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Cases in the Management of Chemotherapy-Induced Nausea and Vomiting: Integrating Updated Guidelines into Clinical Practice

Moderator

Lee S. Schwartzberg, MD, FACP
Clinical Oncologist
Medical Director
The West Clinic
Memphis, Tennessee

Discussants

Steven M. Grunberg, MD
Professor of Medicine
The University of Vermont
College of Medicine
Burlington, Vermont

Gary R. Morrow, PhD, MS
Professor of Radiation Oncology
Professor of Psychiatry
University of Rochester Medical Center
Rochester, New York

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) is one of the most significant side effects of cancer treatment, impacting patients' quality of life and treatment compliance and potentially necessitating changes in patients' therapy. The optimal strategy for CINV management is prophylaxis; in fact, prevention of CINV—rather than management—is one of the major treatment paradigm changes that has occurred in recent decades. This knowledge, as well as a better understanding of the emetogenic potential of various chemotherapeutic agents and the varying risk factors associated with CINV, has led to major improvements in CINV prophylaxis. Several evidence-based guidelines now exist to guide clinicians regarding the best regimens for CINV prevention, and these guidelines have recently been updated to reflect the publication of major clinical trials and the approval of new agents. Incorporating these guidelines into clinical practice can provide clinicians with an excellent starting point for CINV management, but clinicians must also be familiar with the evidence upon which the guidelines are based in order to alter antiemetic regimens as needed for individual patients. Additionally, clinicians should understand many of the special considerations related to CINV, such as the fact that chemotherapy-induced nausea is actually more frequent than chemotherapy-induced vomiting. Finally, several nontraditional therapies are available as alternative strategies for patients who do not benefit from currently approved antiemetic agents.

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Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and oncology nurses who treat cancer patients who receive chemotherapy.

Statement of Need/Program Overview

Chemotherapy-induced nausea and vomiting (CINV) is a significant issue in the management of cancer patients. Even with the availability of multiple effective antiemetic agents, up to 80% of patients will experience CINV. Not only does CINV affect quality of life and treatment compliance, it may also necessitate a change in the patient's treatment, which could affect prognosis. Advances in the understanding of the underlying biology of CINV have allowed for the development of agents targeted against the pathways important for this condition. Guidelines to the management of CINV are produced by several major groups, including the American Society of Clinical Oncology (ASCO), the Multinational Association for Supportive Care in Cancer (MASCC), and the National Comprehensive Cancer Network (NCCN). These guidelines are updated regularly in order to incorporate the latest clinical data. The implementation of these guidelines into clinical practice has been shown to improve patient outcomes.

Educational Objectives

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

- Describe recent clinical trial data in the management of chemotherapy-induced nausea and vomiting (CINV)
- Identify updates to the latest CINV guidelines
- Devise personalized CINV management strategies
- Identify future research directions in the management of CINV

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Updated Guidelines on Chemotherapy-Induced Nausea and Vomiting

Lee S. Schwartzberg, MD, FACP

Chemotherapy-induced nausea and vomiting (CINV) is a significant issue in the management of cancer patients. Not only does CINV affect quality of life and treatment compliance, it may also necessitate a change in the patient's treatment, which could reduce the benefit of chemotherapy. The incidence of CINV is influenced mainly by the emetogenicity of the treatment as well as the tools used to measure vomiting and/or nausea. Research and clinical experience clearly show that CINV can be effectively prevented in most patients with a prophylactic strategy. Thus, several major organizations have published evidence-based guidelines to help clinicians implement the most effective antiemesis prophylaxis for patients undergoing chemotherapy.

Comparison of Current Guidelines

For clinicians in the United States, the 3 most important CINV guidelines are those developed by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the Multinational Association of Supportive Care in Cancer (MASCC). The NCCN guidelines have the advantage of being frequently updated—at least once per year or whenever new practice-changing developments emerge.[1] In comparison, the ASCO guidelines are updated less frequently; these guidelines were first released in 1999, and they have been updated twice since that time (in 2006 and 2011).[2,3] Finally, the MASCC formally updated its CINV guidelines in 2009 following a consensus conference that was held in Perugia, Italy; informal updates to the MASCC guidelines have been added since that time, with the most recent update added in 2011.[4,5]

While differing in the frequency with which they are updated, these 3 guidelines are largely similar in the approach they take towards the management of CINV. A major similarity among the 3 guidelines is their categorization of particular chemotherapy agents into emetogenic risk groups. This classification helps clinicians to determine the most appropriate antiemetic strategy based on a particular agent's likelihood of causing nausea and/or vomiting. A number of strategies have been developed to classify chemotherapeutic agents based on their emetogenic potential. Experts involved in developing each of the major antiemetic guidelines have used 1 of these classification schemes—first developed by Hesketh and colleagues in 1997 and more recently updated by Grunberg and colleagues in 2010—to determine the emetogenic potential of various chemotherapeutic agents.[6-8]

This scheme defines the emetogenic potential of chemotherapy agents as high, moderate, low, or minimal, corresponding to the proportion of patients who experience acute emesis when treated with that particular chemotherapeutic agent in the absence of antiemetic prophylaxis: at least 90% of patients treated with a high-risk agent; 30–90% of patients treated with a moderate-risk agent; 10–30% of patients treated with a low-risk agent; and less than 10% of patients treated with a minimal-risk agent. This classification scheme is updated annually to reflect the introduction of new anticancer agents.[4,7,9] In this scheme, oral and intravenous chemotherapeutic agents are ranked separately, due to inherent differences in the emetogenicity of each group plus differences arising from the dosing schedules and routes of administration. Both the NCCN and MASCC guidelines recommend antiemetic prophylaxis for both intravenous and oral chemotherapy agents, while the ASCO guidelines only include recommendations for intravenous agents.

Another similarity across the NCCN, ASCO, and MASCC guidelines is the inclusion of management strategies for special cases. All 3 guidelines contain recommendations for the prophylactic treatment of radiation-induced nausea and vomiting, although this situation is most comprehensively addressed in the ASCO and MASCC guidelines. In addition, the NCCN and MASCC guidelines (and, to a lesser degree, the ASCO guidelines) address emetogenic chemotherapy regimens that are administered over multiple days. In the ASCO guidelines, a section is also devoted to antiemesis in special populations, including pediatric cancer patients and patients undergoing high-dose chemotherapy coupled with stem cell or bone marrow transplantation. Other special sections include recommendations regarding the management of both breakthrough CINV and anticipatory CINV.

