended before chemotherapy.
        i(b). High risk: noncisplatin
          The combination of a 5-HT_3 antagonist plus a corticosteroid is recommended before chemotherapy.
        ii. Intermediate risk
          A corticosteroid is suggested for patients being treated with agents of intermediate emetic risk.
        iii. Low risk
          It is suggested that for patients being treated with agents of low emetic risk, no antiemetic be routinely administered before chemotherapy.
        iv. Combination chemotherapy
          It is suggested, that when combination chemotherapy is given, the patient be given antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.
        v. 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.
  B. Delayed Emesis (vomiting occurring >24 hours after chemotherapy)
    1. Antiemetic Agents
      a. Single Agents
        i. Corticosteroids
        ii. Metoclopramide and serotonin receptor antagonists
      b. Combinations of Agents
    2. Risk Factors for Delayed Emesis
      a. Patient Characteristics
      b. Chemotherapeutic Agents
      c. Guidelines
        i(a). High risk: cisplatin
          For all patients receiving cisplatin, a corticosteroid plus metoclopramide or plus a 5-HT_3 antagonist is recommended for the prevention of delayed emesis.
        i(b). High risk: noncisplatin
          A prophylactic corticosteroid as a single agent, a prophylactic corticosteroid plus metoclopramide, and a prophylactic corticosteroid plus a 5-HT_3 antagonist are regimens suggested for the prevention of delayed emesis.
        ii. Intermediate—low risk
          No regular preventive use of antiemetics for delayed emesis is suggested for patients receiving these chemotherapeutic agents.

Table 1. Summary of Guidelines (Cont'd)

C. Anticipatory Emesis
  1. Prevention
     Use of the most active antiemetic regimens appropriate for the chemotherapy being given to prevent acute or delayed emesis is suggested. Such regimens must be used with the initial chemotherapy, rather than after assessment of the patient's emetic response to less effective treatment.
  2. Treatment
     If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and is suggested.

D. Special Emetic Problems
  1. Emesis in Pediatric Oncology
     The combination of a 5-HT_3 antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high emetic risk.
  2. High-Dose Chemotherapy
     A 5-HT_3 antagonist plus a corticosteroid is suggested.
  3. Vomiting and Nausea Despite Optimal Prophylaxis in Current or Prior Cycles
     It is suggested that clinicians (1) conduct a careful evaluation of risk, antiemetic, chemotherapy, tumor, and concurrent disease and medication factors, (2) ascertain that the best regimen is being given for the emetic setting, (3) consider adding an antianxiety agent to the regimen, and (4) consider substituting a dopamine receptor antagonist, such as high-dose metoclopramide, for the 5-HT_3 antagonist (or add the dopamine antagonist to the regimen).

II. Radiation-Induced Emesis
A. Risk Factors for Radiation-Induced Emesis
  1. Guidelines
     a. High Risk: Total Body Irradiation
        A serotonin receptor antagonist should be given with or without a corticosteroid before each fraction and for at least 24 hours after.
     b. Intermediate Risk: Hemibody Irradiation, Upper Abdomen, Abdominal-Pelvic, Mantle, Cranial Radiosurgery, and Craniospinal Radiotherapy
        A serotonin receptor antagonist or a dopamine receptor antagonist should be given before each fraction.
     c. Low Risk: Radiation of the Cranium Only, Breast, Head and Neck, Extremities, Pelvis, and Thorax
        Treatment should 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.

which better treatment is of paramount importance. In that guideline development involves a review and synthesis of the latest literature, practice guidelines also serve to identify important questions for further research and those settings in which investigational therapy should be considered.

Table 2. Levels and Grade of Evidence for Recommendations[280,281]

Level	Type of Evidence
I	Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials have with low false-positive and low false-negative errors (high power).
II	Evidence is obtained from at least one well-designed experimental study. Randomized trials have high false-positive and/or -negative errors (low power).
III	Evidence is obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled, single-group, pre-post, cohort, time, or matched case-control series.
IV	Evidence is from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies.
V	Evidence is from case reports and clinical examples.
Grade	**Grade for Recommendation**
A	There is evidence of type I or consistent findings from multiple studies of types II, III, and IV.
B	There is evidence of types II, III, and IV, and findings are generally consistent.
C	There is evidence of types II, III, and IV, but findings are inconsistent.
D	There is little or no systematic empirical evidence.

METHODS

A methodology similar to that applied in prior ASCO practice guidelines documentation[5] was used and is described in more detail below.

Expert Panel Composition

The Panel was composed of experts in clinical medicine, clinical research, outcomes/health services research, medical decision-making, and health economics, with a focus on expertise in supportive care and in antiemetics. A patient representative was also included on the Panel. Clinical experts represented all relevant disciplines, including medical oncology, oncology nursing, radiation oncology, pediatric oncology, and oncologic pharmacy practice. A steering committee under the auspices of the Health Services Research Committee chose Panel participants for the clinical practice guideline development process.

