Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology March 2014

New Data in Emerging Treatment Options for Chemotherapy-Induced Nausea and Vomiting

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A CME Activity
Approved for
1.0 *AMA PRA Category 1 Credit(s)™*

Release Date: March 2014
Expiration Date: March 31, 2015
Estimated time to complete activity: 1.0 hours
Project ID: 9607

Abstract: Chemotherapy-induced nausea and vomiting (CINV) has long been one of the most troublesome adverse effects of chemotherapy, leading to significant detriments in quality of life and functioning, increased economic costs, and, in some cases, the discontinuation of effective cancer therapy. The past 2 decades have witnessed a dramatic increase in the number of effective antiemetic agents, with the introduction of the serotonin (5-hydroxytryptamine [5-HT_3]) receptor antagonists (ondansetron, granisetron, and palonosetron), the neurokinin-1 (NK_1) receptor antagonists (aprepitant and fosaprepitant), and the identification of other agents that have demonstrated efficacy against CINV, including corticosteroids. These agents often provide excellent control of emesis. Nausea, however, has proven more intractable, particularly in the days after administration of chemotherapy. Newer antiemetic agents under study may provide additional CINV control, particularly against delayed nausea. New agents undergoing review by the US Food and Drug Administration for the prevention of CINV include the novel NK_1 receptor antagonist rolapitant and a fixed-dose combination consisting of the novel NK_1 receptor antagonist netupitant and palonosetron (NEPA). Adherence to clinical practice guidelines has been shown to significantly improve CINV control. As antiemetic therapy continues to evolve, it will be important for clinicians to stay informed of new developments and changes in guidelines.

Sponsored by the Postgraduate Institute for Medicine

Supported through an educational grant from Eisai Inc.

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Target Audience

This activity has been designed for all oncologists, hematologists, and oncology nurses who treat cancer patients who receive chemotherapy.

Statement of Need/Program Overview

Most patients who receive chemotherapy will experience chemotherapy-induced nausea and vomiting (CINV). CINV can have an enormous impact on the course of cancer management and quality of life. Control of CINV must take into account multiple factors, including the chemotherapy agents being used, the dose and schedule of the agents, and patient characteristics. CINV prevention is the primary principle of emesis control, as outlined by the major antiemetic guidelines. These guidelines characterize chemotherapies according to emetogenic risk and adjust management approaches accordingly. Adherence to guidelines has been shown to improve control of emesis and nausea. Multiple effective antiemetic agents are available, such as the second-generation 5-hydroxytryptamine (5-HT_3) antagonists ondansetron, granisetron, and palonosetron and the neurokinin-1 (NK_1) receptor antagonists aprepitant and fosaprepitant. Nausea and vomiting should be considered distinct events. Newer antiemetic agents under study, such as the fixed-dose combination consisting of the novel NK_1 antagonist netupitant and palonosetron (known as *NEPA*), show promise in clinical trials.

Educational Objectives

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

- Identify patient-related and/or treatment-related factors that heighten the risk of developing CINV
- Manage the impact of CINV on general patient functioning
- Implement evidence-based treatment strategies to incorporate antiemetic agents as CINV prophylaxis for patients with cancer in clinical practice
- Discuss with patients and colleagues the efficacy and safety data of novel and emerging antiemetic agents to improve CINV outcomes for patients with cancer

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Gary R. Morrow, PhD, MS—No real or apparent conflicts of interest to report.
Rudolph M. Navari, MD, PhD—No real or apparent conflicts of interest to report.
Hope S. Rugo—Eisai Inc. has provided research funding to the University of California, San Francisco.

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The Impact of Chemotherapy-Induced Nausea and Vomiting

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Since chemotherapy began to be used for the treatment of cancer, nausea and vomiting have been among the adverse events of greatest concern to patients.[1,2] Before the introduction of antiemetic drugs, chemotherapy-induced nausea and vomiting (CINV) affected almost all patients, often causing symptoms severe enough to necessitate extended hospitalization. Today, virtually all chemotherapy agents are administered on an outpatient basis, largely because of the development of effective antiemetic drugs.

Multiple factors influence the incidence and severity of CINV. The primary risk factor is the chemotherapy regimen—both the type of agent and the dosage. Patient-related factors include sex and age.[3,4] Women experience more chemotherapy-associated adverse events, including CINV, than men. Elderly patients report fewer side effects than younger patients.

Chemotherapy-induced nausea must be considered separately from vomiting. The development of effective antiemetic therapy has substantially reduced the incidence and severity of chemotherapy-associated vomiting. In contrast, nausea has proven more difficult to control. Patients receiving effective antiemetic regimens usually report more nausea than vomiting.[5]

Classification of CINV

CINV is classified as acute, delayed, or anticipatory based on its time of onset. Acute CINV typically develops within a few minutes to hours after administration of chemotherapy and resolves within 24 hours. Delayed CINV occurs more than 24 hours after chemotherapy. Delayed CINV is more common with certain agents, including cisplatin, carboplatin, cyclophosphamide, and doxorubicin.[6] Anticipatory nausea and/or vomiting occurs in approximately 20% of patients receiving chemotherapy.[7,8] Anticipatory CINV is a classically conditioned learned response that occurs before the administration of chemotherapy, typically in patients who experienced acute or delayed CINV in previous cycles. For some patients, seeing their doctor or nurse can trigger anticipatory CINV. Anticipatory CINV can also occur outside the medical setting; for example, a patient I know experienced anticipatory CINV while traveling along the route she usually used to visit the clinic.