The most important message delivered by the guidelines, with absolute consensus among all, is that prevention of CINV is critical, as treatment after CINV has occurred is much less successful. Clinicians should thus choose the most appropriate antiemetic prophylaxis regimen for each patient; while this decision will be based primarily on the

Case 1

A 45-year-old female is diagnosed with stage IIb breast cancer measuring 2.4 cm in diameter. Upon biopsy, her tumor is classified as an infiltrating ductal carcinoma that is hormone receptor–negative (both estrogen receptor–negative and progesterone receptor–negative) and HER2-negative. Because of a positive sentinel lymph node, the patient undergoes a lumpectomy with axillary lymph node dissection; 3 of 12 lymph nodes are found to be positive. Her oncologist recommends a chemotherapy regimen comprised of dose-dense doxorubicin/cyclophosphamide followed by paclitaxel. Evaluation of the patient's history reveals that she has mild gastroesophageal reflux disease (GERD).

For this patient, the combination of an anthracycline with cyclophosphamide poses a high risk of CINV, and therefore prophylactic antiemesis treatment should begin with the first cycle of chemotherapy and continue through all subsequent cycles of chemotherapy. To prevent both acute and delayed CINV, the following prophylactic antiemetic regimen is chosen:

- **Intravenous palonosetron (0.25 mg on Day 1)**
- **Dexamethasone (12 mg intravenously on Day 1, 8 mg orally on Day 2, and 8 mg orally twice daily on Days 3 and 4)**
- **Intravenous fosaprepitant (150 mg on Day 1)**

In addition, due to the patient's history of GERD, the patient is prescribed a histamine receptor (H_2) antagonist. In order to prevent the development of anticipatory CINV, the oncologist discusses the possibility of adding lorazepam to the CINV regimen if the patient begins to experience any anxiety.

Because doxorubicin/cyclophosphamide therapy is associated with a significant risk of breakthrough delayed nausea, the patient is also given a prescription for prochlorperazine to be taken as needed at the first sign of any significant nausea or any vomiting that occurs despite the antiemetic prophylaxis. The oncologist also informs the patient that they could consider switching to an alternative agent for breakthrough therapy, such as metoclopramide or the newer agent olanzapine, if she were to experience any further breakthrough CINV after the first cycle of chemotherapy.

emetogenicity of the highest–emetic risk agent, patient-specific risk factors and the patient's previous experience with antiemetic treatments should also be considered. The ASCO guidelines also note that clinicians should provide patients with a prescription for rescue therapy before the patient leaves the treatment facility on their first day of therapy, which is an important practical point.

Significant Updates to Guidelines

The NCCN, ASCO, and MASCC guidelines have all undergone significant changes with their last round of updates. Many of these changes involved updates to the evidence supporting particular recommendations, which resulted from the recent conclusion and publication of several practice-changing clinical trials.

One of these clinical trials, a study conducted by Saito and colleagues, was published in *Lancet Oncology* in 2009.[10] This study was a double-blind, double-dummy, randomized, comparative, multicenter, phase III trial that compared the efficacy and safety of granisetron versus palonosetron, which are first-generation and second-generation 5-HT_3 receptor antagonists, respectively. Both agents were administered with dexamethasone. A total of 1,143 Japanese cancer patients were randomized to receive either granisetron or palonosetron. All patients received a single dose of highly emetogenic chemotherapy: either cisplatin (at a dose of ≥50 mg/m^2) or a regimen consisting of an anthracycline (doxorubicin or epirubicin) combined with a cyclophosphamide. Each 5-HT_3 receptor antagonist was administered as a single, fixed, intravenous dose 30 minutes prior to chemotherapy on Day 1. Dexamethasone was administered within 45 minutes prior to palonosetron or granisetron on Day 1 and was also given on Days 2 and 3.

The primary efficacy endpoint in this study was complete response for both acute and delayed CINV; complete response was defined as no emetic episodes and no need for rescue medication. A similar proportion of patients in each treatment arm achieved a complete response for acute CINV (75.3% vs 73.3% in the palonosetron and granisetron arms, respectively), demonstrating that palonosetron was noninferior to granisetron for control of acute CINV (Table 1). In terms of delayed CINV, however, a significantly higher proportion of patients in the palonosetron arm achieved a complete response (56.8% in the palonosetron arm vs 44.5% in the granisetron arm; $P<.0001$). Indeed, palonosetron proved to be superior to granisetron in terms of the proportion of patients achieving a complete response over the entire 120-hour period following chemotherapy administration.

Importantly, palonosetron seemed to be particularly effective against delayed nausea. Although a similar proportion of patients in each group experienced severe nausea within the first 24 hours following chemotherapy (6.1% and 5.9% in the palonosetron and granisetron arms, respectively), this

Case 2

A 65-year-old male is diagnosed with stage IIIA squamous cell lung carcinoma. This patient has a 40 pack-year history of smoking. Because of his decreased pulmonary function, the patient is deemed to be unsuitable for surgical resection. Instead, his oncologist selects combined modality treatment with radiation therapy and adjuvant chemotherapy. Specifically, treatment includes cisplatin (70 mg/m^2 on Days 1 and 22) and etoposide (50 mg/m^2 on Days 1–5 and Days 22–26) plus radiation therapy.

Because cisplatin is associated with a high risk of CINV, prophylactic antiemesis treatment is needed beginning with the first cycle of chemotherapy and continuing through all subsequent cycles of chemotherapy. To prevent both acute and delayed CINV, the prophylactic antiemesis regimen chosen for the beginning of the chemotherapy cycle is as follows:

- **Intravenous palonosetron (0.25 mg on Day 1)**
- **Dexamethasone (12 mg intravenously on Day 1, 8 mg orally on Day 2, and 8 mg orally twice daily on Days 3 and 4)**
- **Intravenous fosaprepitant (150 mg on Day 1)**

In contrast to cisplatin, etoposide is associated with a moderate emetic risk; therefore, the patient is prescribed oral dexamethasone (12 mg) to be taken each day of treatment during the etoposide-only portion of the chemotherapy cycle. The oncologist could also consider re-dosing palonosetron on Day 3 or Day 4 since etoposide is a moderately emetogenic chemotherapy agent and requires a 5-HT$_3$ blocker.

The oncologist also informs the patient about the risk of breakthough CINV occurring with cisplatin therapy, and the patient is given a prescription for prochlorperazine to be taken as needed at the first sign of any significant nausea or any vomiting that occurs despite the antiemesis prophylaxis.