Literature Review and Data Collection

Pertinent information from the published literature as of July 1998 was retrieved and reviewed for the creation of these guidelines. MEDLINE (National Library of Medicine, Bethesda, MD) and other databases were searched for pertinent articles. The following keywords or phrases were used: antiemetics, neoplasms, adverse effects, anticipatory + nausea, anticipatory + vomiting, serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, corticosteroids, and metoclopramide. Directed searches were made of the primary articles.

Consensus Development Based on Evidence

The Panel identified topics to be addressed by the guidelines, developed a strategy for completion of the guidelines, and reviewed the literature. The Panel emphasized the inclusion of prospective random-

assignment studies. Phase II trials and clinical reports that evaluated less-well-studied areas of antiemetic treatment were also reviewed. The recommendations made by the Expert Panel are based on current methods of emetic treatment and prevention. The guidelines were circulated in draft form through several iterations, and all members of the Panel had opportunities to comment on the recommendations.

The Panel did not attempt to codify established practice. The experts reviewed the available evidence and added their best clinical judgment to make final recommendations, using standardized language to characterize the strength of the evidence. In accordance with the ASCO Health Services Research Policies and Procedures for guidelines, "recommendation" was used when there was level I or II evidence and Panel consensus. "Suggestion" was used when there was level III, IV, or V evidence and Panel consensus. "No guideline possible" was used when there were no data or the Panel could not reach consensus.

Guidelines and Conflict of Interest

The content of the guidelines and the manuscript were reviewed and approved by the Health Services Research Committee and by the ASCO Board of Directors before dissemination. In addition, several practitioners who had not been directly involved in the development of the guidelines were asked to assess the clarity and utility of the document. All participants in the guideline development process complied with the ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict.[6]

Revision Dates

At annual intervals, the Panel chairpersons and two Panel members designated by the chairpersons will determine the need for revisions to the guidelines based on an examination of current literature. The entire Panel will be reconvened every 3 years to discuss potential changes, or more frequently if new information suggests that more timely modifications may be warranted. Where appropriate, the Panel will recommend the revised guideline to the Health Services Research Committee and the ASCO Board for review and approval.

Definition of Terms

For cisplatin, high risk is defined as emesis that has been documented to occur in more than 99% of patients. For the high-risk, noncisplatin group, the incidence of emesis is in the 30% to greater than 90% range. Chemotherapeutic agents in the intermediate-risk category induce emesis in 10% to 30% of patients. A less than 10% risk of emesis in patients receiving chemotherapeutic drugs was categorized as low risk.

I. CHEMOTHERAPY-INDUCED EMESIS

In discussing evidence for the control of emesis, it is necessary to outline definitions of control. Emesis, or vomiting, is usually measured by counting the number of vomiting episodes and is the most important end point. With currently available agents, complete control of emesis, ie, no vomiting, is achievable in the majority of patients in the first 24 hours and in approximately 45% of patients during the first 5 to 7 days of chemotherapy. Studies have documented that the complete control end point is a highly accurate and reliable measure.[7-9] The validity of this measure is demonstrated by the fact that complete control of vomiting correlates highly with patients' perception of emesis and with patients' satisfaction with their emetic control.

In contrast, the mechanisms responsible for mediating nausea are less well explained.[10] Nausea, or the perception that emesis may occur, can be judged only by the patient. Various questionnaires, using either visual analog or categorical scales, are in widespread use.[9,11,12] The incidence of nausea correlates well with the incidence of vomiting[13]; however, chemotherapy-induced nausea occurs at a greater frequency than vomiting. Many large random-assignment trials have shown that complete control rates for vomiting are higher than those for the complete control of nausea.[14,15]

The concept of total control (no vomiting or nausea) is attractive; however, recent large studies have indicated that the total control rate is essentially identical to the complete nausea control rate. It seems that this additional category does not provide further useful information.[14,15]

Lesser control rates, such as major control (zero to two or one to two emetic episodes) or minor control (three to five emetic episodes), have been useful in the past and may still have some value in particularly difficult emetic situations. However, the panelists reached consensus in advising the use of complete control rates for the evaluation of most emetic situations and for use in the guideline development process.

A. Acute Emesis
(Vomiting Occurring 0 to 24 Hours After Chemotherapy)

1. Antiemetic Agents: Highest Therapeutic Index

Two classes of agents are in this category, the serotonin receptor antagonists and corticosteroids (Table 3).[16-37] Both classes are highly effective, with few significant side effects when used appropriately, and can be given safely in combination when indicated. These agents have been largely responsible for the ease of use and high effectiveness of antiemetics in clinical practice.

a. Serotonin Receptor Antagonists. The issues of agent equivalence, drug dosage, drug schedule, and route of administration are discussed separately below. Specific guidelines for differing acute emetic risk settings are given in a later section.

i. *Agent equivalence*:

Guideline: At equivalent doses, serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably based on convenience, availability, and cost.

