

Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

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New and Emerging Therapeutic Options for the Management of Chemotherapy-Induced Nausea and Vomiting

Discussants



Lee S. Schwartzberg, MD
Professor of Medicine
Chief, Division of Hematology & Oncology
The University of Tennessee Health Science Center
Memphis, Tennessee



Hope S. Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, California



Matti S. Aapro, MD
Dean of the Multidisciplinary Oncology Institute
Clinique De Genolier
Genolier, Switzerland

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) remains one of the most challenging adverse events of chemotherapy, and one that has substantial negative effects on patients, clinicians, and the wider health care system. Use of CINV prophylaxis consistent with clinical practice guidelines is essential for attaining optimal CINV control. In recent years, there has been a dramatic improvement in the control of CINV with the introduction of effective antiemetic agents, including the serotonin (5-hydroxytryptamine [5-HT₃]) receptor antagonists (ondansetron, granisetron, and palonosetron) and the neurokinin-1 (NK₁) receptor antagonists (aprepitant and fosaprepitant). An important benefit of the newer antiemetic agents is their improved ability to control the delayed CINV that can develop in the days after chemotherapy administration. In October 2014, a fixed-dose oral combination containing the novel NK₁ receptor antagonist netupitant and palonosetron (NEPA) received approval from the US Food and Drug Administration. The combination of 2 effective antiemetic agents in a single, oral capsule may help simplify CINV management. Ongoing studies are evaluating new CINV approaches (eg, the novel NK₁ receptor antagonist rolapitant), as well as the optimal use of existing therapies. Patient education regarding the timing, prevention, and treatment of CINV is another key component of CINV management.

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Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and oncology registered nurses involved in the management of cancer patients receiving chemotherapy.

Statement of Need/Program Overview

Chemotherapy-induced nausea and vomiting (CINV) continues to be a concern for patients who receive chemotherapy. Substantial progress has been made in the prevention and treatment of acute CINV, which occurs within 24 hours of treatment. In contrast, effective control of delayed CINV has been more difficult to attain. Use of CINV prophylaxis consistent with clinical practice guidelines is essential. The recommended strategies for prevention of CINV, and for treatment of acute and delayed CINV, vary based on the emetogenicity of the regimen. The first-generation 5-hydroxytryptamine (5-HT₃) receptor antagonists include the commonly used agents ondansetron and granisetron. These agents can prevent or diminish acute CINV, but they have limited efficacy for delayed CINV. The second-generation 5-HT₃ antagonist palonosetron is effective for both acute and delayed CINV. In October 2014, a fixed-dose oral combination containing the novel neurokinin-1 (NK₁) receptor antagonist netupitant and palonosetron (NEPA) received approval from the US Food and Drug Administration for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy. The administration of 2 effective antiemetic agents in a single, oral capsule may help simplify CINV management. Patient education regarding the timing, prevention, and treatment of CINV is another key component of CINV management. In addition, maintaining contact with patients after treatment can help to quickly address any symptoms to reduce the risk of uncontrollable CINV.

Educational Objectives

After completing this activity, the participant should be better able to:

- Discuss the pathophysiology of CINV
- Explain the mechanism of action and rationale for the use of antiemetic agents in the prevention of CINV
- Identify the incidence and impact of CINV associated with both highly and moderately emetogenic therapy
- Evaluate the efficacy and safety data supporting the use of approved antiemetic agents in the prevention of CINV
- Assess clinical trial results of new and novel agents for the management of CINV

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Challenges in the Management of Chemotherapy-Induced Nausea and Vomiting

Lee S. Schwartzberg, MD
 Professor of Medicine
 Chief, Division of Hematology & Oncology
 The University of Tennessee Health Science Center
 Memphis, Tennessee

Chemotherapy-induced nausea and vomiting (CINV) remains an important challenge in cancer care, as it can have a substantial impact on patients, health care providers, and the health care system. Patients continue to rank nausea and vomiting among their greatest concerns about starting chemotherapy.¹ Uncontrolled CINV can have a substantial negative effect on patients' health and well being, leading to impairments in quality of life and activities of daily living that may be prolonged (Figure 1).² Some patients who develop CINV require delays in chemotherapy that can impact prognosis. In rare cases, patients will decline chemotherapy—whether it be palliative, life-prolonging, or curative—because of their experience with CINV in prior courses of therapy.

CINV also remains a clinical problem at the provider level. Patients with CINV may require additional resources such as clinic appointments, emergency department visits, or even hospitalization for severe cases. Interventions may include intravenous fluids and other medications. Overall, these resource requirements contribute to increased health care costs.³ Given the wide-ranging impact of CINV at the patient, provider, and societal levels, effective prevention and management of CINV remains an important aspect of cancer care.

Types of CINV

CINV is divided into categories based on the time of symptom onset in relation to the administration of chemotherapy. These categories are considered separately in clinical trials. Acute CINV is defined as occurring within the first 24 hours after receiving chemotherapy.⁴ Delayed CINV starts after the first 24 hours and can last approximately 1 week after administration, although in clinical trials, 5 days (120 hours) is used as an endpoint. In general, nausea and vomiting that develop after this period are caused by something other than chemotherapy. Many chemotherapeutic regimens induce a biphasic pattern characterized by acute CINV followed by delayed CINV.

Anticipatory CINV is a conditioned response typically triggered by physical cues such as arrival at the clinic,

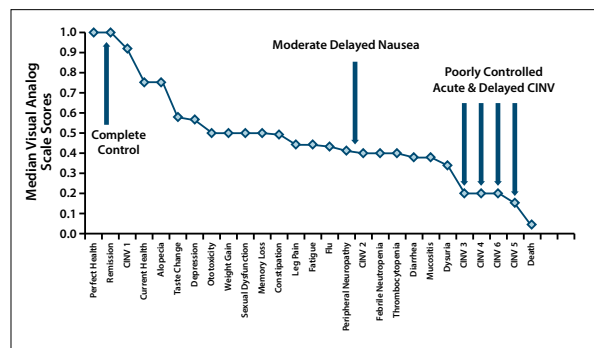


Figure 1. The impact of health states as ranked by ovarian cancer patients receiving chemotherapy. CINV, chemotherapy-induced nausea and vomiting. Adapted from Sun CC et al. *Support Care Cancer*. 2005;13:219-227.²

by sensory cues such as specific smells or sounds, or by the patients' thoughts. Refractory CINV refers to the development of CINV in patients who have received adequate prophylaxis. These patients may require rescue medication and alterations in their treatment regimens in subsequent cycles.