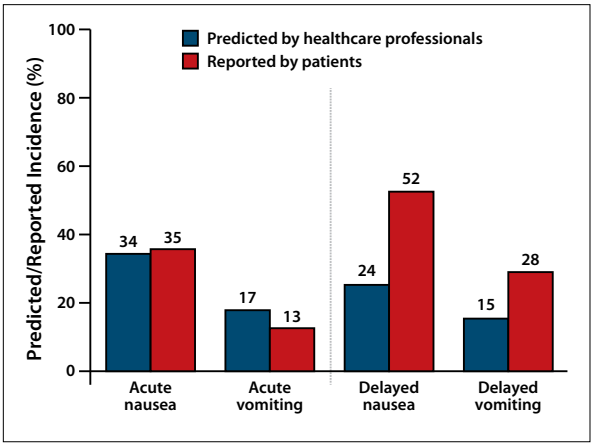

Figure 1. In a prospective, observational study of 24 nurses and physicians and 298 patients receiving highly or moderately emetogenic chemotherapy, clinicians underestimated the prevalence of delayed nausea and vomiting. Adapted from Young A et al. *Ecancermedicalscience*. 2013;7:296. doi: 10.3332/ecancer.2013.296. Print 2013.[9] Data from Grunberg SM et al. *Cancer*. 2004;100(10):2261-2268.[10]

Clinicians may underestimate the prevalence of CINV (Figure 1).[9,10] Assessment of CINV is an essential component of care for patients receiving chemotherapy. However, this assessment is challenging, particularly in the case of nausea, which is a subjective experience and therefore difficult to quantify. Like pain or fatigue, nausea lacks an external frame of reference and is dependent upon patients' perceptions, which vary widely. Therefore, it is important to ask patients about nausea as well as vomiting.

Consequences of CINV

CINV can have significant negative effects on quality of life and can lead to reduced adherence to therapy or an unwillingness to continue with effective therapy. Other potential effects of nausea and vomiting include electrolyte imbalances, impaired self-care and functional

Table 1. Multivariate Analysis of Factors Associated With Monthly Direct Medical Cost

	Coefficients	% Difference in Costs	*P* Value
Age	–0.008	–0.76	.005
Male (vs female)	0.068	7.07	.255
Employee (vs spouse)	0.057	5.82	.222
Uncontrolled CINV	0.262	29.97	<.001
Comorbidity	0.258	29.43	<.001
Highly Emetic (vs moderately emetic)	0.332	39.38	<.001
Cancer Type (reference group: breast cancer)			
Lung Cancer	0.555	74.25	<.001
GI Cancer	0.250	28.45	.002
Lymphoma	0.349	41.72	<.001
Other cancers	0.259	29.57	<.001
Metastasis	0.530	69.90	<.001
Region (reference group: Northeast)			
North Central	0.120	12.75	.036
South	–0.009	–0.92	.864
West	–0.211	–19.04	.02

CINV, chemotherapy-induced nausea and vomiting.

Data from Tina Shih YC et al. *Cancer*. 2007;110(3):678-685.[11]

ability, reductions in energy, and strains on relationships. Caregivers can be strongly affected when a loved one is experiencing nausea and vomiting.

There are substantial economic costs associated with CINV. In a study of working-aged adults receiving highly or moderately emetogenic chemotherapy, uncontrolled CINV was associated with higher monthly costs of $1300 for medical issues (eg, need for hospitalization; Table 1) and $433 for indirect costs (eg, lost work time).[11]

Given the numerous potential negative effects of CINV, proper control through the use of effective antiemetic therapy is an essential part of the planning for chemotherapy. Management of CINV should begin at the start of treatment.

Acknowledgment

Dr Morrow has no real or apparent conflicts of interest to report.

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Clinical Trial Data in Chemotherapy-Induced Nausea and Vomiting

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Antiemetic therapy has undergone a substantial evolution in the past few decades. In the early 1990s, therapeutic options included prochlorperazine and metoclopramide. In the current era, there are several new agents targeting different physiologic pathways. Table 2 lists the mechanisms of action of the various commonly used antiemetics. By combining agents with multiple mechanisms of action, greater antiemetic efficacy can be achieved. The development of antiemetic agents has been based on the identification of the main neurotransmitters involved in CINV: dopamine, serotonin, and substance P (Figure 2). These neurotransmitters are detectable in both the periphery and the central nervous system, to varying degrees.

Serotonin (5-HT$_3$) Receptor Antagonists

The first generation of serotonin (5-hydroxytryptamine [5-HT$_3$]) receptor antagonists—ondansetron, granisetron, and dolasetron—were developed in the 1990s and represented a significant advance in the control of CINV. In numerous clinical trials, these 5-HT$_3$ antagonists demonstrated a significant improvement over previous therapies for CINV, controlling approximately half of patients' emesis over the first 24 hours and the subsequent days after administration of chemotherapy.[1,2] In the late 1990s, multicenter, double-blind, randomized trials demonstrated comparable outcomes among the 3 first-generation 5-HT$_3$ receptor antagonists. Intravenous dolasetron was equivalent to ondansetron,[3] and oral granisetron was equivalent to intravenous ondansetron.[4] Thereafter, these agents were selected based primarily on economic factors.

