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Advances in the Management of Chemotherapy-Induced Nausea and Vomiting: New Data From Recent and Ongoing Trials

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) is among the most feared and debilitating adverse events experienced by cancer patients. Left unaddressed, CINV symptoms not only decrease quality of life, but may also affect patients' willingness to continue chemotherapy treatment. Detailed guidelines are available that outline best practices for prophylaxis of acute and delayed CINV. However, adherence to guideline recommendations continues to be suboptimal, and many patients still suffer unnecessarily from CINV. In addition, breakthrough/refractory CINV continues to present particular challenges. The development of effective CINV treatments with diverse mechanisms of action has expanded the options available for preventing symptoms. The US Food and Drug Administration has recently approved several new therapies for the management of CINV. NEPA is a fixed-dose combination of netupitant (300 mg) plus palonosetron (0.5 mg). In combination with dexamethasone, NEPA has demonstrated superior efficacy to palonosetron alone in patients receiving highly or moderately emetogenic chemotherapy. Rolapitant is a next-generation neurokinin 1 (NK_1) receptor antagonist. Both palonosetron and rolapitant have proven particularly effective in controlling delayed CINV. Regimens that combine a serotonin 5-hydroxytryptamine–3 receptor antagonist, an NK_1 receptor antagonist, and a corticosteroid now represent the standard of care for managing both acute and delayed CINV in patients receiving highly emetogenic chemotherapy.

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Target Audience

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

Statement of Need/Program Overview

Chemotherapy-induced nausea and vomiting (CINV) is among the most feared and debilitating adverse events experienced by cancer patients. Symptoms not only decrease quality of life, but may also lead patients to delay or postpone chemotherapy. Patients must be educated regarding CINV management before they begin chemotherapy and then asked about specific symptoms after treatment. Options for prevention and treatment of CINV are based on the emetogenic risk of the chemotherapy and the type of CINV (acute, delayed, anticipatory, or breakthrough/refractory). The US Food and Drug Administration has recently approved new therapies for the management of CINV. NEPA is a fixed-dose combination of netupitant plus palonosetron. In combination with dexamethasone, NEPA has demonstrated superior efficacy over palonosetron alone in patients receiving highly or moderately emetogenic chemotherapy. Rolapitant is a next-generation neurokinin 1 receptor antagonist. Both palonosetron and rolapitant have proven particularly effective in controlling delayed CINV. Detailed management guidelines, with recommendations based on data from phase 3 clinical trials, provide effective approaches for prevention and treatment. Adherence to guidelines is suboptimal but can be improved with the use of programs incorporating provider education sessions, monthly audit-feedback sessions, and risk assessment tools.

Educational Objectives

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

- Describe the impact, incidence, and risk factors of CINV
- Distinguish chemotherapy regimens with high, moderate, and low emetogenic risk
- Implement strategies for CINV prevention and management based on recommendations from guidelines
- Evaluate the efficacy and safety data supporting the use of approved antiemetic agents in the prevention of CINV
- Assess results from recent and ongoing clinical trials in CINV management

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Guiding Principles in the Management of Chemotherapy-Induced Nausea and Vomiting

Eric Roeland, MD

Chemotherapy-induced nausea and vomiting (CINV) continues to be a major concern for patients undergoing chemotherapy. In the past 2 decades, significant progress has been made in developing effective drugs that can prevent or mitigate CINV. It is important for oncologists to proactively anticipate CINV and to educate patients regarding the availability and efficacy of these agents.

Depending on the timing of onset and the cause of occurrence, CINV is categorized as acute, delayed, anticipatory, or breakthrough/refractory. Acute CINV occurs within 24 hours of administration of chemotherapy, and delayed CINV occurs during days 2 to 5 after treatment. Anticipatory CINV is nausea and/or vomiting triggered by the expectation of receiving chemotherapy.[1] It can arise from various stimuli associated with treatment, including driving past the cancer center or even thinking about a chemotherapy session. Low-dose benzodiazepines are effective in treating this type of CINV.

Chemotherapy-induced emetogenesis occurs primarily through the peripheral or central pathways that stimulate the vomiting center.[2] The peripheral pathway includes the gut and the vagal afferent pathway. Its activity is mediated primarily by serotonin receptors on the vagus nerve. The peripheral pathway is mostly involved in mediating acute CINV. The central pathway is located primarily in the brain and includes the chemoreceptor trigger zone and vestibular centers. It is associated with delayed-onset CINV. The central pathway contains receptors for several neurotransmitters, including substance P, which is closely related to neurokinin 1 (NK_1); histamine; and serotonin. Many therapies for CINV modulate the activity of these receptors.

Consensus guidelines that describe best practices for the prophylaxis and treatment of CINV are available from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the Multinational Association of Supportive Care and Cancer/European Society for Medical Oncology (MASCC/ESMO).[3-5] Chemotherapeutic drugs are categorized by emetogenic risk (Table 1). Highly emetogenic therapies induce nausea and/or emesis in more than 90% of patients, moderately emetogenic therapies induce nausea and/or emesis in 30% to 90% of patients, and chemotherapies with a low risk induce nausea and/or emesis in 10% to 30% of patients.

Table 1. Emetic Risk of Common Therapies

High Emetogenic Risk
Cyclophosphamide plus an anthracycline Cisplatin (high doses)
Moderate Emetogenic Risk
Cyclophosphamide Carboplatin Irinotecan
Low Emetogenic Risk
Fluorouracil Paclitaxel Docetaxel Targeted antibodies

Patient factors also affect the incidence of CINV. CINV is more likely to occur in patients younger than 50 years and in women.[6,7] Patients with a history of motion sickness, low alcohol intake, or severe nausea and vomiting associated with pregnancy also have a higher incidence of CINV. These patients can be challenging to treat, but they often benefit from the addition of a third antiemetic agent to the prophylactic regimen.

Risk-Based Treatment

Prophylactic treatment is recommended for patients receiving chemotherapy with high or moderate emetogenic risk. Patients receiving highly emetogenic therapies are treated with triple therapy, which includes a serotonin 5-hydroxytryptamine–3 ($5\text{-}HT_3$) receptor antagonist in combination with an NK_1 antagonist and a corticosteroid, usually dexamethasone. For example, among women receiving cisplatin-based chemotherapies or combinations of doxorubicin and cyclophosphamide, the 3-drug antiemetic combinations are essential. For moderately emetogenic chemotherapy, patients should receive a $5\text{-}HT_3$ antagonist and a corticosteroid. For chemotherapies associated with a low risk, prophylactic treatment is usually not advised; instead, patients are treated based on symptoms.