In the past several decades, substantial progress has been made in the prevention and treatment of acute CINV. In contrast, effective control of delayed CINV has been more difficult to attain. Some of the most commonly used chemotherapeutic regimens are associated with delayed nausea, and occasionally delayed vomiting, in a substantial proportion of patients.

CINV Risk Factors

The risk of CINV is influenced by both treatment-related and patient-related factors. Chemotherapy agents and regimens differ substantially in their likelihood to induce nausea and vomiting and have been categorized accordingly. An understanding of the emetogenicity of a regimen is an important component of CINV management. The recommended strategies for prevention of CINV, and for treatment of acute and delayed CINV, vary based on the emetogenicity of the regimen.

Table 1. Emetic Risk of Common Chemotherapy Agents and Regimens

Emetic Risk	Percentage of Patients With Emesis	Chemotherapy
High	>90	Anthracycline Platinum-based agents Cisplatin Anthracycline/cyclophosphamide
Moderate	30 to 90	Bendamustine Carboplatin Irinotecan
Low	10 to 30	Fluorouracil Paclitaxel Docetaxel Pemetrexed
Minimal	<10	Bortezomib Cetuximab Decitabine Rituximab

Highly emetogenic chemotherapy regimens, such as those incorporating anthracycline, platinum-based agents, or cisplatin, induce emesis in more than 90% of patients without the use of prophylaxis (Table 1).⁴ Notably, the commonly used regimen of combined anthracycline and cyclophosphamide has been reclassified as highly emetogenic.⁵ Moderately emetogenic chemotherapeutic agents, such as bendamustine, carboplatin, and irinotecan, induce emesis in 30% to 90% of patients. Agents with a low emetic risk, such as fluorouracil, paclitaxel, docetaxel, and pemetrexed, are associated with emesis in 10% to 30% of patients.⁴ Minimally emetogenic regimens induce emesis in less than 10% of patients.⁴

Although patient-related risk factors for CINV are less well-characterized, several relevant characteristics have been identified. The risk of CINV tends to be higher in women vs men and in younger patients vs older patients.^{6,7} Patients with greater alcohol exposure over their lifetime tend to have less risk.⁷ Some potential risk factors that are less well-established include history of motion sickness, emesis with other drugs, and postoperative anesthesia-related nausea.

Reducing the Gap Between Patients and Providers

Surveys have shown that clinicians underestimate the severity of CINV. In particular, both nurses and physicians have been shown to underestimate the incidence of delayed nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy.⁸ Therefore, awareness of CINV remains a challenge.

Patient education about CINV is an important aspect of management. Modern cancer chemotherapy

is complex, with many elements to consider. Patients starting chemotherapy are often presented with an overwhelming amount of information related to their cancer and its treatment. It is important that CINV be included in this educational process. In my opinion, a degree of complacency about CINV has crept into the medical profession in recent years. Those of us who were practicing medicine before the development of relatively effective CINV therapy remember the importance of placing CINV front and center in regard to patient education.

There are likely multiple factors that contribute to the decreased amount of attention given to CINV today. First, nurses and other patient educators have significant demands on their time and have many important topics to cover. Second, because acute CINV can usually be prevented, most patients do not develop symptoms until after they have left the clinic or hospital. The delayed CINV that occurs at home must be managed by patients and caregivers. It is important to educate patients so that they are aware of the time period during which they are at risk, know the appropriate use of prophylactic medications to prevent delayed CINV, and can treat CINV if it does occur. A challenge to managing CINV is that patients may be reluctant to report episodes of nausea and vomiting. Therefore, encouraging patients to be proactive in reporting and managing CINV should also be included in patient education.

In addition to providing patient education, clinicians can also minimize the risk of uncontrolled CINV by checking in with patients during the first week after chemotherapy. Staying in contact with patients through some mechanism—whether it be a phone call, a repeat clinic visit, or an electronic system—can help manage CINV. This way, it is possible to assess whether CINV has developed and quickly address any symptoms to reduce the risk of uncontrollable CINV. Assessing patients after they have left the clinic is a challenging task, and one that is not widely practiced. However, it is an important goal for optimizing patient care and reducing the risk of uncontrollable CINV.

Disclosure

Dr Schwartzberg is a consultant for Eisai, Helsinn, Merck, and Tesaro.

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Current Management Strategies for Chemotherapy-Induced Nausea and Vomiting

Hope S. Rugo, MD
 Professor of Medicine
 Director, Breast Oncology and Clinical Trials Education
 UCSF Helen Diller Family Comprehensive Cancer Center
 San Francisco, California

Incorporating the principles of CINV management is critical to the success of cancer therapy.¹ The most essential component of CINV management is the appropriate use of prophylaxis. Effective prophylaxis starting with the first cycle of therapy not only reduces the immediate risk of CINV but also helps to ensure that patients will continue with subsequent treatment. Therefore, it is important to start with the recommended treatment approach appropriate for the intensity of nausea and vomiting expected for a given regimen.¹

A second key point in CINV management is that the treatment strategy may need to be modified based on a patient's individual response. Patients differ in how they metabolize chemotherapeutic agents and nausea medications, and these differences can alter the severity of CINV. It is critical to adjust the CINV regimen to the patient's needs as the treatment course progresses. The goal is to have a "zero tolerance policy" in regard to preventing nausea and emesis.