The use of first-generation 5-HT$_3$ receptor antagonists has changed throughout the years. Table 3 shows the recommended doses for the commonly used agents. In 2010, the US Food and Drug Administration (FDA) issued a warning about dolasetron and QTc prolongations, particularly in patients with ischemic heart disease or arrhythmias.[5] As a result of this warning, dolasetron is rarely used or available. In 2012, the FDA issued a safety warning about ondansetron, noting that the intravenous dose should not exceed 16 mg owing to the risk of QTc prolongation, which could potentially precipitate a serious arrhythmia[6] (although clinical reports are rare).

Clinical trials of antiemetic therapy in the 1990s also focused on the role of dexamethasone, which was found to be an effective antiemetic agent. The combination of dexamethasone and a 5-HT$_3$ receptor antagonist protected up to 60% of patients from delayed emesis.[7] The optimal

Table 2. Antiemetic Receptor Antagonists

Dopamine Receptor Antagonists	5-HT$_3$ Receptor Antagonists	Dopamine 5-HT$_3$ Receptor Antagonists	NK$_1$ Receptor Antagonists
Butyrophenones Olanzapine Phenothiazines	Dolasetron* Granisetron Olanzapine Ondansetron† Palonosetron	Metoclopramide Olanzapine	Aprepitant Fosaprepitant Netupitant Rolapitant

*Not recommended for use per the FDA.

†Intravenous dose restriction per the FDA.

FDA, US Food and Drug Administration; 5-HT$_3$, 5-hydroxytryptamine; NK$_1$, neurokinin-1.

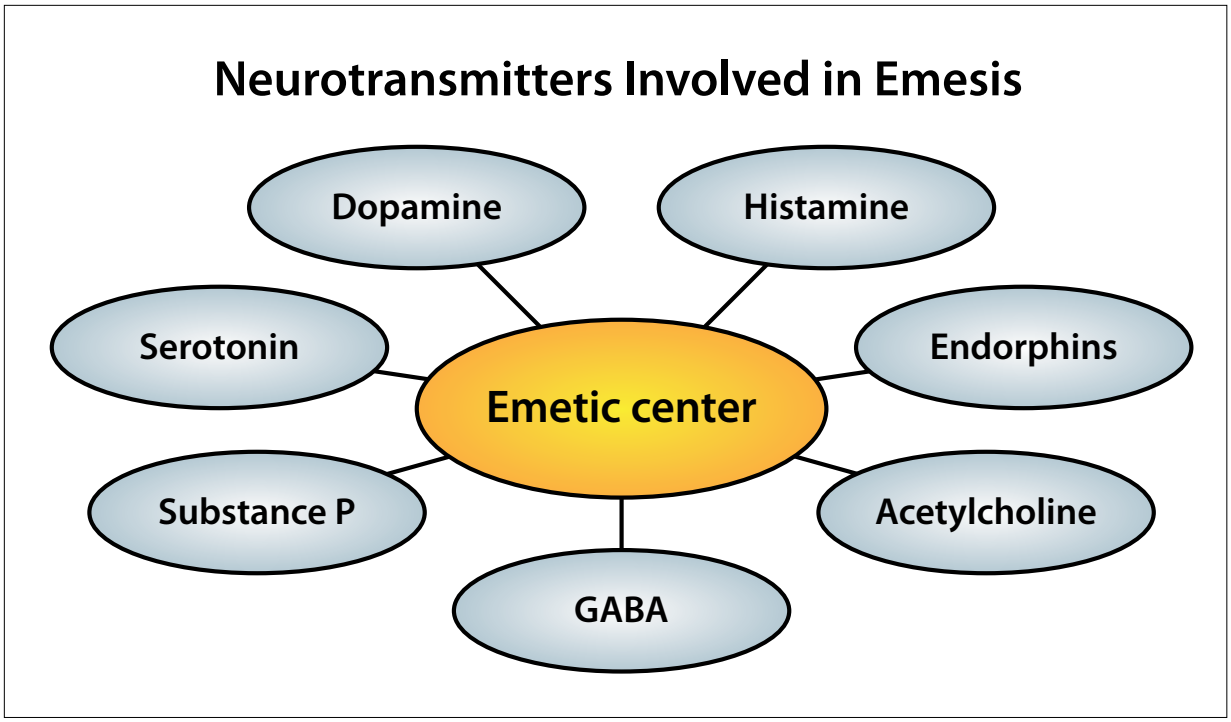

Figure 2. The development of antiemetic agents has been based on the identification of the main neurotransmitters involved in chemotherapy-induced nausea and vomiting: dopamine, serotonin, and substance P. GABA, γ-aminobutyric acid.

dose of dexamethasone has been a topic of investigation. Data from the Italian Group for Antiemetic Research suggest that the most appropriate dexamethasone dosages are 20 mg administered 1 day before administration of highly emetogenic chemotherapy (eg, regimens with cisplatin or an anthracycline) and 8 mg administered 1 day prior to the administration of moderately emetogenic chemotherapy.[8]

Palonosetron is a second-generation 5-HT_3 antagonist approved by the FDA for the treatment of acute and delayed CINV. Palonosetron has demonstrated superior efficacy over first-generation 5-HT_3 antagonists in multiple clinical trials. It has shown greater efficacy compared with dolasetron in patients receiving moderately emetogenic chemotherapy,[9] and greater efficacy compared with ondansetron in patients receiving moderately emetogenic[10] or highly emetogenic[11] chemotherapy. In a combined analysis of 2 trials, palonosetron was more effective than either ondansetron or dolasetron.[12] Palonosetron plus dexamethasone demonstrated significantly greater efficacy vs granisetron plus dexamethasone in patients receiving highly emetogenic chemotherapy.[13] In this study, the superiority of palonosetron was observed in the acute phase (the first 24 hours), the delayed phase (days 2-5 postchemotherapy), and the overall combined 120-hour period after chemotherapy administration.