Table 1. Phase III Trial of Palonosetron Versus Granisetron (Both with Dexamethasone) in Highly Emetic Chemotherapy

	Palonosetron plus Dexamethasone (n=555) %	Granisetron plus Dexamethasone (n=558) %	*P* Value
Complete Response, Acute (0–24 hours)	75.3	73.3	ND
Complete Response, Delayed (24–120 hours)	56.8	44.5	<0.0001
Complete Response, Overall (0–120 hours)	47.9	38.1	0.0007
No Nausea: 0–120 hours	32	25	0.01
No Emesis: 0–120 hours	58	49	0.006

Adapted from Saito M et al. *Lancet Oncol.* 2009;10:115-124.[10]

ND=not done.

rate dropped to 1.6% in the palonosetron arm at 96 hours, while remaining relatively high (5.0%) in the granisetron arm. Palonosetron also proved to be associated with a longer time to treatment failure, defined as time to first emetic episode or administration of rescue medication, compared to granisetron (hazard ratio: 1.299; 95% confidence interval: 1.106–1.526), reaching a median of over 120 hours for the palonosetron group, compared with a median of only 79 hours in the granisetron group. Based in part on this trial, palonosetron is now considered to be the preferred 5-HT$_3$ receptor antagonist for prevention of CINV in patients receiving highly emetogenic intravenous chemotherapy.

Another trial included in the updated guidelines is a double-blind, parallel-group, multicenter, phase III noninferiority trial conducted by Boccia and colleagues in which a novel transdermal formulation of granisetron was compared to the standard oral formulation of granisetron.[11] The transdermal formulation was designed to deliver continuous granisetron over a period of 7 days, while the oral formulation was administered for 3–5 days. A total of 641 patients were initially randomized to receive treatment with either formulation, and the primary endpoint of the study was complete control—defined as no emesis and no more than mild nausea without the use of rescue medications—during the acute phase (within the first 24 hours after chemotherapy administration). All patients were scheduled to receive a new multiday chemotherapy regimen that was either moderately or highly emetogenic.

To ensure blinding, the trial was placebo-controlled, with patients receiving either a placebo patch and active pills or placebo pills and an active patch. The transdermal patch was positioned 24–48 hours prior to initiating chemotherapy in order to allow adequate dermal penetration of the drug; pills were administered 1 hour prior to chemotherapy on each day.

Results of the per-protocol analysis, which included 582 patients, showed that transdermal granisetron was indeed noninferior to oral granisetron. Complete control was achieved by 60% of patients in the group treated with transdermal granisetron and by 65% of patients in the oral granisetron group. There were no significant differences between the 2 granisetron formulations across patient subgroups, which subdivided patients by sex, exposure to prior chemotherapy, planned chemotherapy duration, and type of chemotherapy administered. Patients reported similar satisfaction with both the transdermal and oral granisetron formulations.

In this study, most treatment-emergent adverse events were mild or moderate in severity, and the incidence of adverse events was similar in the transdermal granisetron arm (41%) and the oral granisetron arm (39%). Constipation was the most common treatment-related adverse event; constipation was reported more frequently among patients treated with oral granisetron than among those treated with transdermal granisetron (7% vs 3%). Finally, there was 1 death that was considered to be related to the study treatment; this death occurred in a patient in the oral granisetron arm who developed toxic megacolon. As a result of this trial, updated CINV guidelines include the transdermal granisetron formulation as a choice for patients who are receiving treatment with either moderate–emetic risk or high–emetic risk intravenous chemotherapy.

Finally, Grunberg and colleagues recently published results of a randomized, double-blind, active-controlled, multicenter, phase III trial that evaluated the safety and efficacy of fosaprepitant, an intravenous analogue of aprepitant that is rapidly metabolized to the latter agent upon administration.[12] This study tested whether a single high-dose (150 mg) infusion of fosaprepitant was noninferior to the standard 3-day regimen of oral aprepitant; patients were followed for 120 hours following chemotherapy. All patients in this study were scheduled to undergo highly emetogenic, cisplatin-based chemotherapy for the first time.

A total of 2,322 patients were stratified by sex at randomization, and placebos for both intravenous fosaprepitant and oral aprepitant were used. The study agent was given as part of an antiemesis regimen that also included ondansetron and dexamethasone. The primary efficacy endpoint in this study was complete response—defined as no emesis and no need for rescue medication—during the overall risk period (the first 120 hours following chemotherapy initiation). Baseline characteristics were well distributed across treatment arms, with the most common cancers including lung tumors (46.9%), gastrointestinal tumors (21.4%), and reproductive or genitourinary cancers (15.1%).

A similar proportion of patients in the fosaprepitant and aprepitant arms achieved complete response (71.9% vs 72.3%; Figure 1). During the delayed CINV phase, specifically, the rates of complete response were similar between the fosaprepitant and aprepitant arms (74.3% vs 74.2%). An exploratory analysis found that the proportion of patients reporting no significant nausea during the overall risk period was also similar between treatment arms (70.1% vs 70.4%). Thus, a single, high-dose infusion of fosaprepitant was considered to be noninferior to a standard 3-day regimen of aprepitant for control of CINV during the overall risk period. In terms of safety, this study showed a modest increase in the number of patients who developed hypertension in the fosaprepitant arm versus the aprepitant arm; in contrast, patients treated with aprepitant had slightly higher rates of asthenia and anorexia. Based on these results, a single 150-mg intravenous dosage of fosaprepitant on Day 1 is included as a choice in the recommendations for CINV prevention in patients receiving high–emetic risk intravenous chemotherapy.

Evidence-Supported Antiemesis Recommendations

For prevention of CINV resulting from highly emetogenic intravenous chemotherapy, recommended prophylaxis consists of a 3-drug regimen comprised of a 5-HT_3 receptor antagonist (either dolasetron, granisetron, ondansetron, or palonosetron, with palonosetron preferred in all 3 guidelines), a steroid (dexamethasone), and an NK-1 receptor antagonist (either aprepitant or fosaprepitant).

For CINV prophylaxis in patients treated with moderately emetogenic intravenous chemotherapy, recommendations for antiemetic prophylaxis include a 5-HT_3 receptor antagonist (either dolasetron, granisetron, ondansetron, or palonosetron, with palonosetron preferred in the NCCN guidelines) plus dexamethasone on Day 1; in selected patients, an NK-1 receptor antagonist (either aprepitant or fosaprepitant) can also be added. On Days 2 and 3, patients should continue antiemetic prophylaxis with either a single-agent 5-HT_3 receptor antagonist (either dolasetron, granisetron, or ondansetron), dexamethasone monotherapy, or the NK-1 receptor antagonist aprepitant (in cases where either aprepitant or fosaprepitant was given on Day 1); this therapy can be administered with or without dexamethasone. However, there is little guidance regarding which cancer patients receiving moderately emetogenic chemotherapy should receive the 3-drug antiemesis regimen (including the NK-1 receptor antagonist) versus the 2-drug regimen.