The management strategy differs according to the type of CINV. Anticipatory CINV, which is caused by the patient's expectations, previous experiences, and sensory input (eg, specific smells), can be treated with anxiolytic agents such as lorazepam. Behavioral modifications have also been found to be useful for some patients²; such strategies can include imagery, music therapy, biofeedback, acupressure, and acupuncture. These approaches are important to consider in patients who have already experienced anticipatory CINV or who are at significant risk. We tend to see less anticipatory CINV today with the availability of more effective CINV prophylaxis and with the incorporation of appropriate management guidelines in the first and subsequent cycles of chemotherapy.¹

Corticosteroids

Dexamethasone was the first major antiemetic agent used for CINV prevention. This highly effective drug helps to prevent emesis and can be useful in the rescue setting in patients receiving minimally to moderately emetogenic chemotherapy.¹ Although dexamethasone is an essential and effective component of combination regimens for the management of CINV, alone it is less effective in preventing CINV in patients receiving highly or moderately emetogenic chemotherapy. This unmet need led to the development of the newer antiemetic drugs that are now the cornerstone of CINV management.

5-HT₃ Receptor Antagonists

The next major class of agents to be developed was the serotonin (5-hydroxytryptamine [5-HT₃]) receptor antagonists. These drugs serve as antagonists for 5-HT₃ receptors, which are located on the vagal afferent neurons in the gastrointestinal tract and the central nervous system. Research into CINV has shown that chemotherapy induces serotonin release by enterochromaffin cells in the small intestine, resulting in the activation of vagal afferent neurons and consequent stimulation of the central vomiting system.³ Central mechanisms are also involved, as 5-HT₃ receptors are located in the central nervous system in the chemoreceptor trigger zone for emesis. Therefore, blocking both peripheral and central 5-HT₃ receptors prevents the emetogenic effects of serotonin.

The first-generation 5-HT₃ receptor antagonists include the commonly used agents ondansetron and granisetron. (A third agent, dolasetron, is no longer used for CINV in the United States.) These agents were shown

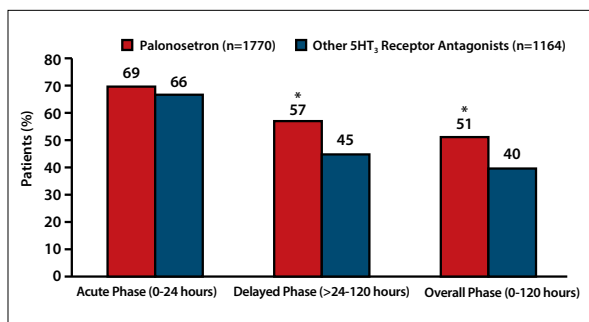


Figure 2. Complete response rates for prevention of CINV in a pooled analysis of moderately emetogenic chemotherapy trials evaluating palonosetron and comparative 5-HT₃ receptor antagonists. Significant differences between palonosetron and other 5-HT₃ receptor antagonists were seen in the delayed and overall phases. Complete response refers to no emetic episodes and no use of rescue medication. * $P < .0001$, palonosetron vs other 5-HT₃ receptor antagonists. 5HT₃, 5-hydroxytryptamine. Adapted from Schwartzberg L et al. *Support Care Cancer*. 2014;22(2):469-477.¹³

in multiple trials to be equally effective in preventing or diminishing acute CINV,^{4,5} and to have limited efficacy in the prevention of delayed CINV.⁶ In addition, drug interactions are a concern with the first-generation 5-HT₃ receptor antagonists.

Subsequently, the second-generation 5-HT₃ antagonist palonosetron was developed. Palonosetron has structural differences that confer more selective binding to the 5-HT₃ receptor and an extended half-life of approximately 40 hours (compared with 4 hours for ondansetron and 9 hours for granisetron).⁷ Palonosetron is administered as a single, fixed intravenous dose that provides a prolonged duration of activity.⁸ Palonosetron is available as an intravenous formulation in the United States and as an oral formulation in other countries. Multiple clinical trials have demonstrated that palonosetron is at least as effective as the first-generation 5-HT₃ antagonists for preventing acute CINV, and it is more effective against delayed CINV following moderately emetogenic or highly emetogenic chemotherapy.⁹⁻¹²

In a pooled analysis of moderately emetogenic chemotherapy trials, palonosetron demonstrated superiority over comparative 5-HT₃ receptor antagonists for preventing delayed CINV (Figure 2).¹³ A higher proportion of patients receiving palonosetron had no episodes of emesis and a longer time to the first episode of emesis.

The toxicity profile of palonosetron appears to be similar to that of the first-generation 5-HT₃ antagonists. The most frequent toxicity is headache, occurring in approximately 8% to 16% of patients.¹⁴⁻¹⁶ In most cases, headache is mild¹⁵ and short-lived, and can be managed by medical intervention, such as nonsteroidal anti-inflammatory agents. The second most common adverse event associated with the 5-HT₃ antagonists is constipation,

which occurs in approximately 5% to 8% of patients and is typically mild and manageable.¹⁴⁻¹⁶ It is important to educate patients about the possibility of constipation and instruct them to take preventive agents, such as the laxative senna, in order to avoid more severe symptoms that could cause additional gastrointestinal effects. The use of routine prevention should be balanced against the risk of diarrhea from the chemotherapy regimen.

In terms of drug clearance, approximately 50% of palonosetron is metabolized by the liver,¹⁷ and 40% is cleared by the kidneys.¹⁶ Clearance is not affected by sex, age, renal function, or use of other medications. Palonosetron does not impact cytochrome P450, which results in a low potential for drug interactions. Therefore, compared with first-generation 5-HT₃ receptor antagonists, palonosetron provides additional protection in the delayed setting and has several other advantages.

NK₁ Receptor Antagonists

Substance P is a neuropeptide found in high concentrations in the vomiting center in the brain. Binding of substance P to the neurokinin-1 (NK₁) receptor promotes emesis. NK₁ receptor antagonists have been developed as antiemetic agents that selectively block the binding of substance P to the NK₁ receptor. NK₁ receptor antagonists, the newest class of antiemetic therapy, represent a unique mechanism of antiemesis therapy that is complementary to 5-HT₃ receptor antagonism.