The structure of palonosetron differs from that of the first-generation 5-HT_3 receptor antagonists. Laboratory studies suggest that the enhanced efficacy of palonosetron may relate to its unique ability to not only block the 5-HT_3 receptor, but also to change the receptor, triggering 5-HT_3 receptor internalization and inhibiting receptor function.[14] Evidence from the past 10 to 15 years confirms that administering a first- or second-generation 5-HT_3 receptor antagonist plus dexamethasone before chemotherapy controls emesis. Even with these effective agents for emesis, however, nausea has remained poorly controlled.

NK_1 Receptor Antagonists

Neurokinin-1 (NK_1) receptor antagonists selectively block binding of substance P to the NK_1 receptor, primarily in the central nervous system. The primary effect of blocking the NK_1 receptor appears to be in controlling delayed emesis. The first NK_1 receptor antagonist to receive FDA approval was aprepitant. In 2 randomized, double-blind, placebo-controlled trials in patients receiving highly emetogenic chemotherapy, the addition of aprepitant to standard antiemetic therapy (a 5-HT_3 antagonist and dexamethasone) was associated with substantial reductions in delayed emesis and some reduction in acute emesis.[15,16]

Aprepitant also demonstrated efficacy in preventing CINV when added to ondansetron and dexamethasone in patients with breast cancer receiving moderately emetogenic chemotherapy.[17] In the study, the addition of aprepitant was associated with a small improvement over the control regimen in acute CINV, no improvement in delayed

Table 3. Serotonin Antagonists for the Prevention of CINV

Antiemetic	Route	Dosage Before Initiation of Chemotherapy*
Dolasetron†	IV PO	100 mg or 1.8 mg/kg 100 mg
Granisetron	IV PO	10 µg/kg or 1 mg 2 mg (or 1 mg twice daily)
Ondansetron	IV PO	8 mg (restricted to <16 mg) 24 mg
Palonosetron	IV PO	0.25 mg 0.50 mg

*The same doses are used for highly and moderately emetic chemotherapy.

†Not recommended for use by the US Food and Drug Administration.

CINV, chemotherapy-induced nausea and vomiting; IV, intravenous, PO, oral.

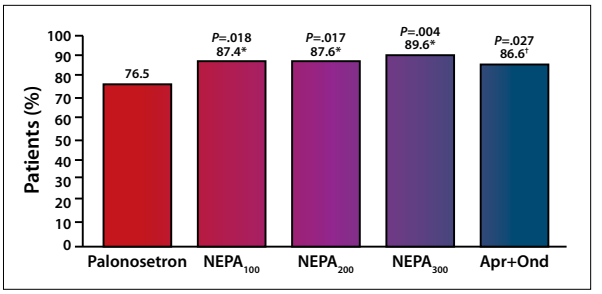

Figure 3. In a phase 2, dose-finding trial of NEPA plus dexamethasone, the 300-mg dosage was associated with the highest complete response rate. **P* value from logistic regression analysis vs palonosetron. †*P* value from a post-hoc logistic regression analysis vs palonosetron. Apr, aprepitant; Ond, ondansetron. Adapted from Hesketh PJ et al. ASCO abstract 9512. *J Clin Oncol.* 2013;31(suppl).[21]

CINV, and a small improvement overall in CINV. There was no improvement specifically in nausea throughout the entire 120 hours after administration of chemotherapy. Overall, the role of aprepitant for patients receiving moderately emetogenic chemotherapy is still under study, and the agent is not routinely used in this setting.

A clinical issue with aprepitant had been its formulation, which was limited to an oral form that is administered on days 1, 2, and 3. Access to oral medications has been a challenge for some patients, perhaps owing to insurance and co-pay issues. Subsequently, an intravenous formulation of aprepitant, known as fosaprepitant, was developed. It showed noninferiority to the 3-day oral dosing of aprepitant.[18] The ability to administer CINV medications intravenously before highly emetogenic chemotherapy has had a substantial benefit on CINV management in clinical practice.

Additional NK_1 receptor antagonists have been studied in recent years. Rolapitant has completed phase 3 trials in patients receiving moderately and highly emetogenic chemotherapy.[19] Specific detailed data from these trials are not yet available, but it is assumed that the results of the rolapitant clinical trials will be submitted to the FDA for approval in the near future.

