Evidence-Based Prevention of CINV: What's New in ASCO Guidelines?

Since the publication of the initial American Society of Clinical Oncology (ASCO) antiemetic guidelines in 1999, significant clinical developments have necessitated revision of recommendations for preventing chemotherapy-induced nausea and vomiting (CINV). This new information was summarized by Paul J. Hesketh, MD, Professor of Medicine, Tufts University School of Medicine, and Chief, Division of Hematology and Oncology, Caritas St. Elizabeth's Medical Center, Boston, Massachusetts.

CINV is one of the most feared side effects of chemotherapy. When inadequately controlled, it adds to the morbidity and cost of therapy and impairs quality of life. The main clinical syndromes are acute CINV (which occurs within 24 hours of chemotherapy) and delayed CINV (which occurs at least 24 hours after dosing). Effective prophylaxis has made anticipatory CINV only a minor problem.

The highly emetogenic nature of cisplatin, which "universally" causes CINV, led to the development of better antiemetic agents. The efficacy of the 5-hydroxytryptamine-3 (5-HT_3, serotonin) antagonists and the neurokinin-1 antagonist aprepitant (Emend) now may prevent CINV completely in at least 70% of patients receiving highly emetogenic chemotherapy, Dr. Hesketh noted.

Changing the Guidelines

The updated ASCO guidelines *(Kris MG et al. J Clin Oncol 2006;24:2932–2947)* included a new emetogenic classification schema, described the integration of aprepitant into antiemetic management, noted the addition of a new 5-HT_3 antagonist palonosetron (Aloxi), and defined the role of serotonin antagonists in delayed emesis that is induced by highly emetogenic chemotherapy.

Dr. Hesketh first reviewed the risk for CINV, noting that the most predictive patient-related factors of the condition are young age, female gender, prior chemotherapy (especially when emesis occurred), and low or no chronic intake of alcoholic beverages. Polymorphisms pertaining to neurotransmitter receptors and the metabolism of antiemetics also may be important.

The most predictive treatment-related factor is the emetogenicity of chemotherapy. Attendees of the 2004 Perugia International Antiemetic Consensus Conference changed the emetogenic potential of antineoplastic agents from the original five-level Hesketh model into a four-level schema (Table 1) that now is promoted by ASCO. "I recommend these for your institutional guidelines," Dr. Hesketh told attendees.

The development of aprepitant, a drug that selectively antagonizes the binding of substance P to the neurokinin-1 receptor, was significant to CINV prevention; given at 125 mg orally on day 1 and then 80 mg orally on days 2 and 3, aprepitant and its role against CINV were defined in the ASCO update.

In phase III studies, at least 20% of patients receiving highly emetogenic chemotherapy were completely free of emesis if they received aprepitant, representing a drop in relative risk of almost 50%.

A more recent study in breast cancer patients receiving an anthracycline plus cyclophosphamide (AC; *Warr DG et al. J Clin Oncol 2005;23:2822–2830)* compared standard prophylaxis (ie, 8 mg of ondansetron twice daily plus 20 mg of dexamethasone on day 1, followed by 8 mg of ondansetron twice daily on days 2 and 3) with a regimen that included aprepitant (ie, 8 mg of ondansetron twice daily plus 12 mg of dexamethasone on day 1 followed by 80 mg of aprepitant on days 2 and 3). Complete responses 0–120 hours after chemotherapy were observed in 50.8% of the aprepitant group and 42.5% of the standard treatment group, yielding a significant difference of 8.3% ($P = 0.015$). The team reported that 75.7% and 57.7% of patients, respectively, experienced no vomiting 0–120 hours after chemotherapy, representing a 17% difference ($P < 0.001$).

"The magnitude of the aprepitant benefit with AC was less than with a cisplatin-based regimen," Dr. Hesketh noted. "Aprepitant improved control, though less robustly."

Based on these studies, ASCO updated its guidelines to recommend use of a 5-HT_3 antagonist, dexamethasone, and aprepitant to prevent acute CINV; this applies to patients receiving highly emetogenic chemotherapy or AC. For patients receiving highly emetogenic chemotherapy, a two-drug regimen of aprepitant plus dexamethasone is recommended for preventing delayed CINV.