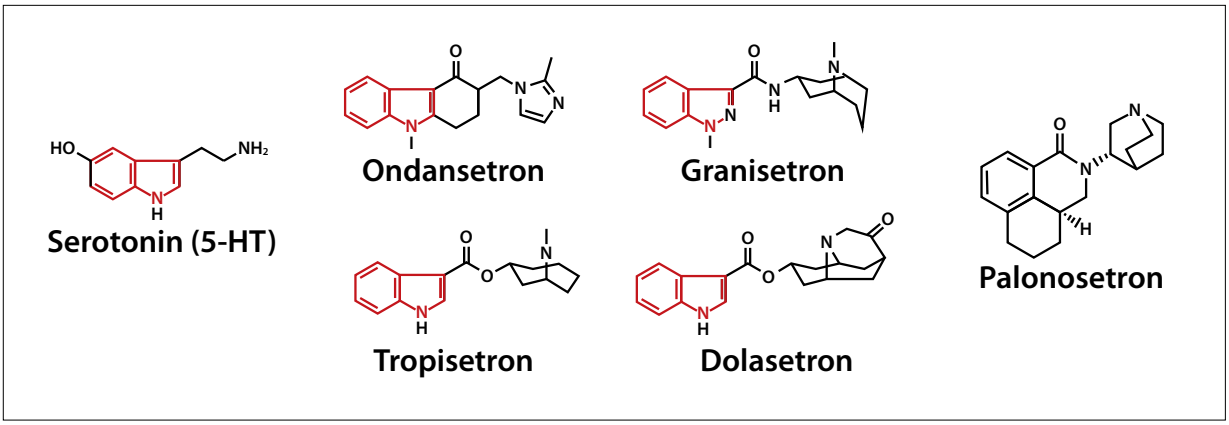

Figure 1. Chemical structures of serotonin (also known as 5-hydroxytryptamine [5-HT]) and the 5-HT_3 receptor antagonists. Palonosetron is a second-generation antagonist.

Dolasetron mesylate, granisetron, ondansetron, and palonosetron are 5-HT_3 receptor antagonists and have been a mainstay of CINV therapy, starting with approval of ondansetron by the US Food and Drug Administration (FDA) in 1991 (Figure 1). They are particularly effective in controlling acute emesis. A recently developed intranasal formulation of granisetron showed drug release for up to 3 hours in vitro, and it may provide a more convenient delivery method.[8] Palonosetron is a second-generation antagonist of the 5-HT_3 receptor.[9,10] It has a half-life of approximately 40 hours and binds to the 5-HT_3 receptor with a much greater affinity than its predecessors. It is thought that palonosetron prevents emesis by inhibiting the binding of serotonin to 5-HT_3 receptors peripherally, in the vagus in the gastrointestinal tract, and centrally, in the chemoreceptor trigger zone. After palonosetron binds to the 5-HT_3 receptor, the complex is internalized, further contributing to the prolonged inhibition of serotonin signaling.

Despite its longer plasma half-life and tighter binding affinity, palonosetron has demonstrated an acceptable safety profile. A phase 3 trial of 570 patients receiving moderately emetogenic chemotherapy compared single doses of palonosetron (0.25 mg or 0.75 mg) with ondansetron.[11] The most common treatment-related adverse events (AEs) associated with palonosetron were headache (5%), constipation (2%-3%), and dizziness (0%-1%). Dose adjustments are generally not required for elderly patients or those with renal or hepatic impairment. The NCCN guidelines list palonosetron as the preferred 5-HT_3 receptor antagonist for patients receiving intravenous chemotherapy with a moderate emetic risk.[3]

Breakthrough and Refractory CINV

Despite the progress seen with the use of new antiemetic agents, approximately one-third of patients receiving moderately or highly emetogenic chemotherapy develop breakthrough CINV, which occurs despite antiemetic prophylaxis.[12] One approach to the management of breakthrough CINV involves the use of a drug from a different class than the ones in the patient's previous treatment regimen. Refractory CINV occurs when patients develop symptoms despite medication, but the term is used inconsistently in the literature.[3,13] It can be defined as CINV that occurs after the first cycle of chemotherapy despite guideline-based prophylaxis and after first-line rescue medication (eg, a dopamine receptor antagonist, a corticosteroid, and/or benzodiazepine) has failed to control symptoms. Refractory CINV is a particularly vexing problem because these patients experience persistent symptoms despite receiving guideline-based prophylaxis.

A double-blind, randomized phase 3 study compared olanzapine vs metoclopramide for the treatment of breakthrough CINV in patients receiving highly emetogenic chemotherapy.[14] Prophylactic CINV treatment consisted of dexamethasone (12 mg), palonosetron (0.25 mg), and fosaprepitant (150 mg) administered before chemotherapy on day 1 of the treatment cycle, followed by dexamethasone (4 mg twice daily) administered on days 2 through 4. Patients who developed breakthrough CINV were randomized to receive olanzapine (10 mg daily) for 3 days or metoclopramide (10 mg 3 times daily) for 3 days. Patients were monitored for emesis and nausea for 72 hours after taking breakthrough medication. During the 72-hour observation period, 39 of 56 patients (70%) who received olanzapine were free of emesis compared with 16 of 52 patients (31%) who received metoclopramide ($P<.01$). The proportion of patients without nausea was also superior for patients taking olanzapine vs metoclopramide (68% vs 23%; $P<.01$).

Nausea: A Continuing Concern

Between the CINV symptoms, vomiting has received more attention owing to the violent nature of the experience and because it is easier to observe and measure. However, nau-

sea is a greater concern for many patients because it can be incapacitating and long-lasting. The subjectivity of nausea has led to the use of validated questionnaires to capture patient-reported outcomes. These tools can be used to identify the occurrence of nausea and to measure the efficacy of interventions. The Functional Living Index for Emesis (FLIE) is a patient-reported questionnaire that measures the impact of CINV on patients' daily quality of life. It was originally developed to assess the impact of CINV during the 3 days after administration of chemotherapy and has subsequently been validated for 5-day recall.[15,16] The FLIE can thus capture the impact of acute and delayed CINV. Alternatively, the MASCC Antiemesis Tool (MAT) is an 8-item scale for the assessment of acute and delayed CINV that is completed once during each cycle of chemotherapy. It is slightly shorter than the FLIE, is more convenient for patients, and includes the 24-hour recall period.

Despite the availability of extensive consensus treatment guidelines, compliance rates among oncologists are suboptimal. In a study of patients with malignant glioma who were receiving moderately emetic chemotherapy, provider adherence to treatment guidelines at baseline was only 58%.[17] Therefore, despite the availability of detailed treatment guidelines, many patients continue to experience CINV. Asking patients specific questions and listening attentively to their answers can elicit important details, thereby enabling providers to recommend appropriate treatment.