For CINV prophylaxis in patients treated with intravenous chemotherapy that has a low risk of emesis, recommendations for antiemetic prophylaxis include dexamethasone, metoclopramide, or prochlorperazine. In all risk groups,

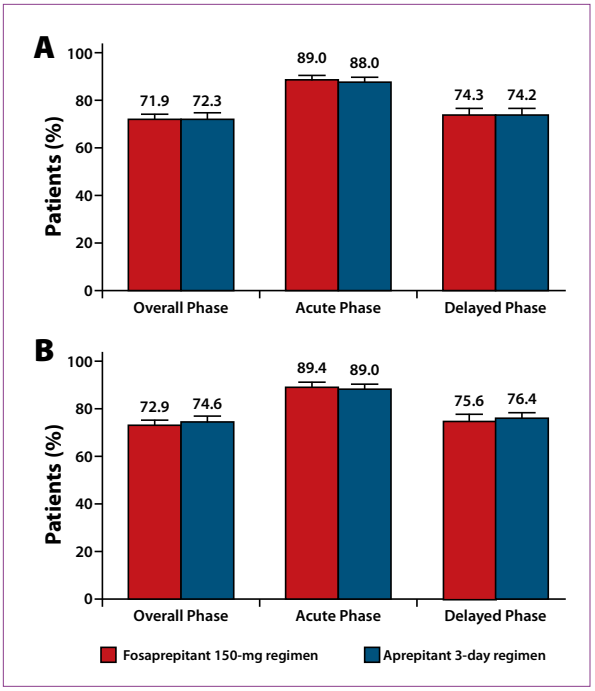

Figure 1. Complete response (**A**) and no vomiting (**B**) by phase.

Adapted from Grunberg S et al. *J Clin Oncol*. 2011;29:1495-1501.[12]

patients may additionally be treated with lorazepam and/or an H_2 receptor blocker or a proton pump inhibitor, as needed.

For patients receiving oral chemotherapy, the guidelines recommend the use of a 5-HT_3 receptor antagonist (either granisetron or ondansetron) if the chemotherapy drugs are associated with a high or moderate emetogenic risk. For oral chemotherapy agents with low or minimal emetogenic risk, CINV management should be incorporated as necessary, and may include metoclopramide, prochlorperazine, or haloperidol. Again, lorazepam and/or an H_2 receptor blocker or a proton pump inhibitor may also be incorporated into CINV prophylaxis strategies, as needed.

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Maximizing the Utility of Guidelines to Prevent Chemotherapy-Induced Nausea and Vomiting

Steven M. Grunberg, MD

For the clinician who is managing a patient with CINV, an important consideration is the contribution of CINV to the patient's overall morbidity. This assessment can be difficult, however, as the overall impact of CINV on a patient has both objective and subjective components. For example, in addition to causing nausea and vomiting, CINV can also cause the patient to have an overall poor outlook. Depending on the degree of CINV, patients may not participate in normal daily activities and/or family or social gatherings, which can significantly affect quality of life. Further, CINV is an important determinant of whether patients fear their cancer treatment, and such fear can potentially impact treatment adherence.

Impact of Nausea and Vomiting on Cancer Patients

One of the earliest studies to examine the impact of CINV on cancer patients was reported by Coates and colleagues.[1] This study surveyed 99 cancer patients and ranked their

perception of various side effects of chemotherapy. Nausea and vomiting were among the highest-ranking physical side effects of concern to these patients. Subsequent studies more extensively probed the impact of CINV on cancer patients receiving emetogenic chemotherapy. For example, Dubey and colleagues conducted a survey of 464 lung cancer patients and found that, if given the option, 73% of patients would select a chemotherapy regimen based on its side effect profile if the treatment would be equivalently effective.[2] Nearly half of the patients (48%) ranked nausea/vomiting as the most important side effect of chemotherapy.

In a small pilot study, 30 cancer patients who were completing a cycle of chemotherapy were asked to use a visual analogue scale to rate their global quality of life during their prior chemotherapy cycle, given the hypothetical presence or absence of CINV as the only variable.[3] On a 100-mm scale, the mean score was 79 mm for the quality of life during chemotherapy without associated CINV; the mean score dropped to 27 mm when CINV was present ($P<.001$). Sun and colleagues more formally measured the impact of CINV using a "time trade-off" technique; this decision analysis technique assesses how much of their remaining lifespan patients would be willing to sacrifice in order to avoid experiencing a particular toxicity—in this case, CINV.[4] This study found that patients were willing to give up approximately half of their remaining lifespan in order to avoid experiencing severe CINV (Figure 2). In comparison, these same patients were unwilling to give up any of their remaining lifespan to avoid alopecia.

The Functional Living Index–Emesis (FLIE) is a patient questionnaire designed to assess the impact of CINV on daily functioning during the 3–5 days following chemotherapy.[5,6] Some of the activities reported by patients that were negatively impacted by CINV included routine household tasks, enjoyment of meals, spending time with family and friends, ability to be substantively employed, and maintenance of daily activities and recreation.[7] When the FLIE questionnaire was used in a prospective evaluation of 178 cancer patients, 37.2% of patients reported reduced daily functioning due to CINV. Among those patients who had poorly managed CINV, approximately 90% reported a significant negative impact on their daily functioning.[8] Separately, the FLIE questionnaire was used to assess Italian cancer patients who were receiving cisplatin-based chemotherapy.[9] Overall, more than 90% of patients who experienced both acute and delayed CINV reported an impact on their daily functioning. Most recently, Hilarius and colleagues used the FLIE to show that nearly one third of cancer patients who reported CINV incurred a substantial impact on their daily lives.[10]

Reductions in quality of life and daily functioning are not the only effects of CINV. Burke and colleagues recently demonstrated that, during the first cycle of treatment with

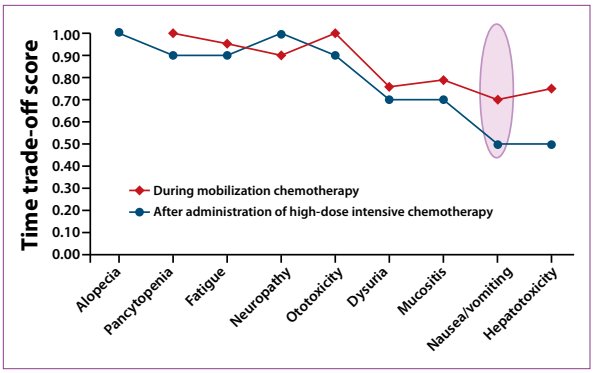

Figure 2. Median time–trade-off scores, which measure the relative value of life with a given toxicity compared to life without that toxicity.