The approach to preventing delayed emesis has been modified from ASCO's 1999 guidelines, which advised giving dexamethasone plus either metoclopramide or a 5-HT_3 antagonist after highly emetogenic chemotherapy. Since 1999, three large trials enrolling over 1,200 patients compared granisetron (Kytril) or ondansetron plus dexamethasone with dexamethasone alone; the results of all three showed that the combination was not superior to dexamethasone monotherapy. The ASCO Update Committee, therefore, no longer recommends the combination of a 5-HT_3 antagonist plus dexamethasone in this setting. Further, noted Dr. Hesketh, metoclopramide's role in preventing delayed emesis has been supplanted by aprepitant.

Role of Palonosetron

Palonosetron is an active, safe, new 5-HT_3 antagonist that differs from other agents in this class in a number of ways. It has a prolonged half-life (~ 40 hours) and offers enhanced receptor binding affinity (30-fold) when compared with agents developed earlier.

The dose of palonosetron approved by the US Food and Drug Administration is 0.25 mg intravenously (IV) before chemotherapy.

Clear-cut superiority of palonosetron over first-generation agents has not been defined; however, three large, multicenter trials with multiple cycle extensions showed the drug's benefit against the effects of highly and moderately emetogenic chemotherapy. Rubenstein et al *(Proc Am Soc Clin Oncol 22;2003:2932)* compared 0.25 mg and 0.75 mg of palonosetron IV with 32 mg of ondansetron IV and 100 mg of dolasetron (Anzemet) IV, all given as single doses on day 1; both palonosetron doses produced numerically better outcomes in terms of complete responses.

Palonosetron outperformed ondansetron and dolasetron in a number of parameters, yet the absence of prospective trials specifically designed to prove the superiority of palonosetron over first-generation 5-HT_3 antagonists resulted in the ASCO Update Committee not recommending use of a preferred 5-HT_3 antagonist.

"The palonosetron trials were not designed to show superiority," noted Dr. Hesketh. "The data are not compelling enough to argue for a preferred agent at this time. If palonosetron proves superior to regimens incorporating corticosteroids and using multiple-day schedules for the first-generation 5-HT_3 antagonists, the recommendation would then change. Until then, we can't recommend a specific 5-HT_3 antagonist."

Table 1

Modified Hesketh Classification of Emetic Risk of Intravenous Antineoplastic Agents

EMETIC RISK (ESTIMATED INCIDENCE WITHOUT PROPHYLAXIS)	ANTINEOPLASTIC AGENT
High (> 90%)	Carmustine Cisplatin Cyclophosphamide (≥ 1,500 mg^2) Dacarbazine Mechlorethamine Streptozocin
Moderate (30%–90%)	Carboplatin Cyclophosphamide (< 1,500 mg^2) Cytarabine (> 1 g/m^2) Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin
Low (10%–30%)	Bortezomib Cetuximab Cytarabine (≤ 100 mg/m^2) Docetaxel Etoposide 5-Fluorouracil Gemcitabine Methotrexate Mitomycin Mitoxantrone Paclitaxel Pemetrexed Topotecan Trastuzumab
Minimal (< 10%)	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Fludarabine Rituximab Vinblastine Vincristine Vinorelbine

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Limitations of Guidelines

More research is needed to answer several questions. For example, none of the current guidelines, including the ASCO Update, addresses the issue of oral chemotherapy agents and the need for prophylaxis in this setting. "Guidelines were predicated on intravenously administered chemotherapy agents. We have not addressed this topic yet, because data are still lacking," he said.

Additionally, published data with aprepitant are limited to the setting of cisplatin and AC; its potential role with other moderately emetogenic chemotherapeutic agents is undefined. "We, therefore, do not yet know how to integrate aprepitant in other settings," he added.

Finally, emetogenic potential, especially for delayed emesis, is poorly characterized for many highly and moderately emetogenic agents (eg, oxaliplatin [Eloxatin], irinotecan [Camptosar]), which weakens the strength of current antiemetic treatment recommendations. "The emetogenic potential of many newer agents is based mainly on opinion," Dr. Hesketh commented, "so we made recommendations broadly applicable to agents in the same class, based on our best guess."