Disclosure

Dr Roeland is a member of the speakers bureaus of Teva and Eisai; the Data Safety Monitoring Board of Cellceutix; and the advisory boards of Eisai, Inform Genomics, and Helsinn. He has performed consulting for Eisai.

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Management of Chemotherapy-Induced Nausea and Vomiting: A Review of Current Data

Matti S. Aapro, MD

Nausea is a common AE associated with chemotherapy and a major concern of cancer patients. The armamentarium of antiemetic drugs has expanded considerably during the previous 2 decades, with the addition of numerous new agents that target a variety of physiologic pathways. Prophylactic regimens to prevent CINV have included a corticosteroid plus a 5-HT_3 antagonist since the development of the latter class of drugs in the 1990s. The last decade has seen the emergence of a new class of antiemetics designed to inhibit activity of the NK_1 receptor. These drug classes each employ a different mechanism of action to control CINV.

Aprepitant, fosaprepitant, netupitant, and rolapitant attenuate the activity of the NK_1 receptor.[1] Aprepitant is an oral agent that selectively blocks binding of substance P to the NK_1 receptor. In patients receiving highly emetogenic, cisplatin-based chemotherapy, the addition of aprepitant to the dual therapy consisting of a corticosteroid and a 5-HT_3 receptor antagonist improved outcome compared with the dual therapy alone and was generally well tolerated.[2] This 3-drug combination is recommended in the current consensus treatment guidelines for controlling CINV in patients receiving highly emetogenic chemotherapy.[3-5]

Fosaprepitant is a parenteral, water-soluble prodrug of aprepitant. After intravenous administration, fosaprepitant is rapidly converted to aprepitant. A 1-day dosing schedule for fosaprepitant (150 mg) was approved by the FDA in 2010, based on the demonstration of its equivalence with 3-day dosing of aprepitant in preventing CINV in the 120 hours after administration of cisplatin-containing chemotherapy.[6]

Netupitant is a highly selective NK_1 receptor antagonist that has demonstrated efficacy in controlling delayed CINV symptoms. It has a dose-dependent ability to inhibit the substance P response by NK_1 receptors in vitro.[7] The combination of netupitant and palonosetron has demonstrated a synergistic ability to inhibit the substance P response. Netupitant (300 mg) has been combined with palonosetron (0.5 mg) into a single capsule, known as NEPA.[8-10] The single-capsule coformulation of these 2 drugs provides a more convenient option for patients and has demonstrated sustained activity throughout several treatment cycles.[10]

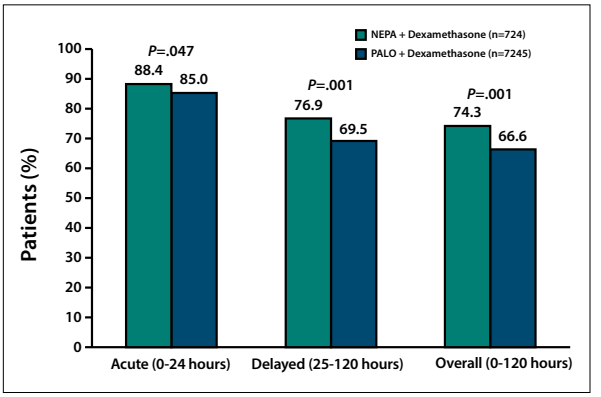

Figure 2. Rates of complete response among patients receiving moderately emetogenic chemotherapy who were randomized to NEPA or palonosetron (palo), both with dexamethasone, in a phase 3 trial. Complete response was defined as no emesis or no use of rescue medication. Adapted from Aapro M et al. *Ann Oncol.* 2014;25(7):1328-1333.[8]

A randomized phase 3 trial investigated the efficacy of NEPA vs palonosetron in preventing CINV in patients receiving moderately emetogenic chemotherapy containing cyclophosphamide plus either doxorubicin or epirubicin.[8] This multinational, double-blind, parallel group trial included 1455 chemotherapy-naive patients. All patients received oral dexamethasone on day 1 (12 mg in the NEPA arm and 20 mg in the palonosetron arm). Patients were randomized to receive a single oral dose of NEPA (300 mg netupitant/0.5 mg palonosetron) or a single oral dose of palonosetron (0.5 mg). The primary efficacy endpoint was the first treatment cycle rate of complete response (CR), defined as no emesis and no rescue medication during the delayed phase, occurring from hours 25 through 120. The rate of CR was significantly improved in patients who received NEPA during the delayed CINV phase (76.9% vs 69.5%; *P*=.001), the overall phase (74.3% vs 66.6%; *P*=.001), and the acute phase (88.4% vs 85.0%; *P*=.047; Figure 2).

A separate phase 3 study investigated the safety and efficacy of NEPA throughout multiple cycles of highly (24%) or moderately (76%) emetogenic chemotherapy.[10] The multinational, double-blind phase 3 study random-

ized 413 chemotherapy-naive patients in a 3:1 ratio to receive either a single oral dose of NEPA (300 mg netupitant/0.5 mg palonosetron) given on day 1 with dexamethasone or oral, 3-day aprepitant plus palonosetron and dexamethasone. In the NEPA group, constipation and headache were observed in 3.6% and 1.0% of patients, respectively, with no apparent increase in AEs throughout multiple cycles. The majority of AEs were of mild or moderate severity, with 2 patients experiencing serious events related to treatment. The overall CR rates, evaluated through 120 hours after treatment administration, were 81% for NEPA and 76% for aprepitant plus palonosetron. Efficacy was maintained throughout repeated cycles.

Rolapitant also inhibits the NK_1 receptor. It has long-lasting activity and does not interact with the CYP3A4 pathway, which allows a reduction in the dose of corticosteroids in some settings. A study of 454 patients evaluated rolapitant doses ranging from 9 mg to 180 mg, in combination with ondansetron and dexamethasone, in patients receiving highly emetogenic chemotherapy regimens containing cisplatin.[11] The highest dose of 180 mg was well tolerated and yielded greater CR rates vs the active control arm overall (*P*=.032) and during the acute (*P*=.001) and delayed (*P*=.045) phases. A randomized, double-blind, active-control phase 3 trial evaluated rolapitant (200 mg) in combination with granisetron and dexamethasone in patients receiving moderately emetic chemotherapy.[12] This combination was also well tolerated and yielded a higher CR rate compared with placebo for control of delayed CINV (71.3% vs 61.6%; *P*<.001).