The first commercially available NK₁ receptor antagonist was aprepitant, an orally administered agent used solely as adjunctive treatment along with a 5-HT₃ antagonist and dexamethasone. Aprepitant is FDA-approved for the prevention of nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy. A 3-drug combination of aprepitant, a 5-HT₃ antagonist, and dexamethasone has demonstrated substantial efficacy for preventing CINV in patients receiving highly emetogenic chemotherapy, including with high-dose cisplatin and doxorubicin/cyclophosphamide (Figure 3).¹⁸⁻²⁰ Overall, aprepitant has been a critical addition in our efforts to control CINV.

In regard to safety, the main consideration with aprepitant is its potential for drug interactions. Examples of nonchemotherapeutic agents that can interact with aprepitant include warfarin, dexamethasone, and methylprednisolone.²¹ Coadministration with warfarin can result in a clinically significant decrease in the international normalized ratio (INR) of the prothrombin time. Therefore, care must be taken to monitor the INR when using oral aprepitant in patients receiving warfarin. The potential interactions between aprepitant and dexamethasone are a minor concern; clinical trials of aprepitant used a lower

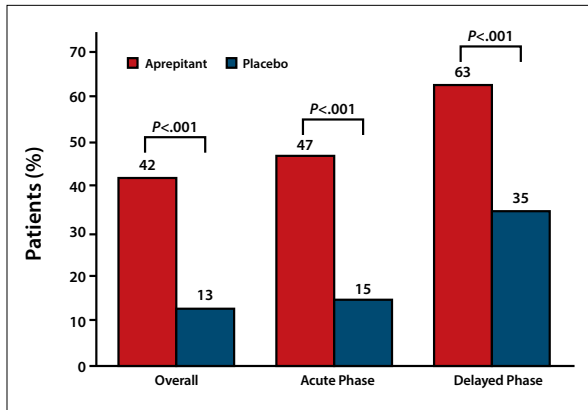


Figure 3. Complete response rate in a phase 3 trial evaluating the addition of aprepitant to standard antiemetic prophylaxis (a 5HT₃ receptor antagonist and dexamethasone). Complete response was defined as no emesis and no use of rescue therapy. 5HT₃, 5-hydroxytryptamine. Adapted from Albany C et al. *J Clin Oncol.* 2012;30(32):3998-4003.¹⁸

dose of dexamethasone to account for the increased dexamethasone exposure and reduced metabolism observed when administering both agents together.²⁰

A related NK₁ receptor antagonist is fosaprepitant, a prodrug of aprepitant that is administered intravenously 30 minutes before chemotherapy.²² Fosaprepitant is converted to aprepitant 30 minutes postinjection, and a single dose provides the same duration of benefit as the 3-day regimen of oral aprepitant. This approach may have a financial benefit in terms of lower copays compared with oral aprepitant, and ensures delivery of the drug.

The newest NK₁ receptor antagonist is netupitant, which has been formulated into an orally administered fixed-dose combination with palonosetron (known as NEPA). As Dr Aapro will discuss in the following article, phase 3 trials of NEPA demonstrated superior efficacy over palonosetron alone in patients receiving moderately emetogenic or highly emetogenic chemotherapy.^{23,24} The combination agent received FDA approval in October 2014 for the prevention of acute and delayed CINV.²⁵

Additional Antiemetic Agents

Although 5-HT₃ receptor antagonists and NK₁ receptor antagonists represent the major antiemetic therapies, other classes of drugs can also be beneficial, particularly in the rescue setting and for anticipatory CINV. In some cases, benzodiazepines may be useful. For example, lorazepam can help with anxiety, anticipatory CINV, and sleep disturbances, and it has a short half-life (14 hours).¹

Cannabinoids are also an important class of agents that have been very helpful. The various preparations have become more widely used with the broader availability of medical marijuana. Metoclopramide and prochlorper-

Table 2. Key Principles in the Management of CINV

Chemotherapy
Prevention of nausea and/or vomiting is the goal
Oral and intravenous 5-HT ₃ antagonists have equivalent efficacy when used at the appropriate doses
The toxicity of antiemetics should be considered
The choice of antiemetics should be based on the emetic risk of the therapy and patient factors, such as his or her prior experience with antiemetics
Causes of emesis other than chemotherapy should be considered
For multidrug chemotherapy regimens, the antiemetic should be selected based on the chemotherapeutic agent with the highest emetic risk
An H ₂ blocker or proton pump inhibitor can help prevent dyspepsia, which can mimic nausea
Lifestyle measures, such as eating small, frequent meals and choosing healthful foods, may help helpful

5HT₃, 5-hydroxytryptamine. Data from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Antiemesis. Version 2.2014. http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Updated April 18, 2014. Accessed January 27, 2015.¹

zine are also used routinely for prophylaxis for minimally emetogenic drugs and as rescue therapy. Olanzapine is a newer antipsychotic agent that has been evaluated in combination with 5-HT₃ receptor antagonists in several phase 2 and 3 clinical trials.²⁶⁻²⁸ Although this agent appears to be effective in acute CINV and also as rescue therapy, toxicity is an issue. Olanzapine can induce significant somnolence and thus should be used with caution. There are also safety concerns in elderly patients and in patients with type 2 diabetes and hyperglycemia owing to associated toxicities. However, for patients with refractory CINV, olanzapine is an important option to consider.

Optimizing CINV Prophylaxis

The cornerstone of CINV management is appropriate use of CINV prophylaxis upfront using guideline recommendations (Table 2).¹ Excellent guideline recommendations are available from various organizations, including the Multinational Association of Supportive Care in Cancer (MASCC),²⁹ the National Comprehensive Cancer Network (NCCN),¹ and the American Society of Clinical Oncology (ASCO).³⁰ However, multiple surveys have shown that many patients do not receive CINV according to clinical guidelines, for unclear reasons.^{31,32} Administration of prophylaxis consistent with guidelines is the best approach for controlling CINV. In addition, education regarding the appropriate use of antiemetics, individualized to the patient and the regimen, will improve quality of life and treatment tolerance for patients receiving emetogenic chemotherapy.