Netupitant is another NK_1 receptor antagonist that has been formulated in a fixed-dose combination with palonosetron known as *NEPA*. Two phase 3 trials presented at the 2013 Annual Meeting of the American Society of Clinical Oncology evaluated the efficacy and safety of NEPA. One study compared NEPA vs palonosetron alone for the prevention of CINV in patients receiving moderately emetogenic chemotherapy.[20] The combination of NEPA was associated with higher complete response rates than palonosetron alone in the acute phase (88.4% vs 85.0%; *P*=.047), the delayed phase (76.9% vs 69.5%; *P*=.001), and the full 120 hours (74.3% vs 66.6%; *P*=.001). In a companion study examining 3 different dosages of NEPA plus dexamethasone, all dosages were associated with greater efficacy vs palonosetron plus dexamethasone in patients receiving highly emetogenic chemotherapy (Figure 3).[21] The fixed-dose combination of netupitant and palonosetron was submitted to the FDA for approval in December 2013.

The NK_1 receptor antagonists have not been directly compared, and any differences in the efficacy and safety are unknown. However, the newer agents will likely have at least similar efficacy and a similar toxicity profile to aprepitant.

Other Antiemetic Combinations

Other combinations of antiemetic drugs may have some applicability in the future. Olanzapine was originally developed as an antipsychotic agent and found to have significant effects on preventing emesis and nausea in patients taking it for other indications, leading to off-label use as an antiemetic agent to prevent CINV. A phase 2 trial demonstrated the efficacy of olanzapine, dexamethasone, and palonosetron for the prevention of acute and delayed CINV in patients receiving both moderately and highly emetogenic chemotherapy.[22] The regimen effectively controlled emesis and reduced nausea in many cases. In another study, a combination of olanzapine, the 5-HT_3 receptor agonist azasetron (used in East Asia), and dexamethasone demonstrated significantly greater efficacy than azasetron plus dexamethasone in patients receiving moderately or highly emetogenic chemotherapy.[23] The results with the olanzapine-containing regimen were striking, yielding a complete response rate of 70% to 80% and a high degree of nausea control in patients receiving highly emetogenic chemotherapy. Among patients receiving moderately emetogenic chemotherapy, the regimen was associated with a complete response rate of 89% throughout the 120-hour period after administration of chemotherapy.

A subsequent randomized phase 3 trial compared olanzapine vs aprepitant, each with dexamethasone and palonosetron, in patients receiving highly emetogenic chemotherapy.[24] Overall complete response rates were similar (77% with olanzapine and 73% with aprepitant). Olanzapine was associated with better nausea control, with 69% of patients reporting no nausea for the overall period, compared with 38% for aprepitant. The olanzapine regimen has recently been added to the National Comprehensive Cancer Network (NCCN) guidelines as an alternative first-line preventative therapy for patients receiving highly emetogenic chemotherapy.[25]

Acknowledgment

Dr Navari has no real or apparent conflicts of interest to report.

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Management of Chemotherapy-Induced Nausea and Vomiting in Clinical Practice

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The primary goal of antiemetic therapy in patients receiving chemotherapy is to attain the best possible control of CINV with the best quality of life. Control of CINV must take into account multiple factors, including the chemotherapy agents being used, the dose and schedule of the agents, and patient characteristics.

Highly emetogenic therapies (eg, anthracycline and platinum-based combinations, higher-dose cisplatin) induce emesis in more than 90% of patients; this incidence decreases to approximately 30% with the use of appropriate antiemetic agents.[1] Therapies with a moderate emetic risk (eg, bendamustine, carboplatin, and irinotecan) induce emesis in 30% to 90% of patients. Agents with a low emetic risk (eg, fluorouracil, paclitaxel, docetaxel, and pemetrexed) are associated with emesis in 10% to 30% of patients. Agents in the fourth category, minimal emetic risk, induce emesis in less than 10%.

There are some limitations to this classification system. First, the use of combination chemotherapy may alter the emetogenic classification; single agents with a moderate emetogenic risk may become highly emetogenic when administered in combination with other chemotherapies. Second, individual risk factors (eg, age, sex, and alcohol use) affect the likelihood of CINV. Third, pharmacogenomics, although not well understood, may also influence CINV risk, resulting in unusual responses to specific chemotherapy agents in individual patients.

A prospective observational study from Europe evaluated the significance of various patient-related and treatment-related risk factors for CINV in nearly 1000 patients receiving highly and moderately emetogenic chemotherapy.[2] Patients completed daily diaries for 6 days per chemotherapy cycle to report on episodes of nausea/vomiting, expectations of nausea, prechemotherapy anxiety, and prechemotherapy nausea. The investigators found that different variables contributed to the acute, delayed, and overall phases of CINV. Notably, a key predictive factor associated with CINV was the use of antiemetic therapy in ways that were inconsistent with international guidelines. Other independent predictive variables included younger age, prechemotherapy nausea, and history of CINV in prior cycles. Factors that were important predictors in some phases of CINV included anxiety, history of nausea/vomiting, and expectations of nausea.

These findings highlight the importance of following evidence-based guidelines for preventing CINV, but data suggest that these guidelines are not adequately followed in clinical practice. In a prospective observational study of 1295 chemotherapy-naive patients in the Southeastern United States receiving single-day highly or moderately emetogenic chemotherapy, only 57% of patients received CINV prophylaxis that was consistent with guideline recommendations.[3] Treatment that adhered to the guidelines significantly decreased the proportion of patients

Table 4. Rates of CINV According to Whether Guidelines Were Followed

	Guidelines Followed (n=742)	Guidelines Not Followed (n=553)	*P* Value	Adjusted Odds Ratio (95% CI)	Adjusted *P* Value
No CINV	396 (53.4%)	242 (43.8%)	.0006	1.34 (1.04-1.73)	.0225
No Emesis	674 (90.8%)	481 (87.0%)	.0271	1.58 (1.07-2.36)	.0229
No Clinically Significant Nausea	397 (53.5%)	246 (44.5%)	.0013	1.31 (1.02-1.68)	.0379

CINV, chemotherapy-induced nausea and vomiting.