Adapted from Sun CC et al. *Gynecol Oncol.* 2002;87:118-128.[4]

either high–emetic risk or moderate–emetic risk chemotherapy, healthcare utilization was both common and costly.[11] In this retrospective assessment, over half (64%) of CINV-associated healthcare visits were inpatient visits, with the remainder of CINV-associated healthcare visits being either outpatient visits (26%) or emergency room visits (10%). The average cost per patient for each type of healthcare visit was $7,448 for an inpatient visit, $1,494 for an outpatient visit, and $918 for an emergency room visit. Separately, Craver and colleagues reported that the average daily treatment cost across all outpatient healthcare settings was $1,854.[12]

Incorporating Guidelines into Patient Care

In a recent editorial, Stuebe noted that clinicians learn intellectually from Level 1 evidence, which is primarily comprised of randomized controlled clinical trials.[13] However, clinicians learn more profoundly from Level 4 evidence, such as anecdotes from colleagues and/or personal experience. Indeed, many of the barriers that limit incorporation of CINV guidelines into patient care are related to challenges in education of clinicians and/or poor communication between clinicians and their patients.

Mertens and colleagues studied adherence to the ASCO CINV guidelines and analyzed associated outcomes in a group of cancer patients who were receiving treatment at the Baystate Medical Center in Springfield, Massachusetts.[14] In this study, the majority of patients experienced delayed nausea that peaked on Day 3. While physicians followed most of the recommendations related to acute CINV prevention, the recommendations related to prevention of delayed CINV were largely not followed; only 25% of chemotherapy administrations were followed by postchemotherapy corticosteroids, and only 52% were followed by postchemotherapy treatment with a 5-HT_3 receptor antagonist. Another important finding from this study was that physicians' performance in terms of

Case 3

A 60-year-old female is diagnosed with stage IV, non–small cell lung cancer and is assigned to a chemotherapy regimen of carboplatin (AUC 6 on Day 1) plus paclitaxel (200 mg/m^2 on Day 1). Because of a risk of hypersensitivity reactions, paclitaxel requires preadministration of several medications, including a corticosteroid, a histamine receptor subtype 1 (H_1) antagonist (such as diphenhydramine), and a histamine receptor subtype 2 (H_2) antagonist. In this case, oral dexamethasone can be administered on Day 1 prior to treatment as part of both the antiemetic and hypersensitivity prophylactic regimens.

Carboplatin is generally considered to be a moderately emetogenic agent, although in some patients it may carry a higher risk of CINV. Thus, an NK-1 receptor antagonist may be added to the prophylactic antiemetic regimen, per the NCCN guidelines. For this patient, the following prophylactic antiemetic regimen is chosen:

- **Intravenous palonosetron (0.25 mg on Day 1)**
- **Dexamethasone (12 mg prior to paclitaxel on Day 1, 8 mg orally on Day 2, and 8 mg orally twice daily on Days 3 and 4)**
- **Intravenous fosaprepitant (150 mg on Day 1)**

After discussing the antiemetic regimen with the patient, she expresses concern about developing CINV despite prophylactic therapy. The oncologist gives the patient a prescription for prochlorperazine and also discusses the possibility of increasing the duration of dexamethasone. The oncologist also mentions that a cannabinoid, such as dronabinol or nabilone, could be used as an alternative therapy for breakthrough CINV. The patient is receptive to each of these options.

prescribing an adequate antiemetic regimen did not substantially change over a sustained period despite the use of multiple interventions to encourage adherence: guideline distribution, a lecture by a visiting expert, and sharing of adherence data with the physicians. However, once physicians were given information about the CINV outcomes of their own patients, they were more likely to accept the need for guideline compliance. When antiemetic prescribing by nurse practitioners was instituted, these prescriptions were nearly 100% guideline-compliant and were associated with a concomitant decrease in the incidence of chemotherapy-induced nausea on Day 3.

Another barrier to the incorporation of guidelines is that physicians may underestimate the prevalence and impact of CINV in their cancer patients. This lack of awareness was illustrated by a prospective observational study that surveyed 298 patients who were undergoing chemotherapy treatment for the first time and 24 of their physicians and nurses.[15] Although clinician predictions of the incidence of acute CINV were accurate, over three quarters of clinicians underestimated the incidence of delayed CINV in their patients (Figure 3).

Lack of awareness regarding the true impact of CINV may be attributed, at least in part, to difficulties in efficient communication between clinicians and patients. Salsman and colleagues interviewed both patients and their physicians to evaluate communications-related obstacles that presented barriers to the implementation of antiemetic guidelines.[16] One key area of agreement between patients and physicians involved a desire to minimize the number of agents prescribed in order to reduce the complexity of the antiemetic regimen

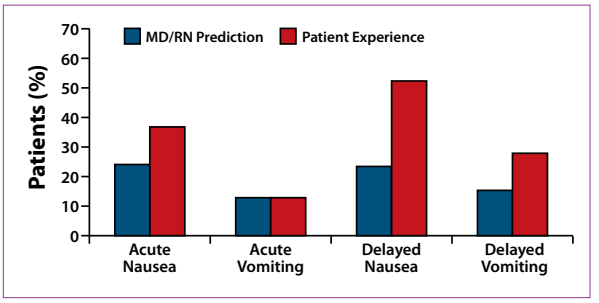

Figure 3. Differences between clinicians' predictions and patients' experience of chemotherapy-induced nausea and vomiting with moderately emetogenic chemotherapy.

Adapted from Grunberg SM et al. *Cancer*. 2002;100:2261-2268.[15]

and make the regimen easier for patients to understand. While the idea of simplifying a regimen is attractive, it should not come at the cost of reduced efficacy.

Another finding was that many patients believed that the presence of CINV indicated that their chemotherapy was working; somewhat disturbingly, a fair number of physicians shared this belief. The prevalence of such a misconception among physicians is unacceptable, as clinicians should realize that CINV is not necessary for the efficacy of anticancer treatment. If both physicians and their patients share this misconception, however, they will be less likely to try to mitigate this side effect.

An important disparity between the patients and their physicians related to patients' tendency to complain about CINV. Patients reported that they wanted to appear "strong" for their physicians and did not want to complain about the side effects of chemotherapy for fear that the

physician would reduce or discontinue their potentially life-saving treatment. However, physicians interpreted this lack of complaint to mean that the patient was doing fine with treatment and was not troubled by CINV.