Two phase 3 trials conducted at 155 cancer centers evaluated rolapitant in patients receiving highly emetogenic, cisplatin-based chemotherapy.[13] Patients were randomized to receive rolapitant (180 mg) or placebo, plus granisetron (10 µg/kg) and dexamethasone (20 mg) on day 1, followed by dexamethasone (8 mg twice daily) on days 2 through 4. In both studies, the rate of CR in the delayed phase was significantly improved for patients who received rolapitant compared with patients in the control arm (*P*=.0006 and *P*=.0001; Figure 3). No treatment-emergent AEs were considered related to treatment, and no treatment-related, treatment-emergent AEs were fatal.

Moderately emetogenic chemotherapy is a broad category of drugs that induce CINV in as few as 30% and as many as 90% of patients. Although NK_1 antagonists are recommended for patients receiving highly emetogenic chemotherapy, the guidelines are inconsistent regarding their use in patients receiving moderately emetogenic chemotherapy. MASCC does not recommend them, ASCO recommends consideration of their use, and the NCCN guidelines recommend them in certain patient populations.

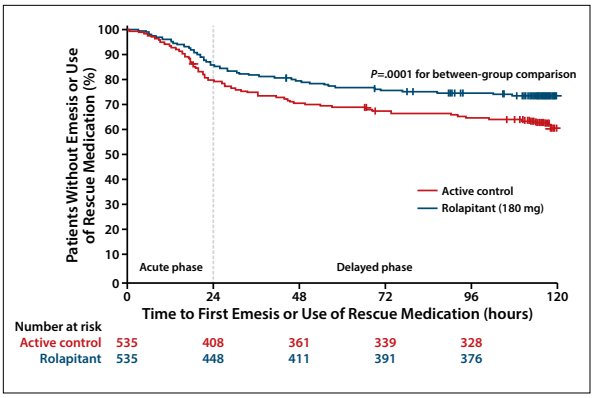

Figure 3. Efficacy of rolapitant in a pooled analysis of two phase 3 trials conducted at 155 cancer centers. Adapted from Rapoport BL et al. *Lancet Oncol*. 2015;16(9):1079-1089.[13]

For patients receiving carboplatin-based regimens, triple combinations are of great interest. A retrospective analysis of results from prospective phase 3 trials suggested that the addition of aprepitant to antiemetic regimens containing ondansetron and dexamethasone significantly improved the odds ratio of experiencing 5 days without emesis among patients receiving platinum-containing chemotherapy.[14] Recently, a post-hoc analysis of 196 patients receiving carboplatin-containing chemotherapy for a variety of tumor types demonstrated high rates of emesis control in patients who had received antiemetic regimens that included an NK_1 receptor antagonist.[15] Overall CR rates ranged from 80% to 93% and were similar for patients receiving aprepitant, palonosetron, and dexamethasone or NEPA and dexamethasone during chemotherapy cycles 1 through 4. For the NEPA patients, the CR rates in cycles 1, 2, 3, and 4 were 83%, 91%, 92%, and 95%, respectively. The forthcoming update to the MASCC/ESMO treatment guidelines may incorporate the addition of NK_1 receptor antagonists for patients receiving carboplatin.

Olanzapine is a psychotropic agent that blocks activity of many types of receptors and reduces nausea in the delayed phase.[16] In a phase 2 trial of 30 chemotherapy-naive patients treated with cyclophosphamide, doxorubicin, and/or cisplatin, olanzapine demonstrated efficacy in preventing both acute and delayed emesis.[17] A phase 3 trial of patients receiving highly emetogenic chemotherapy also demonstrated that olanzapine (10 mg), combined with palonosetron (0.25 mg) and dexamethasone (20 mg) on day 1, followed by olanzapine (10 mg) on days 2 through 4, was effective in controlling nausea during the acute and delayed periods.[18]

A recent phase 2 study investigated the efficacy and safety of olanzapine added to aprepitant, palonosetron, and dexamethasone for preventing CINV in patients receiving highly emetogenic, cisplatin-based chemo-

Table 2. Efficacy of Olanzapine in a Phase 2 Trial

	Study Phase	%	95% CI	*P* Value[a]
Complete response	Acute	97.5	86.8-99.9	1.000
	Delayed	95.0	83.1-99.4	
	Overall	92.5	79.6-98.4	
Complete control[b]	Acute	92.5	79.6-98.4	.683
	Delayed	87.5	73.2-95.8	
	Overall	82.5	67.2-92.7	
Total control[c]	Acute	87.5	73.2-95.8	.013
	Delayed	67.5	50.9-81.4	
	Overall	67.5	50.9-81.4	
No vomiting	Acute	100.0	92.8-100.0	1.000
	Delayed	97.5	86.8-99.9	
	Overall	97.5	86.8-99.9	
No rescue therapy	Acute	97.5	86.8-99.9	1.000
	Delayed	95.0	83.1-99.4	
	Overall	92.5	79.6-98.4	
No nausea	Acute	87.5	73.2-95.8	.013
	Delayed	67.5	50.9-81.4	
	Overall	67.5	50.9-81.4	
No significant nausea	Acute	95.0	83.1-99.4	.248
	Delayed	90.0	76.3-97.2	
	Overall	87.5	73.2-95.8	

[a]Comparison of acute phase and delayed phase.

[b]Complete control refers to no vomiting, no rescue, and no significant nausea.

[c]Total control refers to no vomiting, no rescue, and no nausea.

Adapted from Abe M et al. *Support Care Cancer*. Published online July 1, 2015.[19]

therapy.[19] The prospective, multicenter study enrolled 40 chemotherapy-naive patients with gynecologic cancer. Patients received oral olanzapine (5 mg) along with triple therapy 1 day before cisplatin therapy and on treatment days 1 to 5. The CR rates for the acute, delayed, and overall phases were 97.5%, 95.0%, and 92.5%, respectively (Table 2). No grade 3 or 4 AEs occurred.

The ability of olanzapine to bind to multiple receptor types provides a mechanistic rationale for its efficacy. However, the drug also appears to cause sedation in many patients, and therefore may not be advisable for the outpatient setting. The NCCN guidelines include olanzapine-containing regimens as an option for patients receiving highly emetogenic chemotherapy for the prevention of acute and delayed emesis.[3] Phase 3 data evaluating olanzapine in this setting are needed to expand the recommendations of olanzapine to other guidelines. Preliminary results from the Olanzapine for the Prevention of Chemotherapy Induced Nausea and Vomiting (CINV) in Patients Receiving Highly Emetogenic Chemotherapy (HEC): A Randomized, Double-Blind, Placebo-Controlled Trial will be presented by Dr Rudolph Navari at the ASCO Palliative Care Symposium in mid-October 2015.[20] This phase 3 trial will compare triple combination antiemetic treatment with or without olanzapine in patients receiving highly emetogenic chemotherapy. Enrolled patients will receive treatment with cisplatin at a dose of 70 mg/m^2 or greater or the combination of cyclophosphamide (600 mg/m^2) and an anthracycline (600 mg/m^2). The primary objective is to compare the number of patients in each arm with no nausea during the acute phase (0-24 hours postchemotherapy), the delayed phase (24-120 hours postchemotherapy), and overall (0-120 hours postchemotherapy).