Disclosure

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Emerging Treatment Options for Chemotherapy-Induced Nausea and Vomiting

Matti S. Aapro, MD
Dean of the Multidisciplinary Oncology Institute
Clinique De Genolier
Genolier, Switzerland

Substantial progress has been made in the management of CINV. However, there are still patients who continue to experience nausea and vomiting, particularly in the delayed setting. Moreover, data from observational studies suggest that many patients are not receiving the optimal CINV prophylaxis according to management guidelines.

Gaps in Guideline Adherence

Multiple studies have shown that many patients are not receiving CINV prophylaxis as recommended by clinical guidelines. In the INSPIRE observational study of 1295 patients receiving highly or moderately emetogenic chemotherapy in US community oncology practices, only 57% of patients were prescribed CINV prophylaxis according to guidelines (Figure 4).¹ The Pan European Emesis Registry (PEER) included 991 patients receiving highly or moderately emetogenic chemotherapy.² Guideline-consistent CINV prophylaxis was administered to 55% of patients during the acute phase and 46% during the delayed phase (Figure 5).² Only 29% of patients received guideline-consistent prophylaxis during both phases. Among the subset of patients receiving highly emetogenic chemotherapy, only 11% received guideline-consistent CINV prophylaxis in both phases.

Administering CINV prophylaxis consistent with guidelines is associated with better CINV control. In the PEER study, complete response rates were significantly higher in patients receiving guideline-consistent prophylaxis than in other patients (59.9% vs 50.7%; $P=.008$). The adjusted odds ratio was 1.43 (95% CI, 1.04-1.97; $P=.027$) for the use of guideline-consistent prophylaxis.

One potential reason that clinicians fail to follow guidelines is the requirement for complicated regimens containing multiple agents. The introduction of simplified regimens may increase adherence rates to recommended guidelines.

Key Clinical Trials of NEPA

NEPA is a fixed-dose combination of the NK₁ receptor antagonist netupitant and the 5-HT₃ receptor antagonist

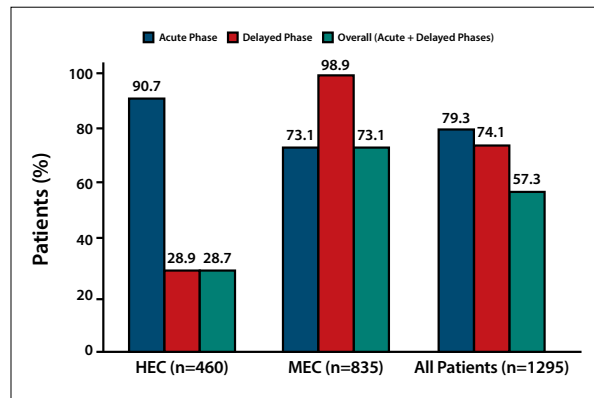


Figure 4. The percentage of patients who received CINV prophylaxis that was consistent with guidelines in the INSPIRE study. CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy. Adapted from Gilmore JW et al. *J Oncol Pract.* 2014;10(1):68-74.¹

palonosetron. The formulation enables patients to take a single capsule with 2 active agents, adding corticosteroids as needed. The half-life of netupitant is approximately 80 hours,³ compared with 9 to 13 hours for aprepitant.⁴ Netupitant, like aprepitant, is metabolized by the CYP3A4 pathway and is an inhibitor of CYP3A4, and therefore has the potential for drug interactions.^{3,4}

Several clinical trials have evaluated the efficacy and safety of NEPA. A randomized, double-blind, dose-ranging pivotal study evaluated 3 doses of netupitant (100 mg, 200 mg, and 300 mg) with palonosetron (0.50 mg).⁵ An exploratory arm of the study evaluated a standard 3-day regimen of aprepitant plus intravenous ondansetron. Patients in all groups also received oral dexamethasone on days 1 to 4.

The study found that all NEPA doses were significantly more effective than palonosetron alone. Complete response rates, defined as the proportion of patients with no emesis and requiring no rescue medication, were 87.4% for the 100 mg dose, 87.6% for the 200 mg dose, and 89.6% for the 300 mg dose, compared with 76.5% for palonosetron alone ($P<.050$).⁵ The highest NEPA dose (which contained 300 mg of netupitant) was incrementally more effective than the other NEPA doses for all endpoints. There was

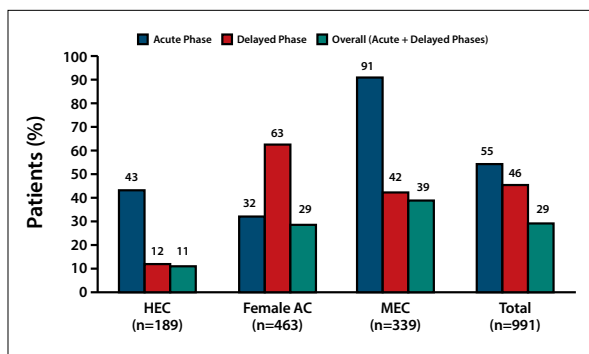


Figure 5. The percentage of patients who received CIN V prophylaxis that was consistent with guidelines in the PEER study. AC, anthracycline plus cyclophosphamide; CIN V, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; PEER, Pan European Emesis Registry. Adapted from Aapro M et al. *Ann Oncol.* 2012;23(8):1986-1992.²

also a trend toward a higher complete response rate with NEPA 300 mg compared with aprepitant plus ondansetron (89.6% vs 86.6%). Based on these findings, the 300-mg netupitant NEPA formulation was selected for further development.