Given these barriers, systematic adoption of CINV guidelines could provide a significant benefit. One of the best strategies to encourage widespread adoption of CINV guidelines is to incorporate a guideline into the medical record as an easy-to-complete form. Preprinted guidelines that must be modified by choice are probably the most effective way to ensure that guidelines are followed as part of the initial treatment plan. While providing a uniform template, such preprinted guidelines should be adaptable so that they can be modified for individual patients, as needed.

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Tailoring Antiemetic Therapy to Specific Patients

Gary R. Morrow, PhD, MS

Several types of CINV have been defined according to when symptoms occur in relation to the timing of chemotherapy administration: acute CINV, delayed CINV, and anticipatory CINV. (Another term related to CINV is "breakthrough" CINV, which refers to CINV that occurs despite the use of prophylactic antiemesis; these patients often require rescue with alternative strategies.) Recognizing the distinction between different types of CINV is important, as different treatments are used for each. Depending on the type of CINV, treatments could involve different classes of drugs, expectancy manipulation, and/or nontraditional treatments.

Acute CINV is the type of CINV that is probably most familiar to clinicians and patients; it is typically associated with rapid onset of symptoms, generally within the first few minutes to hours, but it can occur any time up to 24 hours following chemotherapy administration. The intensity of symptoms typically peaks at 5–6 hours following treatment. The delayed phase of CINV begins after completion of the acute CINV phase; delayed CINV peaks at 48–72 hours and can last up to 7 days in some cases.

Finally, anticipatory CINV is considered to be a conditioned behavioral response that results from a prior CINV experience; anticipatory CINV can occur prior to the start of a new round of chemotherapy in patients who have experienced either delayed or acute CINV in previous round(s) of treatment. Just as with classical or Pavlovian conditioning, some stimulus connected with treatment sets off the unwelcome response to treatment prior to a given treatment.

The expectation or anticipation of CINV is an important topic that should be addressed with all patients, especially new or chemotherapy-naïve cancer patients who may have unrealistically negative expectations regarding

the severity of CINV they are likely to experience. A realistic but optimistic appraisal should be offered, reflecting the substantial armamentarium of prevention and treatment strategies now available for CINV.

Special Considerations for Chemotherapy-Induced Nausea

Although related, vomiting and nausea occur at different frequencies in cancer patients.[1,2] Specifically, chemotherapy-induced nausea occurs with greater frequency than chemotherapy-induced vomiting.[3-5] One prospective observational study showed that nearly 3-fold more patients experienced acute nausea than acute emesis (35% vs 13%).[4] While the underlying reason for this difference in incidence is not well understood, it is likely due to the different pathophysiologic mechanisms responsible for emesis versus nausea. In addition, certain patients are more likely to experience nausea than others; for example, younger patients (especially younger breast cancer patients) are more prone to nausea than older patients.[6]

While control of chemotherapy-induced emesis has unquestionably been advanced over the years through the use of multiple agents—specifically the 5-HT_3 and NK-1 receptor antagonists—a steady improvement in management of chemotherapy-induced nausea is less apparent. Thus, nausea remains a significant side effect of chemotherapy, especially in the delayed phase; compared with acute nausea, delayed nausea is typically more common, more severe, and more resistant to treatment.[5]

Paradigm Shifts Have Contributed to Better Management of Nausea and Vomiting

In addition to the novel agents that have received US Food and Drug Administration approval for management of CINV, 3 major shifts in the treatment paradigm for CINV have occurred over the past 3 decades. These paradigm shifts have made large contributions to improved patient satisfaction and control of CINV.

The first of these paradigm shifts is the concept that, while treatment of CINV is not particularly effective, prevention of CINV can be quite effective. Thus, prevention of CINV is considered to be the goal in cancer patients. The risk of CINV continues for up to 5 days following chemotherapy (covering the acute and delayed phases), and patients need to be fully protected throughout this entire risk period.

The second major paradigm shift relates to the fact that not all chemotherapeutic agents have the same emetogenic potential. This understanding was greatly advanced when the 3 major CINV guidelines accepted a shared classification scheme that divides chemotherapy agents according to their risk for emesis in the absence of prophylaxis (high, moderate, low, and minimal).

The third major paradigm shift relates to the understanding that not all patients are the same when it comes to the risk for developing CINV. For example, younger patients are more prone to experience chemotherapy-induced vomiting compared with older patients. Similarly, females are more likely than males to have chemotherapy-induced vomiting. A lack of history with alcohol is also associated with a higher likelihood for emesis.

In a study examining the likelihood of CINV, Pollera and colleagues identified significant prognostic variables from 209 cancer patients who were enrolled in separate prospective randomized trials of antiemesis regimens.[7] In this analysis, 3 factors were found to be significantly prognostic for the development of chemotherapy-induced emesis: sex (P=.0001), ECOG performance status (P=.006), and age (P=.01). Importantly, these patient characteristics were significantly prognostic regardless of the antiemetic regimen used.

In a larger study of 832 patients, Osoba and colleagues showed in a multivariate analysis that several factors were associated with CINV; these factors included female sex, the presence of nausea prior to chemotherapy, and low social functioning.[8] Fatigue and dyspnea were significantly associated with only postchemotherapy nausea, while ECOG performance status, the emetogenic risk of the chemotherapy, maintenance antiemetics, and low alcohol consumption were significantly associated with only postchemotherapy vomiting. The factors identified in this multivariate analysis were then incorporated into a predictive model for CINV. When compared to patients who had none of the 7 risk factors for postchemotherapy nausea, this model estimated a 30% increase in the incidence of nausea among patients with 6 risk factors (66.7% vs 96.2%, respectively). Compared to patients who had none of the 6 risk factors identified for postchemotherapy emesis, the risk for patients with 4 risk factors increased over 50% (20.0% vs 75.7%, respectively).

Nontraditional Approaches to Management of Nausea and Vomiting

In addition to the antiemetic drugs previously discussed, a number of nontraditional strategies have been attempted as alternatives for CINV control (Table 2). Most of these nontraditional strategies have come about as a result of patients trying them—often out of desperation—after finding information about these treatments through their own research, from family and friends, or from previous patients. Several of these approaches have been evaluated, at least to a certain extent, via scientific observations and controlled studies.