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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Best Use of Guidelines for the Management of Chemotherapy-Induced Nausea and Vomiting

Lee S. Schwartzberg, MD

Three sets of CINV treatment guidelines are used around the world. In general, the guidelines are largely consistent with one another, owing to the large amount of evidence that is now available. Many of the recommendations are based on data from well-designed, randomized controlled phase 3 clinical trials. The MASCC/ESMO guidelines have incorporated input from the European Society for Molecular Oncology.[1] The ASCO and the MASCC/ESMO guidelines are specifically evidence-based, using the highest quality evidence available.[2] The NCCN guidelines rely on high-quality evidence but also incorporate expert opinion to provide currently accepted approaches to treatment.[3]

The guidelines are updated on different schedules. The ASCO guidelines were last updated in 2011. The MASCC Anti-Emetic Guideline Committee met in June 2015, and updated guidelines are expected shortly. NCCN guidelines are updated at least once per year, and some of the disease guidelines are updated several times per year.

Recommendations and Recent Updates

Guidelines are currently organized according to the emetogenicity of the chemotherapy and the type of CINV. In 2015, the NCCN guidelines were updated to include the addition of NEPA for patients receiving highly or moderately emetic chemotherapy.[3] The guidelines include the option of using NEPA plus dexamethasone for acute CINV and dexamethasone alone for delayed CINV. For highly emetogenic chemotherapy, all 3 guidelines recommend a 5-HT_3 receptor inhibitor, an NK_1 receptor antagonist, and dexamethasone for acute CINV, and they generally recommend dexamethasone for delayed CINV. The NCCN guidelines are the only set of guidelines to include the recommendation of olanzapine as an alternative to an NK_1 receptor antagonist. Specifically, as 1 of 3 options for patients receiving highly emetogenic intravenous chemotherapy, the NCCN guidelines recommend olanzapine (10 mg orally), palonosetron (0.25 mg intravenously), and dexamethasone (20 mg intravenously) on day 1 followed by olanzapine (10 mg orally) on days 2, 3, and 4.

For acute CINV in patients receiving moderately emetogenic chemotherapy, the MASCC/ESMO guidelines recommend palonosetron and dexamethasone. Both the NCCN and ASCO guidelines list palonosetron as the preferred 5-HT_3 receptor antagonist in combination with a corticosteroid for these patients.

Adherence to Guidelines

These guidelines are a crucial source of information and recommendations for oncologists trying to optimize management of their patients' CINV. Unfortunately, a large proportion of oncologists do not adhere to the guidelines in their daily practice, as demonstrated by several studies in different countries. A 2012 study examined adherence to the MASCC/ESMO recommendations for prophylaxis of CINV at a single institution in Switzerland.[4] The charts of 299 patients who began a new chemotherapy regimen between November 2008 and April 2009 were reviewed.

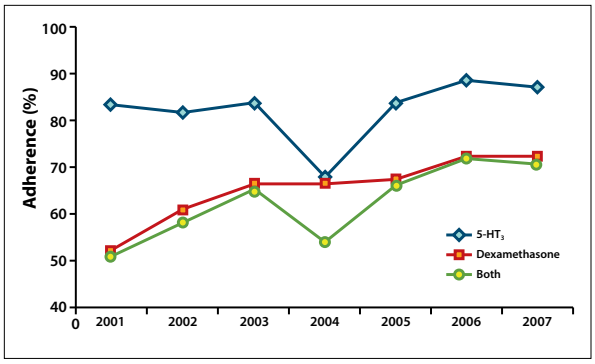

Figure 4. Rates of adherence to guidelines for CINV treatments among lung cancer patients receiving regimens of high or moderate emetogenic risk. CINV, chemotherapy-induced nausea and vomiting. Adapted from Gomez DR et al. *Cancer.* 2013;119(7):1428-1436.[5]

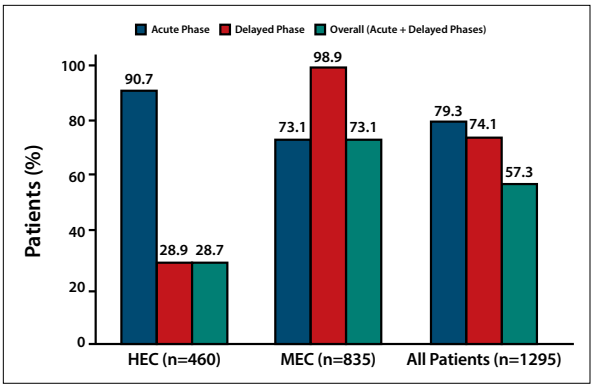

Figure 5. In the INSPIRE review of medical records from oncology centers, guideline-compliant CINV prophylaxis varied according to stage and emetogenic risk. CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy. Adapted from Gilmore JW et al. *J Oncol Pract.* 2014;10(1):68-74.[7]

Seventy-one percent of patients treated with highly emetogenic chemotherapy received CINV prophylaxis that adhered to the MASCC/ESMO guidelines. Prophylaxis of delayed CINV was not adherent to guidelines in 101 of 125 patients (89%) receiving highly or moderately emetogenic, single-day chemotherapy. The study reported frequent overuse of serotonin antagonists for prophylaxis of delayed CINV, in contrast to older studies in which nonadherence was often associated with the omission of corticosteroids. This study and others showed that adherence to recommendations for treatment of delayed nausea and vomiting was better on day 1 compared with days 2 and 3.

A population-based study of data for patients in the Texas Cancer Registry–Medicare-linked database also found inconsistent adherence to the NCCN guidelines (Figure 4).[5] A search of the database identified 4566 patients older than 65 years who received platinum-based chemotherapy within 12 months after a first diagnosis of lung cancer between 2001 and 2007. Adherence rates for each year of the analysis ranged from 55.3% to 90.1% for recommendation of a 5-HT_3 antagonist for patients receiving chemotherapy that was moderately emetogenic (carboplatin) or highly emetogenic (cisplatin). Substance P antagonists were recommended for 10% or fewer patients each year.