Data from Gilmore JW et al. *J Oncol Pract.* 2014;10(1):68-74.[3]

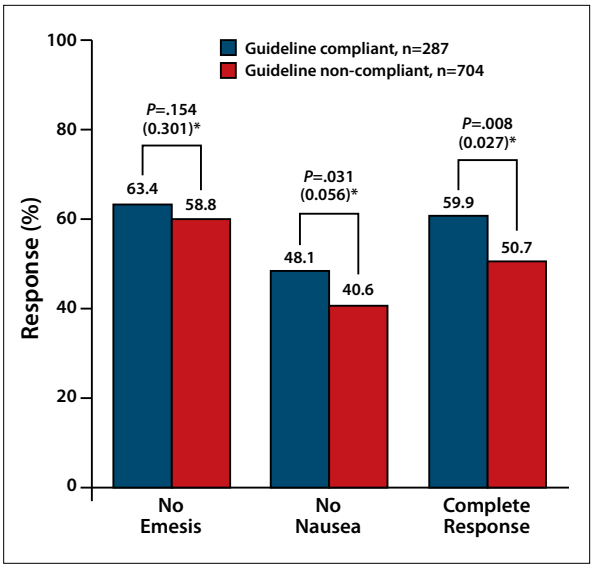

Figure 4. A study from the Pan European Emesis Registry showed that rates of CINV were lower among patients treated according to guidelines. CINV, chemotherapy-induced nausea and vomiting.

Adapted from Young A et al. *Ecancermedicalscience*. 2013;7:296. doi: 10.3332/ecancer.2013.296. Print 2013.[4] Data from Aapro M et al. *Ann Oncol*. 2012;23(8):1986-1992.[5]

with CINV throughout the 5-day postchemotherapy period (44% vs 53%; *P*<.001; Table 4). A study from the Pan European Emesis Registry also showed that rates of CINV were lower among patients treated according to guidelines (Figure 4).[4,5]

General Principles of CINV Management

In general, CINV control is best achieved with the appropriate use of available prophylactic medications and through patient education on how to treat breakthrough CINV. Adjustments may need to be made throughout the duration of treatment based on how patients tolerate chemotherapy and CINV prophylaxis. It is important to be flexible with each cycle of treatment.

A critical aspect of CINV management is to listen to patients. By listening to a patient's description of his or her situation, clinicians may better understand the causes of symptoms and provide more appropriate management. For example, gastric distress may arise as a result of chemotherapy, steroids, and other treatments, as well as from lifestyle factors. For these patients, an H_2 blocker or proton pump inhibitor may help control gastrointestinal symptoms associated with the treatment. Given the demonstrated role of anxiety in contributing to CINV risk, anxiety-reducing strategies, including counseling services and medication, may reduce CINV. These interventions should be discussed with patients upfront and during the treatment period.

Another component of managing CINV involves informing patients about eating habits and other lifestyle measures that may reduce nausea and vomiting, including eating small, frequent meals; selecting foods less likely to induce nausea or vomiting; and eating food at room temperature. Although these strategies have not been studied in the same rigorous way as pharmacologic therapies, they may help patients feel more comfortable during therapy.

Overview of CINV Guidelines

Multiple guidelines are available for the prevention and treatment of CINV, including the NCCN guidelines,[1] which are updated annually; the American Society of Clinical Oncology guidelines,[6] last updated in 2011; and guidelines from the Multinational Association of Supportive Care in Cancer (MASCC)[7] and the European Society of Medical Oncology, last updated in 2010. Tools are also available to assist in CINV prevention and treatment, including the validated MASCC Antiemesis Tool.[8]

Highly Emetogenic Chemotherapy

The NCCN guidelines recommend a combination of agents for CINV prophylaxis regimens for highly emetogenic chemotherapy. The regimen should consist of a 5-HT_3 antagonist (palonosetron is preferred, but other options are dolasetron, granisetron, and ondansetron), a steroid (dexamethasone [with aprepitant or fosaprepitant]), and an NK_1 antagonist (aprepitant or fosaprepitant), lorazepam, or an H_2 blocker or proton pump inhibitor. The NCCN guidelines also list several olanzapine-containing regimens for primary prophylaxis, but this approach tends to be used in countries without access to NK_1 antagonists.[1] In the breast cancer setting, olanzapine seems to be associated with more neuropsychiatric adverse events than the other NK_1 antagonists and is a less preferred and less commonly used agent. Some patients cannot tolerate 5-HT_3 receptor antagonists, and it will be interesting to see whether NEPA, by combining the 5-HT_3 antagonist and the NK_1 antagonist, will be easier for patients to tolerate than current therapies. If NEPA does provide better control of CINV, it will change management moving forward.

Many patients receiving highly emetogenic chemotherapy require additional breakthrough medication. The choice of agent may depend on the patient's tolerance for different classes of agents. Lorazepam and prochlorperazine are commonly used; other agents recommended by the NCCN include olanzapine, cannabinoids, 5-HT_3 antagonists, dexamethasone, promethazine, haloperidol, metoclopramide, or the scopolamine transdermal patch.