Subsequently, a randomized, phase 3 trial was undertaken comparing NEPA with palonosetron, both with dexamethasone, in patients receiving moderately emetogenic chemotherapy.⁶ A total of 1455 patients were randomly assigned to receive a single oral dose of NEPA (netupitant 300 mg with palonosetron 0.5 mg) or a single oral dose of palonosetron (0.50 mg), each with oral dexamethasone (12 mg in the NEPA arm and 20 mg in the palonosetron arm) administered on day 1 only. After the first cycle, NEPA was significantly more effective than palonosetron alone as assessed by complete response rate in the acute phase (88.4% vs 85.0%; $P=.047$), the delayed phase (76.9% vs 69.5%; $P=.001$), and the overall 5-day period (74.3% vs 66.6%; $P=.001$; Figure 6).⁶ Interestingly, this study suggests that the use of corticosteroids beyond day 1 might not be necessary with NEPA.

An updated analysis from the study presented at the 2014 meeting of MASCC/International Society of Oral Oncology showed that the efficacy of NEPA was maintained across multiple treatment cycles.⁷ After cycle 4, NEPA plus dexamethasone was significantly more effective than palonosetron plus dexamethasone. The complete response rates were 84% for NEPA plus dexamethasone vs 75% for palonosetron plus dexamethasone.⁷ The durable efficacy of NEPA was also demonstrated in a randomized, double-blind, phase 3 trial of 413 patients receiving highly emetogenic (24%) or moderately emetogenic (76%) chemotherapy. Patients were randomly assigned to a single oral dose of NEPA administered on day 1 with

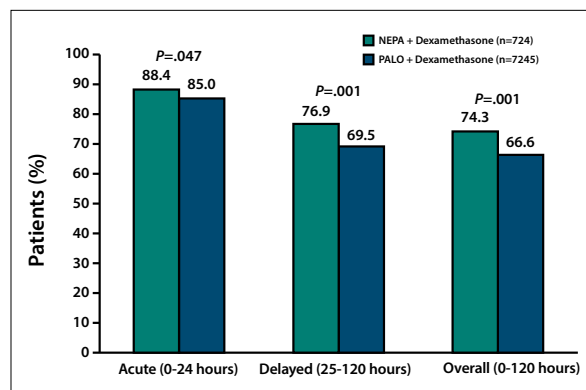


Figure 6. Complete response in a randomized, phase 3 trial comparing NEPA with palonosetron, both with dexamethasone, in patients receiving moderately emetogenic chemotherapy. Complete response refers to no emesis and use of no rescue medication. Adapted from Aapro M et al. *Ann Oncol.* 2014;25(7):1328-1333.⁶

oral dexamethasone or a 3-day regimen of aprepitant, palonosetron, and dexamethasone.⁸ Dexamethasone was administered on days 1 to 4 among patients receiving highly emetogenic chemotherapy and on day 1 among those receiving moderately emetogenic regimens. There was a trend toward higher complete response rates with NEPA plus dexamethasone compared with aprepitant, palonosetron, and dexamethasone throughout the study period, beginning at cycle 1 (81% vs 76%) and continuing through cycle 6 (91% vs 86%).⁸ The investigators noted that 75% of patients completed at least 4 cycles, and 40% completed 6 cycles.

The most frequent adverse events related to NEPA are constipation (2% to 4%) and headache (1% to 3%).^{6,8} Toxicity does not appear to increase with multiple cycles.⁸

Based on the available data, the FDA approved NEPA in October 2014, with an indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.³

Future Directions

Progress continues to be made in the development of new antiemetic agents. One investigational agent is rolapitant, a novel NK₁ receptor antagonist that has a half-life of up to 180 hours.⁹ Rolapitant does not interact with CYP3A4, which gives it a low potential for drug interactions. However, it is not yet known whether this advantage will translate into any clinically significant improvements over the current NK₁ receptor antagonists.

Results from 3 clinical trials of rolapitant were presented at the 2014 MASCC conference. Two phase 3 trials enrolled a total of 1070 patients receiving highly

emetogenic chemotherapy.¹⁰ Rolapitant was significantly more effective than the control as assessed by the complete response rate overall in the first study (70.1% vs 56.5%; $P < .001$). In the second study, rolapitant was superior in the delayed phase (70.1% vs 61.9%; $P = .043$), and showed a nonsignificant improvement overall (67.5% vs 60.4%; $P = .084$). The third phase 3 trial evaluated 1332 patients receiving moderately emetogenic chemotherapy.¹¹ The complete response rates were significantly higher with rolapitant vs the control during the delayed phase (71.3% vs 61.6%; $P < .001$) and throughout the overall 5-day period (68.6% vs 57.8%; $P < .001$). It will be important to see the full publication of these data to consider the efficacy and safety of rolapitant, which is currently under review by regulatory authorities.

There are also efforts underway to optimize the use of dexamethasone in combination with newer antiemetic agents. For example, my colleagues and I have demonstrated the feasibility of using dexamethasone only on day 1 in patients undergoing treatment with moderately emetogenic chemotherapy (eg, an AC-type regimen) who receive palonosetron.¹¹

Another area of current research relates to an understanding of the concept of nausea. As a subjective symptom, nausea can have different meanings for patients, nurses, and physicians. Therefore, there is a need to better understand what patients mean when they say, "I am nauseated." There are multiple areas of CINV management that continue to be explored and optimized.

Disclosure

Dr Aapro has received study grants and has been a consultant or speaker for Helsinn, Eisai, Merck, Roche, and Janssen.

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New and Emerging Therapeutic Options for the Management of Chemotherapy-Induced Nausea and Vomiting: Q&A

Hope S. Rugo, MD, Matti S. Aapro, MD, and Lee S. Schwartzberg, MD

Hope S. Rugo, MD Do you think NEPA offers a benefit over similar approaches?

Matti S. Aapro, MD Yes. One clear advantage is that NEPA simplifies the approach to CINV because it consists of 1 oral capsule that contains 2 very active agents. For the patient, this means taking only a capsule along with a couple of corticosteroid tablets to be protected from CINV. Corticosteroids are administered with cisplatin-based chemotherapy for the first few days after treatment. However, it may be worth conducting a study to see whether corticosteroids are in fact needed or whether they could be administered only when a patient starts to experience nausea.