The 2 largest studies addressing adherence to treatment guidelines are the Pan European Emesis Registry (PEER) trial and the INSPIRE trial. PEER was a prospective, observational, multicenter, European registry trial that examined whether patients received CINV prophylaxis that was compliant or noncompliant with consensus guidelines.[6] Among 991 patients included in cycle 1, compliant prophylactic CINV treatment was prescribed for 55% during the acute phase and 46% during the delayed phase. Overall compliance was disturbingly low at 29%. Underscoring the value of the guideline recommendations, the CR rates were 59.9% in patients who received compliant treatment vs 50.7% in those who received noncompliant treatment (P=.008). The compliance rates in the acute, delayed, and overall phases of CINV were 43%, 12%, and 11% for highly emetic chemotherapy and 91%, 42%, and 39% for moderately emetic chemotherapy.

INSPIRE was a prospective, observational study based on reviews of electronic medical records at 4 oncology practice centers in the United States.[7] The cancer centers were large and well-organized, and the findings likely represent the best care in the community setting. A total of 1295 patients received chemotherapy that was either highly or moderately emetogenic. Guideline-compliant CINV prophylaxis was prescribed in 57% of cases overall. The compliance rates in the acute, delayed, and overall phases of CINV were 91%, 29%, and 29% for highly emetic chemotherapy and 73%, 99%, and 73% for moderately emetic chemotherapy (Figure 5).

Different reasons were reported to account for the failure to adhere to guidelines according to whether the chemotherapy was highly or moderately emetic. For patients receiving highly emetic chemotherapy, the low rate of overall adherence to guidelines was caused by the omission of corticosteroid use in the delayed phase. As observed in many other studies, adherence was superior on chemotherapy treatment day 1 compared with subsequent days. For patients receiving moderately emetic chemotherapy, adherence failure was mainly based on the omission of NK_1 receptor antagonists.

In an effort to improve the rate of adherence to consensus treatment guidelines, a single-center study measured outcomes in malignant glioma patients receiving moderately emetic chemotherapy before and after implementation of a quality improvement program.[8] The improvement program included a provider education session, monthly audit-feedback sessions, and implementation of a risk

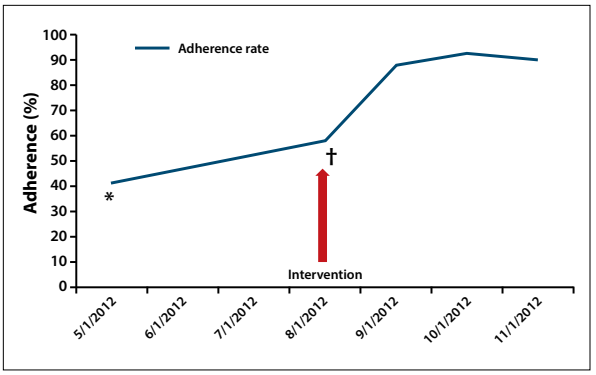

Figure 6. Adherence to antiemetic guidelines before and after implementation of a quality improvement project. *Adherence was 41% over a 1-year period 6 months prior to implementation. †Adherence was 58% over a 3-month baseline period to match project period. Adapted from Affronti ML et al. *Support Care Cancer*. 2014;22:1897-1905.[8]

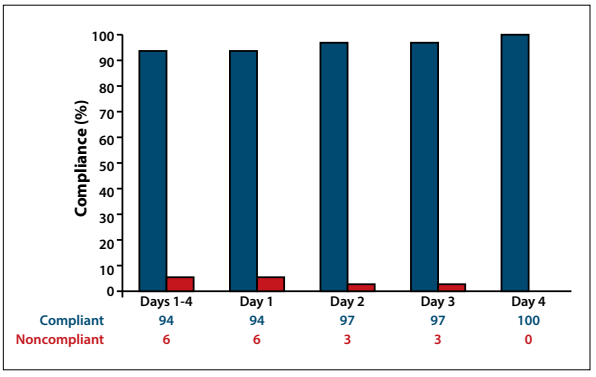

Figure 7. Rates of adherence to CINV guidelines among patients receiving chemotherapy for solid tumors. CINV, chemotherapy-induced nausea and vomiting. Adapted from Kadakia KC et al. *Support Care Cancer*. 2014;22:217-223.[9]

assessment tool with computerized, standardized order sets for antiemetic therapy. After implementation of this program, overall adherence to guidelines, as assessed by orders for recommended emetic therapy, increased to 90% from 58% at baseline (95% CI, 80%-96%; $P<.05$; Figure 6). Among the 32 surveyed patients who received guideline-recommended antiemetic treatment, the acute and delayed CINV CR rates were 75% and 84%, respectively.

Management of CINV can be improved by instituting a continuous quality improvement program. Such a program can provide critical feedback on an ongoing basis, highlighting areas of effective management as well as those that might benefit from a different approach. Numerous studies have shown that treatment based on the guidelines improves patient outcomes; therefore, the consensus guidelines provide an excellent template for optimizing treatment.

Including antiemetics and supportive care in order sets increases the likelihood that treatment will be compliant with guidelines. It is important that the computerized order set includes the supportive care that is appropriate for the emetogenicity of the chemotherapy. One study found that CINV adherence improved with use of a computerized physician order entry system in both the acute and delayed CINV settings (Figure 7).[9] Compliance for the treatment of delayed CINV was 97%, a rate that is considerably higher than results from other studies.

Disclosure

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

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Q&A

Eric Roeland, MD What are your experiences with continuous improvement programs?

Lee S. Schwartzberg, MD I recently participated in an online survey of patients who had received highly or moderately emetogenic chemotherapy. In general, the communication by providers was good. Most of the patients reported that they agreed or strongly agreed that they received educational material and that they would receive medications. However, only approximately half of the patients underwent follow-up with their provider or with someone in the office between office visits to check on nausea and vomiting. This survey showed that a practice may be doing most things right, while still having areas that could be improved.

Eric Roeland, MD Many cancer patients still believe that nausea and vomiting are symptoms that will occur and must be tolerated. Did your survey address this issue?

Lee S. Schwartzberg, MD Yes. More than half of the patients in this small survey thought that nausea and vomiting were to be expected for all patients with cancer. This finding is a cause for concern, because for many patients, CINV is the most feared side effect of chemotherapy.

Matti S. Aapro, MD I agree that patients have this perception, and we need to change it. A patient who expects CINV may fail to report symptoms. Often, when we ask patients about their experience receiving treatment, they will say it was OK. If we then ask, "Did you have nausea and vomiting?" the patient will often say, "Oh yes, but it's OK." This scenario underscores the importance of asking the patient specific questions about CINV.

Lee S. Schwartzberg, MD I strongly agree. It is extremely important for oncologists to be proactive in querying their patients with regard to CINV symptoms. Risk assessment tools such as the MAT are very helpful for evaluating patients and revealing any problems. The MAT is relatively short and quick to administer. The feedback it provides is particularly important during the acute phase, right after the patient leaves the clinic or hospital, when the majority of CINV events occur.