Table 2. Nontraditional Therapies for Chemotherapy-Induced Nausea and Vomiting

Ginger	Can be consumed as gingersnaps, ginger tea, or ginger pills Found to be effective for reduction of acute nausea[9]
Physical interventions	Acustimulation bands found to perform markedly better in males versus females[10] Acupressure bands can have a reasonable effect for the control of chemotherapy-induced nausea[11]
Other nontraditional therapies	Acupuncture found to reduce the incidence of acute chemotherapy-induced emesis[13] Cannabinoids and cannabinoid extracts may be effective in some patients

One of the more popular nontraditional treatments is ginger, which can be consumed in various forms, including gingersnaps, ginger tea, and ginger pills. A large, double-blind, multicenter clinical trial was recently completed in which 744 cancer patients were randomized to 1 of 4 treatments: placebo or ginger (0.5 g, 1.0 g, or 1.5 g) administered in pill form.[9] The pills were administered starting 3 days prior to initiation of chemotherapy, and all patients also received a 5-HT_3 receptor antagonist on Day 1 of all chemotherapy treatment cycles. A final analysis involving 576 patients demonstrated that all 3 doses of ginger significantly reduced the severity of acute nausea (on Day 1) compared to placebo (P=.003).

Certain physical interventions also have been studied to determine their effectiveness against CINV. For example, studies have evaluated acupressure and electrical stimulation, both of which can be provided via wristbands that patients begin wearing prior to treatment. The electrical forms of this modality, known as acustimulation bands, performed markedly better in males versus females.[10] Acupressure bands, such as those sold in drug stores as a remedy for motion sickness, also can have a reasonable effect for the control of chemotherapy-induced nausea.[11] A 3-arm randomized trial reported a 23.8% decrease in nausea among patients who wore acupressure bands versus those who did not.[12]

Many other nontraditional approaches have also been tried for management of CINV, and some of these approaches may be modestly effective in certain patients. A recent meta-analysis showed that acupuncture significantly reduced the incidence of acute chemotherapy-induced emesis but not acute chemotherapy-induced nausea or delayed CINV.[13] Finally, cannabinoids and cannabinoid extracts may also be an effective alternative for some patients.[14]

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Discussion: Incorporating CINV Guidelines into Clinical Practice

H&O Should chemotherapy-induced nausea and vomiting be considered together or separately?

Steven M. Grunberg, MD As the CINV field moves forward, I think there is a definite need to stop considering chemotherapy-induced nausea together with chemotherapy-induced emesis; this would represent another important paradigm shift in the management of CINV.

Gary R. Morrow, PhD, MS I agree that we should consider nausea and vomiting as separate conditions. In the future, it may make more sense to issue separate recommendations guiding the prevention and treatment of each, rather than addressing both in the same guideline.

H&O How is anorexia related to nausea in cancer patients?

SMG Many of the chemotherapeutic agents believed to have efficacy against nausea also have some effect for cancer-related anorexia and cachexia. This finding has led to the idea that nausea and anorexia should be considered together, rather than considering nausea together with emesis. Perhaps by considering anorexia and nausea together, our understanding of each could be advanced and more agents could be identified that would be effective in both conditions.

H&O Why do patients who have more experience with alcohol prior to initiating chemotherapy demonstrate lower levels of CINV?

GRM The protective effect that seems to be associated with prior alcohol use is very curious. However, there are little data providing any biologic underpinnings to this relationship. Some investigators have speculated that heavy alcohol drinkers may have over-activated dopamine receptors in the gut, thus causing them to be less sensitive to the influence of chemotherapy. Related to this hypothesis is the thought that some individuals may express lower levels of these receptors, which would also affect their ability to be affected by chemotherapy.

Lee S. Schwartzberg, MD, FACP There is also some evidence suggesting that chronic alcohol consumption causes substantive anatomical changes in brain structure; because the central nervous system is a critical component in the development of both nausea and vomiting, this change may be another reason for the association between heavy alcohol use and reduced CINV.

H&O How does the availability of the updated CINV guidelines help to improve patient care?

LSS CINV guidelines are important in that they provide a consensus document describing the recommendations for management of CINV, and they describe the clinical trial evidence supporting these recommendations. By listing and describing the major studies that have led to the approval and use of certain antiemesis regimens, these guidelines have the potential to save clinicians an enormous amount of time. However, readers must understand that guidelines should only serve as a starting point in the prevention and management of CINV.

In addition, guidelines can only be useful if they are actually implemented in routine clinical practice. While different strategies may be used to adapt these guidelines to clinical practice, at the heart of the implementation should be a systematic approach to evaluating patients' risk for CINV and a consistent procedure for developing prevention and treatment strategies. Finally, while guidelines are effective for a large number of patients, many patients will require individualization of these antiemesis strategies to achieve optimal control.

SMG ASCO's Quality Oncology Practice Initiative (QOPI) is an oncologist-led, practice-based improvement program that helps practices to create a culture of self-examination and improvement. The QOPI criteria may be helpful for practices seeking to implement these antiemesis guidelines.

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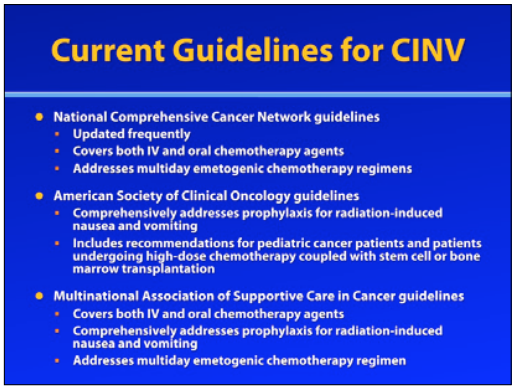