Moderately Emetogenic Chemotherapy

In general, the difference between the approaches for moderately emetogenic regimens and highly emetogenic

regimens lies in the use of the NK_1 antagonist. For moderately emetogenic regimens, an NK_1 antagonist is used prophylactically in selected patients, such as those at a higher risk for CINV.[1] In those patients, it may be preferable to start with a more aggressive antiemetic regimen that includes an NK_1 antagonist and then reduce the intensity of treatment if good CINV control is attained.

It is important to maintain the dosage and intensity of chemotherapy, particularly in early-stage disease. When significant nausea and vomiting are not decreased by guideline recommendations for moderately emetogenic chemotherapy, the recommendations for highly emetogenic chemotherapy should be followed.

Low Emetogenic-Risk Chemotherapy

Occasionally, patients will develop significant CINV from agents that are considered to have low or minimal emetic risk. In these situations, it is essential to consider other potential causes of nausea. For example, a small number of patients develop significant nausea and vomiting from capecitabine, which is considered to have minimal to low emetic risk. These patients may have reduced metabolism of capecitabine (5-fluorouracil), with the potential to develop life-threatening toxicities from this drug.

Other Causes of Nausea and Vomiting

For patients without good CINV control despite adherence to guidelines and use of all available medications, other potential causes of emesis must be considered. Alternative causes of nausea and vomiting vary based on individual circumstances but can be found in both early-stage and advanced disease. Potential contributing factors include direct effects of chemotherapy on the gastrointestinal tract (eg, gastroparesis); coexisting conditions, such as diabetes or gastrointestinal disorders; nausea from other drugs, such as opioids; and direct effects of the disease (eg, bowel obstruction or vestibular dysfunction caused by brain metastases).

Conclusion

Multiple effective antiemetic agents are available for the prevention and treatment of CINV. In clinical practice, the primary goal with antiemetic therapy is to prevent CINV and effectively manage any symptoms that arise. Treatment should be individualized based on risk factors such as the chemotherapy in use and the patient's physiology. The antiemetic regimen should be modified if needed to optimize tolerability. Importantly, adherence to guidelines has been shown to markedly improve control of emesis and moderately control the risk of postchemotherapy nausea. Clinicians should become aware of new guidelines as they are released.

Acknowledgment

Eisai Inc. has provided research funding to Dr Rugo's institution, the University of California, San Francisco.

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New Data in Emerging Treatment Options for Chemotherapy-Induced Nausea and Vomiting in Clinical Practice: General Discussion

Hope S. Rugo, MD: What is your experience in using olanzapine or other rescue medications?

Rudolph M. Navari, MD, PhD: I have done a lot of work with olanzapine. In a recent study, olanzapine (10 mg/day for 3 days) was compared with metoclopramide (10 mg 3 times/day for 3 days) for breakthrough CINV in patients receiving highly emetogenic chemotherapy; all patients received prophylactic aprepitant, palonosetron, and dexamethasone.[1] For patients who developed breakthrough CINV, olanzapine was substantially more effective than metoclopramide. NCCN guidelines now recommend olanzapine as a first-line therapy in breakthrough CINV.[2]

Hope S. Rugo, MD: So your use of olanzapine is primarily for breakthrough CINV?

Rudolph M. Navari, MD, PhD: We have also included olanzapine in CINV prophylaxis for highly emetogenic chemotherapy, particularly in patients who may have done poorly on an aprepitant regimen. For these patients, switching to prophylactic olanzapine plus palonosetron and dexamethasone is quite effective in controlling nausea.

Hope S. Rugo, MD: We often see patients who cannot tolerate 5-HT_3 antagonists because of headaches. For these patients, we tend to rely more on steroids, aprepitant, and other antiemetics. Might olanzapine have a role for those patients?

Rudolph M. Navari, MD, PhD: Our preventive studies have always used olanzapine in combination with a 5-HT_3 antagonist. However, I have used olanzapine as a single agent for the treatment of chronic nausea with some success.

Hope S. Rugo, MD: It is important to mention that olanzapine is associated with sleepiness and other adverse effects to the central nervous system.

Rudolph M. Navari, MD, PhD: I agree that mentioning olanzapine-induced sedation is important. In most trials, olanzapine has been administered at 10 mg/day for 4 days in combination with dexamethasone. Olanzapine at 10 mg administered alone without dexamethasone may be associated with significant sedation; reducing the dose to 5 mg or 2.5 mg may be preferable.

Hope S. Rugo, MD: Why aren't clinicians following CINV guidelines? In my practice, I have seen patients who are receiving fairly emetogenic regimens but are not receiving proper CINV support. I am uncertain of the reason; perhaps clinicians are hesitant to consult the guidelines for each regimen, they have a diverse patient population, or they use many different chemotherapy regimens.

Rudolph M. Navari, MD, PhD: I agree that the guidelines for prevention of emesis and nausea are not followed as much as we would like. I am unsure why; perhaps oncologists are focused on the disease and the chemotherapy, and they leave the antiemetics to their support staff, who may or may not follow the guidelines. Or they may work in an institution in which antiemetics are preprescribed based, at least partially, on cost. Each institution should evaluate the available guidelines and select which set they will follow, to ensure consistency in CINV prevention and management.