The NEPA combination may also simplify the approach in regard to cost, as it would eliminate the need for intravenous administration of a prophylactic CINV treatment and the associated nursing time and resources. A simplified CINV prophylaxis regimen containing only a few oral agents might also help clinicians follow the clinical guidelines. Therefore, the availability of NEPA may help improve adherence from both the patient and the provider perspectives. In some areas, reimbursement may be a consideration. However, NEPA is simple to administer, and clinicians may embrace it because it eliminates the need for intravenous medications.

Lee S. Schwartzberg, MD I agree that there is a resource utilization component to guideline nonadherence, and NEPA has the potential to reduce that issue. Also, given the widespread use of electronic medical records at academic medical centers and in community practices, clinicians can look back at records in their own practices to see whether there may have been missed opportunities to treat patients for CINV according to guidelines. Increasing awareness about CINV with all clinic staff members may also help improve adherence to guidelines.

Hope S. Rugo, MD Do you have any other suggestions for what clinicians can do to improve CINV management?

Lee S. Schwartzberg, MD It is important that clinicians evaluate patient risk factors for CINV. Although this area remains somewhat of an unmet need, with little evidence available, it is important to ask patients about risk factors. This conversation will require additional nurse time, but it helps ensure that the most appropriate CINV therapy will be used.

Matti S. Aapro, MD There are websites and apps (including one I helped develop) that estimate the risk for CINV based on responses to a series of questions. Additional studies are needed to further evaluate these tools. However, it is important to consider the various treatment-related and patient-related factors known to contribute to CINV risk.

Hope S. Rugo, MD These are excellent ideas about increasing adherence to guidelines, particularly the idea of a tool that people can use quickly in the clinic. In the United States, education of our support staff is another area where we can work to improve CINV management. Many patients are seen by nurse practitioners, physician assistants, and infusion nurses. Educating these clinicians on the whole schema of CINV prevention and rescue makes a big difference in terms of adherence to guidelines and application in clinical practice.

Matti S. Aapro, MD I agree. There are 4 groups that require education on the optimal management of CINV: oncologists, patients, nurses, and pharmacists.

Hope S. Rugo, MD Yes, pharmacists are critical. At our institution, they play a big role in helping us manage patients with refractory CINV. On another note, I would suggest that it is important to listen to patients. This can be more challenging today, as patients who come in for routine treatments might not be seen by their physician at every visit. We use our triage nurses and infusion nurses in these situations to try to make a preemptive strike against CINV.

Lee S. Schwartzberg, MD It is important to listen to patients before treatment as well as after treatment to

manage the potential for delayed nausea. Another important aspect of CINV management is the use of other resources, such as health care navigators. Increasingly, we are using navigators in our practice, including both nurse navigators and even lay navigators, who may be former patients with a vested interest in CINV.

Matti S. Aapro, MD It is also important to ask the right questions. A general question of “How have you been in the past 3 weeks?” might elicit a response of “OK, doctor,” and we are happy with that. Then the patient might go to the nurse and say, “Well, I vomited about 3 times a day for 3 days, but that’s normal on the chemotherapy, isn’t it?” It may be better for doctors to ask direct questions about the frequency of nausea and vomiting episodes.

Lee S. Schwartzberg, MD Patients tend to minimize their side effects to doctors more than to other clinicians. They

may fear that their treatment will be changed to a less effective regimen if they mention any nausea or vomiting.

Hope S. Rugo, MD That is a very important point. Also, it is essential to optimize CINV treatment as much as possible with the first dose to reduce the risk of nausea and vomiting. Patients might stop their treatment altogether if they have a horrible experience with the first cycle of chemotherapy.

Disclosures

Dr Rugo receives research funding for the Regents of the University of California from Eisai. She has performed contracted research for Eisai, Amgen, Novartis, Pfizer, Genentech/Roche, Merck, MacroGenics, and BioMarin. She has received fees for non-CME services from Genomic Health. Dr Aapro has received study grants and has been a consultant or speaker for Helsinn, Eisai, Merck, Roche, and Janssen. Dr Schwartzberg is a consultant for Eisai, Helsinn, Merck, and Tesaro.

Slide Library

Types of CINV

- **Acute CINV:** Occurs within the first 24 hours after receiving chemotherapy
- **Delayed CINV:** Starts after the first 24 hours and can last approximately 1 week after administration
- **Anticipatory CINV:** A conditioned response typically triggered by physical cues such as arrival at the clinic, by sensory cues such as specific smells or sounds, or by the patients' thoughts
- **Refractory CINV:** The development of CINV in patients who have received adequate prophylaxis

*In clinical trials, 5 days (120 hours) is used as an endpoint. CINV, chemotherapy-induced nausea and vomiting.

Current Management

- Substantial progress has been made in the prevention and treatment of acute CINV
- In contrast, effective control of delayed CINV has been more difficult to attain
- Some of the most commonly used chemotherapeutic regimens are associated with delayed nausea, and occasionally delayed vomiting, in a substantial proportion of patients

Key Principles in the Management of CINV

- The cornerstone of CINV management is appropriate use of prophylaxis upfront using guideline recommendations
- The management strategy differs according to the type of CINV
- The strategy may need to be modified based on a patient's individual response

CINV Guidelines

- Guidelines are available from organizations such as MASCC, the NCCN, and ASCO
- Administering CINV prophylaxis consistent with guidelines is associated with better CINV control¹
- Multiple studies have shown that many patients are not receiving CINV prophylaxis as recommended by clinical guidelines^{1,2}

1. Aapro M et al. Ann Oncol. 2012;23(8):1986-1992. 2. Gilmore JF et al. J Oncol Pract. 2014; 10(1):68-74. ASCO, the American Society of Clinical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network.