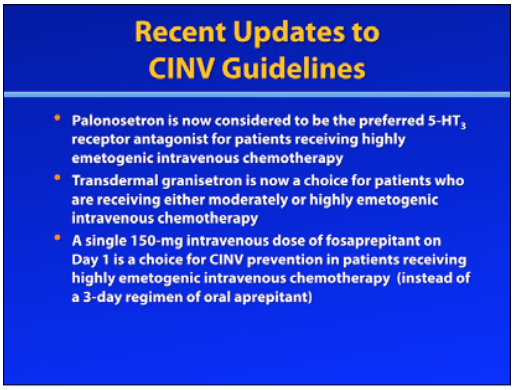

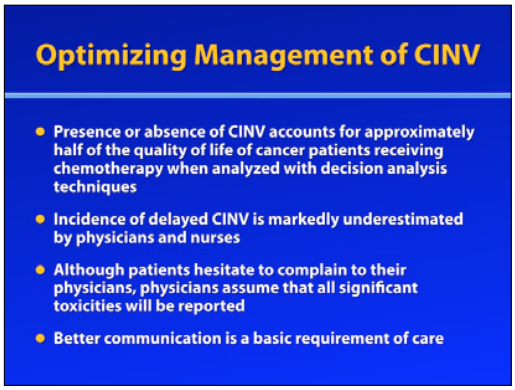

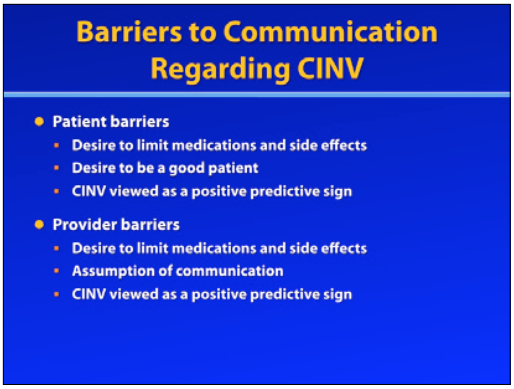

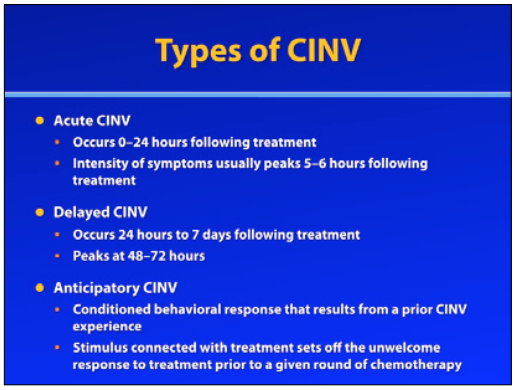

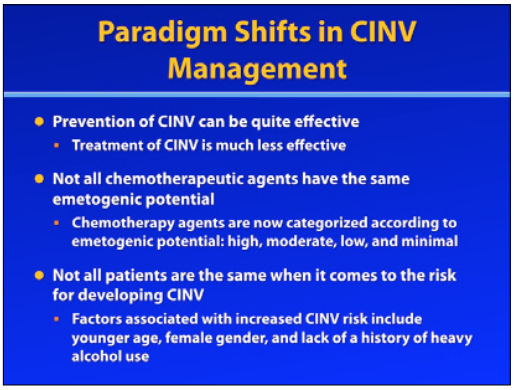

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Cases in the Management of Chemotherapy-Induced Nausea and Vomiting: Integrating Updated Guidelines into Clinical Practice

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

1. Of the 3 major CINV guidelines used by US physicians, which is updated most frequently?

   a. The National Comprehensive Cancer Network (NCCN) guidelines
   b. The American Society of Clinical Oncology (ASCO) guidelines
   c. The Multinational Association of Supportive Care in Cancer (MASCC) guidelines
   d. The NCCN, ASCO, and MASCC guidelines are all updated annually.

2. In the study by Saito and colleagues, how did the palonosetron-based antiemetic regimen compare to the granisetron-based antiemetic regimen?

   a. The 2 regimens were equally effective for both acute and delayed CINV.
   b. The palonosetron-based regimen was superior for both acute and delayed CINV.
   c. The 2 regimens were equally effective for acute CINV, but the palonosetron-based regimen was superior for control of delayed CINV.
   d. The 2 regimens were equally effective for acute CINV, but the granisetron-based regimen was superior for control of delayed CINV.

3. In the trial by Boccia and coauthors, what was the most common treatment-related adverse event associated with granisetron?

   a. Rash
   b. Constipation
   c. Diarrhea
   d. Hypertension

4. In the study by Grunberg and colleagues, how did intravenous fosaprepitant compare to a 3-day regimen of oral aprepitant?

   a. Intravenous fosaprepitant was superior for both acute and delayed CINV.
   b. The 3-day regimen of oral aprepitant was superior for both acute and delayed CINV.
   c. Both regimens were effective for acute CINV, but the 3-day regimen of oral aprepitant was superior for delayed CINV.
   d. Intravenous fosaprepitant was noninferior to the 3-day regimen of oral aprepitant for control of CINV over the first 120 hours following chemotherapy.

5. Of the 464 lung cancer patients surveyed by Dubey and colleagues, what percentage said they would select a chemotherapy regimen based on its side effect profile if the treatment would be equivalently effective?

   a. 19%
   b. 50%
   c. 73%
   d. 95%

6. In the study by Sun and colleagues, how much of their remaining lifespan did patients say they would be willing to give up in order to avoid experiencing severe CINV?

   a. One quarter
   b. One third
   c. One half
   d. Two thirds

7. In the study by Salsman and coauthors, which of the following beliefs differed between patients and physicians?

   a. Desire to minimize the number of agents prescribed in order to reduce the complexity of the antiemetic regimen
   b. Belief that the presence of CINV indicated that the patient's chemotherapy was working
   c. Belief that all side effects of chemotherapy were being reported to the physician
   d. Recognition that CINV was a common side effect of chemotherapy

8. Which of the following factors does NOT increase a patient's risk of experiencing CINV?

   a. Female gender
   b. Younger age
   c. History of alcohol use
   d. Administration of cisplatin-based chemotherapy

9. In the study by Osoba and colleagues, which factor was NOT associated with postchemotherapy vomiting?

   a. Fatigue
   b. ECOG performance status
   c. Maintenance antiemetics
   d. Low alcohol consumption

10. What was the outcome of the study by Ryan and colleagues in which ginger was studied as a nontraditional treatment for CINV?

    a. Ginger was not found to be effective for the management of acute nausea compared to placebo.
    b. Only the 1.5-g dose of ginger yielded a significant reduction in acute nausea compared to placebo.
    c. All 3 doses of ginger (0.5 g, 1.0 g, and 1.5 g) significantly reduced the severity of acute nausea compared to placebo.
    d. All 3 doses of ginger (0.5 g, 1.0 g, and 1.5 g) significantly reduced the severity of both acute and delayed nausea compared to placebo.

Project ID: 8800

Evaluation Form: Cases in the Management of Chemotherapy-Induced Nausea and Vomiting: Integrating Updated Guidelines into Clinical Practice

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. ***You must complete this evaluation form to receive acknowledgment for completing this activity.***

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Describe recent clinical trial data in the management of chemotherapy-induced nausea and vomiting (CINV)	1 2 3 4 5
2. Identify updates to the latest CINV guidelines	1 2 3 4 5
3. Devise personalized CINV management strategies	1 2 3 4 5
4. Identify future research directions in the management of CINV	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.
❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice? _____

_____

How confident are you that you will be able to make this change?
❒ Very confident ❒ Unsure
❒ Somewhat confident ❒ Not very confident

What barriers do you see to making a change in your practice? _____

_____

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

Handout materials were useful: ❒ Yes ❒ No ❒ No handouts for this activity

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

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

_____

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 8800**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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For Physicians Only: I certify my actual time spent to complete this educational activity to be:
❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.