Level of Evidence: I.

Grade of Recommendation: A.

There are currently four agents of this class commercially available in many countries: dolasetron, granisetron, ondansetron, and tropisetron. Other, similar agents are available in

Table 3. Antiemetic Agents, Doses, and Administration Schedule

Antiemetic Agent (trade name)	Dose Range	Schedule (for acute chemotherapy-induced emesis, unless otherwise noted)	Evidence (type and grade)
Agents with highest therapeutic index			
Serotonin receptor antagonists			
Dolasetron (*Anzemet*)	100 mg or 1.8 mg/kg IV	One time, before chemotherapy	I, A
Dolasetron (*Anzemet*)	100 mg PO	One time, before chemotherapy	II, A
Granisetron (*Kytril*)	1 mg or 0.01 mg/kg IV	One time, before chemotherapy	I, A
Granisetron (*Kytril*)	2 mg PO	One time, before chemotherapy	I, A
Ondansetron (*Zofran*)	8 mg or 0.15 mg/kg IV	One time, before chemotherapy	I, A
Ondansetron (*Zofran*)	Oral doses vary (12-24 mg/d) (8 mg doses usually used in delayed or RT emesis)	One time, before chemotherapy (two to three times daily in delayed or RT emesis)	II, B
Tropisetron (*Navoban*)	5 mg IV	One time, before chemotherapy	III, B
Tropisetron (*Navoban*)	5 mg PO	One time, before chemotherapy	III, B
Corticosteroids			
Dexamethasone (*Decadron*)	20 mg IV	One time, before chemotherapy	II, B
Methylprednisolone (*Medrol*)	40 mg to 125 mg	One time, before chemotherapy	V, D
Agents of lower therapeutic index			
Dopamine receptor antagonists			
Metoclopramide (*Reglan*)	2 mg/kg to 3 mg/kg IV	Before chemotherapy and 2 hours after chemotherapy	I, A
Metoclopramide (*Reglan*)	20 mg to 0.5 mg/kg PO for delayed emesis or RT	Two to four times a day for delayed emesis	IV, D
Prochlorperazine (*Compazine*)	10 mg to 30 mg IV	Every 3 to 4 hours	II, B
Prochlorperazine (*Compazine*)	10 to 20 mg PO	Every 3 to 4 hours	III-IV, C

individual countries or are under investigation. The majority of multiple, randomized, well-controlled studies with sufficient patients to precisely estimate differences in treatment have demonstrated that these agents have equivalent antiemetic activity and safety.[38-50] There was unanimity among the Panel members for this conclusion.

These agents exert their activities by the same mechanism, antagonism of the type 3 serotonin (5-hydroxytryptamine [5-HT_3]) receptor.[51-57] They are all highly selective with high affinities for this receptor.[58-60] All clinically relevant antiemetic actions are mediated in this way by these agents. These agents also share the same low side-effect pattern, with mild headache, transient asymptomatic transaminase elevations, and constipation being among the most commonly reported adverse events.[17,18,20,23]

The overall conclusion is based on the excellent evidence available for granisetron, ondansetron, and, more recently, dolasetron. The studies with tropisetron are less rigorous (level of evidence: II; grade of recommendation: B), but the Panel found that they are sufficient to allow the confidence in the above-stated conclusion.

ii. *Drug dosage*:

Guideline: Established, proven doses of all agents are recommended.

Level of Evidence: I.

Grade of Recommendation: A.

Many studies have addressed the question of establishing the ideal doses for these agents. Dolasetron, granisetron, and ondansetron are the best-studied agents in terms of dose-finding[38,40,45,48,61-77]; few studies have carefully examined tropisetron dosing. With excellent safety profiles through large dosing ranges, toxicity has not been the criterion for determining dosage. It is clear that too low a dose can be found for these agents, with attenuated activity observed at less than optimal doses (listed in Table 3).[65,67,73,74,78] Panel members concurred that it is likely that a threshold effect exists. Once all relevant receptors are saturated, higher doses do not enhance any aspect of activity. Two corollaries are also important: sufficient doses must be given to ensure maximum efficacy. Most Panel members agreed that the dose will be the same in all antiemetic settings in which a serotonin receptor antagonist is required. The Panel unanimously concluded that the lowest fully effective dose for each of the agents should be used.

As mentioned above, the question of ideal dose has been best studied with dolasetron, granisetron, and ondansetron. A lesser degree of evidence is found for tropisetron,[79,80] but the conclusion reached was the same.

iii. *Drug schedule*:

Guideline: Single doses of antiemetics are effective and are preferred for convenience and cost.

Level of Evidence: I.

Grade of Recommendation: A.

Several recent studies have examined the issue of multiple antiemetic doses compared with a single administration. The latter approach, if equally effective, enhances convenience and adherence. A single-dose regimen using the lowest fully

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