5-HT₃ Receptor Antagonists

- **First generation:** Ondansetron and granisetron are equally effective in preventing or diminishing acute CINV,^{1,2} but have limited efficacy in the prevention of delayed CINV.³ In addition, drug interactions are a concern
- **Second generation:** Palonosetron is at least as effective as the first-generation 5-HT₃ antagonists for preventing acute CINV, and it is more effective against delayed CINV following moderately emetogenic or highly emetogenic chemotherapy^{4,7}

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NEPA

- A fixed-dose combination of the NK₁ receptor antagonist netupitant and the 5-HT₃ receptor antagonist palonosetron
- Approved by the FDA in October 2014 for the prevention of acute and delayed CINV
- In a phase 3 trial, the complete response rates were 84% for NEPA plus dexamethasone vs 75% for palonosetron plus dexamethasone¹

1. Aapro M et al. Abstract 64. Presented at: MASCC/ISOO International Symposium on Supportive Care in Cancer, June 26-28, 2014, Miami, Florida, FDA, US Food and Drug Administration.

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New and Emerging Therapeutic Options for the Management of Chemotherapy-Induced Nausea and Vomiting

CME Post-Test: Circle the correct answer for each question below.

1. In the past several decades, substantial progress has been made in the prevention and treatment of which type of chemotherapy-induced nausea and vomiting (CINV)?
 - a. Acute
 - b. Delayed
 - c. Recurrent
 - d. Refractory
2. Which of the following chemotherapeutic agents has a low emetic risk?
 - a. Anthracycline
 - b. Carboplatin
 - c. Cisplatin
 - d. Paclitaxel
3. Which type of CINV is most likely to benefit from treatment with anxiolytic agents?
 - a. Acute
 - b. Anticipatory
 - c. Delayed
 - d. Refractory
4. Which agent can be useful in the rescue setting in patients receiving minimally to moderately emetogenic chemotherapy?
 - a. Dexamethasone
 - b. Lorazepam
 - c. Ondansetron
 - d. Senna
5. Which agent can help with anxiety, anticipatory CINV, and sleep disturbances?
 - a. Dexamethasone
 - b. Lorazepam
 - c. Ondansetron
 - d. Senna
6. The antipsychotic agent olanzapine is an option for:
 - a. Older patients
 - b. Patients with anticipatory CINV
 - c. Patients with refractory CINV
 - d. Patients with type 2 diabetes
7. In which way is the second-generation 5-HT₃ antagonist palonosetron similar to the first-generation agents?
 - a. Adverse events
 - b. Binding to the 5-HT₃ receptor
 - c. Half-life
 - d. Treatment of delayed CINV
8. In a study from the Pan European Emesis Registry, what were the complete response rates in patients receiving guideline-consistent prophylaxis vs those who did not?
 - a. 55.7% vs 53.5%
 - b. 59.9% vs 50.7%
 - c. 68.4% vs 63.1%
 - d. 69.3% vs 67.4%
9. In an updated analysis of a study by Aapro presented at the 2014 MASCC/ISOO meeting, NEPA plus dexamethasone was associated with a complete response rate of:
 - a. 51%
 - b. 68%
 - c. 77%
 - d. 84%
10. What type of agent is rolapitant?
 - a. Anxiolytic
 - b. Cannabinoid
 - c. NK₁ receptor antagonist
 - d. 5-HT₃ antagonist

Evaluation Form: New and Emerging Therapeutic Options for the Management of Chemotherapy-Induced Nausea and Vomiting

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 10392**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

- MD/DO PA/PA-C NP RN PharmD/RPh PhD
 Other, please specify:

2. What is your area of specialization?

- Oncology, Hematology/Oncology Oncology, Medical Oncology, Other

3. Which of the following best describes your primary practice setting?

- Solo Practice Group Practice Government
 University/teaching system Community Hospital
 HMO/managed care Non-profit/community I do not actively practice
 Other, please specify:

4. How long have you been practicing medicine?

- More than 20 years 11-20 years 5-10 years 1-5 years
 Less than 1 year I do not directly provide care

5. Approximately how many patients do you see each week?

- Less than 50 50-99 100-149 150-199 200+
 I do not directly provide care

6. How many patients do you currently see each week who are receiving chemotherapy?

- Fewer than 5 6-15 16-25 26-35 36-45 46-55
 56 or more I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Discuss the pathophysiology of CINV

- Strongly Agree Agree Neutral Disagree Strongly Disagree

Explain the mechanism of action and rationale for the use of antiemetic agents in the prevention of CINV

- Strongly Agree Agree Neutral Disagree Strongly Disagree

Identify the incidence and impact of CINV associated with both highly and moderately emetogenic therapy

- Strongly Agree Agree Neutral Disagree Strongly Disagree

Evaluate the efficacy and safety data supporting the use of approved antiemetic agents in the prevention of CINV

- Strongly Agree Agree Neutral Disagree Strongly Disagree

Assess clinical trial results of new and novel agents for the management of CINV

- Strongly Agree Agree Neutral Disagree Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

- Strongly Agree Agree Neutral Disagree Strongly Disagree

The content was evidence based

- Strongly Agree Agree Neutral Disagree Strongly Disagree

The educational material provided useful information for my practice

- Strongly Agree Agree Neutral Disagree Strongly Disagree

The activity enhanced my current knowledge base

- Strongly Agree Agree Neutral Disagree Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

- Strongly Agree Agree Neutral Disagree Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

- Strongly Agree Agree Neutral Disagree Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one of the following options)

I do plan to implement changes in my practice based on the information presented

My current practice has been reinforced by the information presented

I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

- Apply latest guidelines Choice of treatment/management approach
 Change in pharmaceutical therapy Change in current practice for referral
 Change in nonpharmaceutical therapy Change in differential diagnosis
 Change in diagnostic testing Other, please specify:

12. How confident are you that you will be able to make your intended changes?

- Very confident Somewhat confident Unsure Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

- Formulary restrictions Insurance/financial issues Time constraints
 Lack of multidisciplinary support System constraints
 Treatment-related adverse events Patient adherence/compliance
 Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

- Yes No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

Name* _____

Degree* _____

Organization _____

Specialty* _____

City, State, ZIP* _____

Telephone _____ Fax _____

E-mail* _____

Signature* _____ Date* _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

- I participated in the entire activity and claim 1.50 credits.
 I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10