Eric Roeland, MD Some patients fear that if they report their CINV, their oncologist will change their chemotherapy to a less aggressive regimen. It might be helpful to empower our nursing colleagues and pharmacists to also become more engaged on this issue because they may be more likely to hear the patient's real experience.

Lee S. Schwartzberg, MD Another interesting point raised by the survey was that approximately 20% of the patients were concerned about side effects from the CINV medicines. Perhaps we need to inform patients that these drugs are safe and add minimal toxicity.

Matti S. Aapro, MD We should warn patients about constipation.

Eric Roeland, MD In my experience, constipation is the most common adverse event. Unfortunately, it is not widely known that the 5-HT_3 receptor antagonists can cause constipation. Clinicians may be expecting the patient to experience diarrhea, and might be surprised by reports of nausea and constipation. In this setting, we add a more aggressive bowel regimen 3 to 5 days after chemotherapy.

Other areas that need to be defined and further evaluated are breakthrough and refractory CINV. Much energy and money have been spent on prophylaxis, but not on treating persistent symptoms. These types of nausea appear to be more common than is generally believed, and the lack of studies in these areas is frustrating. Additionally, we need to further evaluate the impact of receiving multiday chemotherapy. For example, little is known regarding the best ways to prevent and treat CINV in hematologic malignancy patients receiving multiday chemotherapy.

Matti S. Aapro, MD Nausea is a major concern of patients, and it can mean different things to different patients.

Lee S. Schwartzberg, MD We do not understand the physiology of nausea very well. Although it can occur as a symptom that arises before emesis, there are other causes. Because it is subjective, patients may have different experiences, as Dr Aapro mentioned. The sensation of anorexia may merge into nausea. I would like to see more research elucidating the pathophysiology of nausea, as well as the clinical impact. I agree with Dr Roeland on the importance of finding improved treatments for patients with breakthrough or refractory CINV. It is debilitating and can interfere with the delivery of effective chemotherapy over multiple cycles.

Eric Roeland, MD I would like to stress the need for oncologists to ask patients about their experience with CINV and to listen carefully to the responses. There is still a widely held belief that the presence of nausea indicates that the chemotherapy is working. It is important to educate patients and their families that CINV is not inevitable and that symptoms do not reflect the effectiveness of chemotherapy. I spend time with my patients to encourage them to describe their symptoms. I also assure them that I will not decrease the intensity of their chemotherapy based on the presence of nausea, but rather I will be more aggressive with the available antiemetic agents.

Matti S. Aapro, MD The NCCN guidelines include olanzapine as an option for patients receiving highly emetogenic therapy. Older agents, including metopimazine and chlorpromazine, were also very useful. The fact that olanzapine is a psychotropic agent suggests that other psychotropic agents may be effective as well. Very small amounts of haloperidol are effective to combat that type of nausea.

Eric Roeland, MD With olanzapine, it is important for oncologists to recognize that one of the reasons why it works so well is that it binds to multiple serotonin and dopamine receptors. In your discussion, you raised another key point, which is the widespread concern about the sedation seen with this agent. The studies by Dr Rudolph Navari have embraced the 10 mg dose of olanzapine, which he says is well-tolerated. However, oncologists frequently prescribe smaller doses, such as 2.5 mg or 5 mg. Dr Navari encourages patients to take olanzapine at night, when it can alleviate nausea as well as promote sleep. His phase 3 trial compared oral olanzapine vs aprepitant, each used in combination with infused palonosetron and dexamethasone. Both combinations showed good results.[1] Dr Navari and colleagues also published a study comparing olanzapine vs metoclopramide in breakthrough CINV for patients receiving highly emetogenic chemotherapy.[2] Olanzapine was associated with an impressive improvement for both emesis and nausea that was more than 2 times better than that seen with metoclopramide. These breakthrough studies do not receive enough attention, and they highlight the need to evaluate other psychotropic agents. I am curious if other agents that hit multiple dopamine and serotonin receptors will be more effective.

Matti S. Aapro, MD I would think so. Chlorpromazine is no longer available, but in my modest experience with it, very small doses showed an impressive improvement in breakthrough CINV. However, sedation was always a concern.

Lee S. Schwartzberg, MD It is a complex interaction. Some practitioners still use the more sedating phenothiazines, such as promethazine. This sedation can certainly have a negative impact, but it may also reduce the subjective perception of nausea and can be helpful for patients who develop symptoms in the evening hours.

Do you think there will be a role for cannabinoids in CINV? In the United States, we have seen a remarkable societal change in the past few years with more acceptance of marijuana. It has become legal for medical or even recreational use in some states.

Matti S. Aapro, MD In Europe, there was interest in cannabinoids several years ago, but it has faded away. In some European countries, the drug dronabinol is available.

Eric Roeland, MD I have found the use of dronabinol to be ineffective for most patients. In elderly patients or patients with brain metastases, it can cause delirium that outweighs any improvement in nausea.

Initially, I was reluctant to engage patients in discussions surrounding medical cannabis. An experience I had with a patient in the infusion center shifted my practice. An 80-year-old woman with breast cancer offered me a taste of her "edibles" while she was receiving chemotherapy in the infusion center. That experience taught me that my patients may already be using it, or may be considering it. I began to engage my patients about the use of medical cannabis. I inform them that medical cannabis has been used by other patients, some of whom have found it effective not only for nausea, but also for pain and insomnia. Although I personally do not prescribe medical cannabis, I provide information regarding reputable resources in the community.

Given the risk profile of medical cannabis, I am open to patients using it. The problem is that until it is a regulated product—and we know precisely what is in both the edible and inhaled forms—it is difficult to titrate or understand drug-drug interactions. Medical cannabis can interact with many medications, such as benzodiazepines and opioids.

It should also be mentioned that the marijuana of today is not the marijuana of the 1970s. It is now from 10 to 20 times stronger. The marijuana of today often causes more side effects, so I encourage patients to use low doses. The effects of inhaled marijuana are usually apparent about 10 minutes afterwards, which makes it a little easier to titrate. I usually recommend edible forms to decrease the risk of pulmonary infections. The effects of the edible forms are usually apparent after approximately an hour.

Lee S. Schwartzberg, MD In the United States, it seems likely that the use of medical cannabis will increase. Several years ago, I reviewed the available clinical trial data on the use of cannabinoids, and I was surprised by the low quality of the research. By the current standards of CINV research, virtually none of the studies performed during the 1970s and 1980s would pass muster today. Perhaps the development of a more selective cannabinoid receptor–targeting agent, with fewer toxicities, could be a potential avenue for treatment of CINV in the future.

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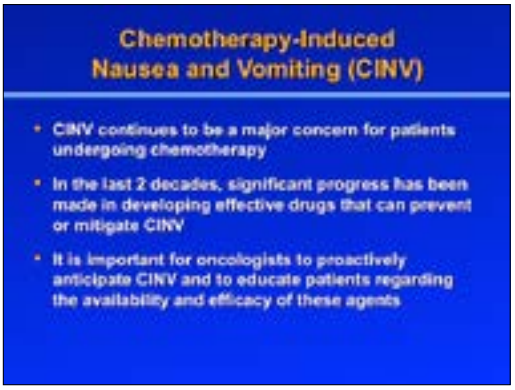

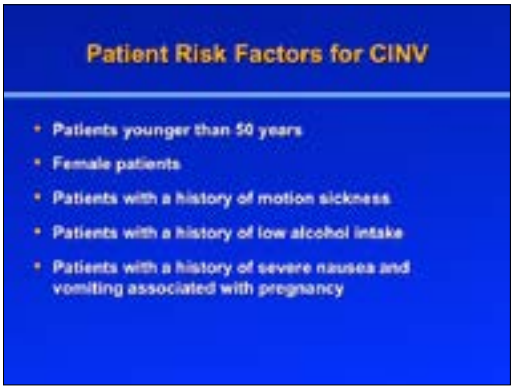

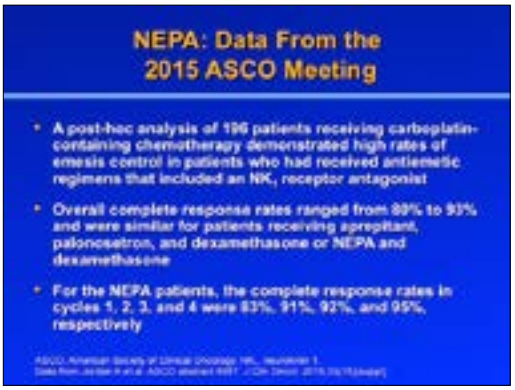

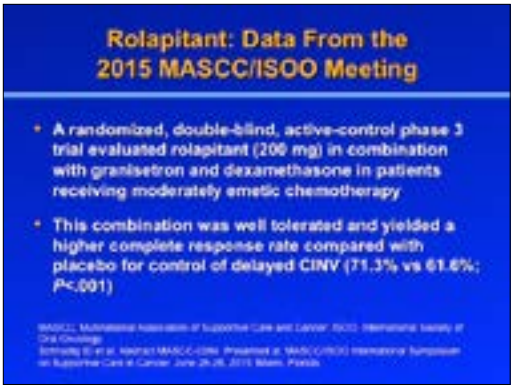

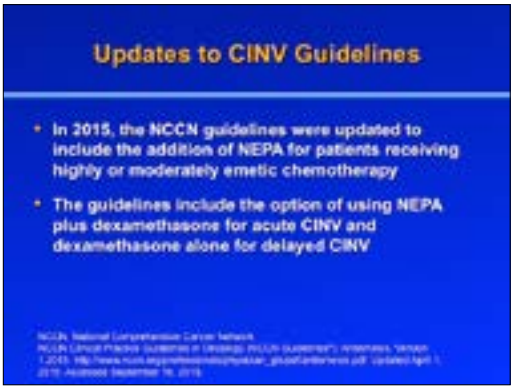

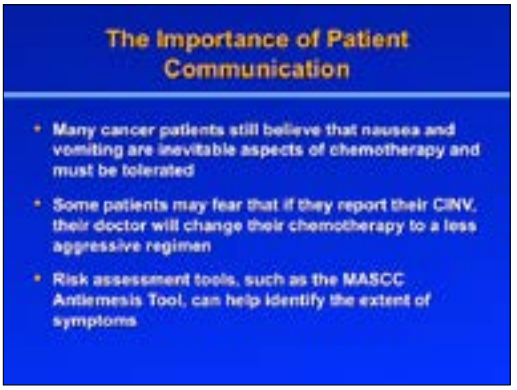

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http://www.hematologyandoncology.net

Advances in the Management of Chemotherapy-Induced Nausea and Vomiting: New Data From Recent and Ongoing Trials

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

1. Which agent is a second-generation 5-HT_3 receptor antagonist?

   a. Dolasetron mesylate
   b. Granisetron
   c. Ondansetron
   d. Palonosetron

2. Approximately how many patients receiving moderately or highly emetogenic chemotherapy develop breakthrough CINV?

   a. One-quarter
   b. One-third
   c. One-half
   d. Three-quarters

3. In a study of patients with malignant glioma who were receiving moderately emetic chemotherapy, what percentage of CINV treatment adhered to guidelines?

   a. 41%
   b. 58%
   c. 65%
   d. 73%

4. In a phase 3 study, NEPA administered throughout multiple cycles of highly or moderately emetogenic chemotherapy was associated with a complete response rate of:

   a. 59%
   b. 65%
   c. 77%
   d. 81%

5. In a phase 3 trial, rolapitant in combination with granisetron and dexamethasone was associated with a complete response rate of __ for control of delayed CINV in patients receiving moderately emetic chemotherapy.

   a. 57.6%
   b. 62.9%
   c. 71.3%
   d. 83.2%

6. Which agent has shown a dose-dependent ability to inhibit the substance P response by NK_1 receptors in vitro?

   a. Aprepitant
   b. Fosaprepitant
   c. Netupitant
   d. Rolapitant

7. In a phase 2 study evaluating olanzapine added to aprepitant, palonosetron, and dexamethasone in patients receiving highly emetogenic, cisplatin-based chemotherapy, what was the complete response rate in the acute phase?

   a. 83.7%
   b. 89.2%
   c. 94.15%
   d. 97.5%

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 a study evaluating use of a quality improvement program to increase adherence to CINV guidelines, what was the rate of adherence after implementation?

   a. 75%
   b. 80%
   c. 85%
   d. 90%

10. Which approach was shown to increase adherence to guidelines for delayed CINV to 97%?

    a. Computerized physician order entry system
    b. Follow-up phone calls to patients
    c. Provider education sessions
    d. Use of risk-assessment tools

Project ID: 11026

Evaluation Form: Advances in the Management of Chemotherapy-Induced Nausea and Vomiting: New Data From Recent and Ongoing Trials

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 11026**. 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:

Describe the impact, incidence, and risk factors of CINV

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Distinguish chemotherapy regimens with high, moderate, and low emetogenic risk

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Implement strategies for CINV prevention and management based on recommendations from guidelines

❒ 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 results from recent and ongoing clinical trials in CINV management

❒ 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 1.25 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

Project ID: **11026**