Hope S. Rugo, MD: I agree. The introduction of electronic health record systems that include electronic chemotherapy orders will likely help improve adherence to guidelines. Electronic orders will likely include guideline-oriented antiemetic regimens that can be selected by checking a box.

The new agents, such as aprepitant and palonosetron, have made a huge impact on patients with breast cancer receiving anthracycline-based regimens. How will newer drugs fit into CINV management?

Rudolph M. Navari, MD, PhD: I am not sure whether the new NK_1 receptor antagonists rolapitant and netupitant will be any more efficacious than current approaches. Their toxicity profiles will likely be similar to existing agents. I predict that there will be 3 drugs in the NK_1 receptor antagonist class, which will compete primarily

on the basis of cost. When speaking with oncologists throughout the country about guidelines and individual antiemetic agents, I get the impression that decisions about antiemetic agents at their institution, whether a hospital or clinical practice, are highly influenced by cost. Therefore, pharmacy committees and formulary committees probably have substantial influence on which antiemetic agents are used.

Hope S. Rugo, MD: Yes, I agree. In order to be used in practice, newer antiemetic agents must have greater efficacy and an affordable price. There is also significant work trying to minimize the emetogenic potential of the regimens we are using. Our ability to control emesis so well has been a great improvement. Our ongoing task now is to control the lingering delayed nausea that can develop.

Acknowledgments

Eisai Inc. has provided research funding to Dr Rugo's institution, the University of California, San Francisco. Dr Navari has no real or apparent conflicts of interest to report.

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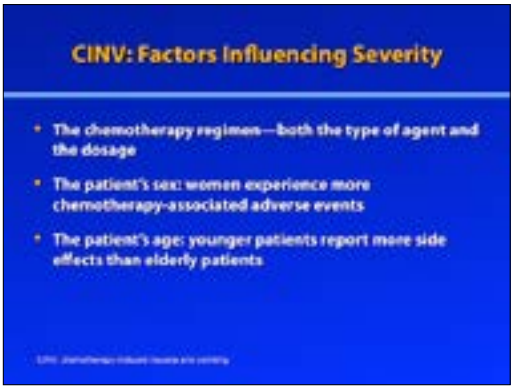

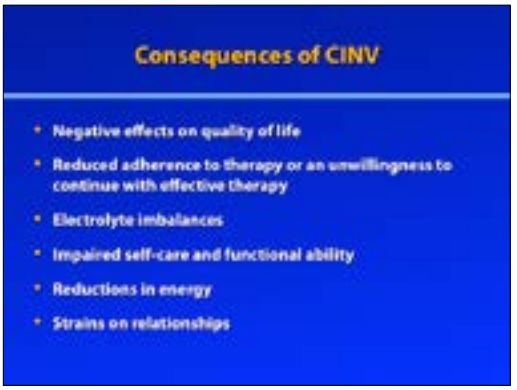

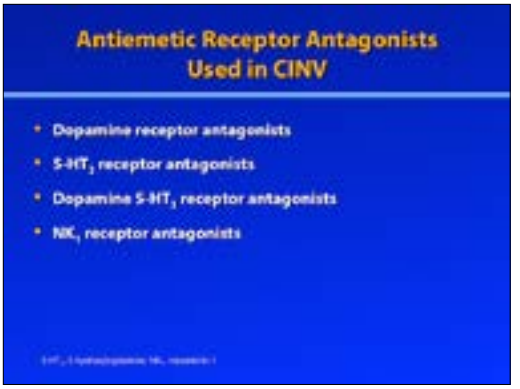

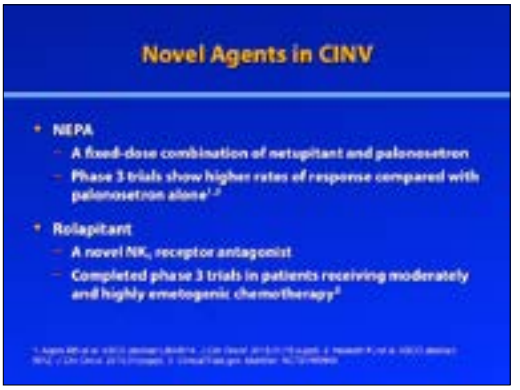

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New Data in Emerging Treatment Options for Chemotherapy-Induced Nausea and Vomiting

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

1. What is the primary factor affecting whether a patient will experience chemotherapy-induced nausea and vomiting (CINV)?

   a. The patient's age
   b. The patient's chemotherapy regimen
   c. The patient's malignancy
   d. The patient's sex

2. Which patient group is most likely to experience CINV?

   a. Younger women
   b. Older women
   c. Younger men
   d. Older men

3. Approximately how many patients experience anticipatory nausea and/or vomiting?

   a. Approximately 20%
   b. Approximately 25%
   c. Approximately 30%
   d. Approximately 35%

4. In a study of working-aged adults receiving highly or moderately emetogenic chemotherapy, uncontrolled CINV was associated with higher monthly costs of ____ for medical issues.

   a. $1000
   b. $1100
   c. $1200
   d. $1300

5. The appropriate use of antiemetic agents can reduce the risk of emesis associated with highly emetogenic therapies to:

   a. Approximately 20%
   b. Approximately 25%
   c. Approximately 30%
   d. Approximately 35%

6. In a study that added aprepitant to ondansetron and dexamethasone in patients with breast cancer receiving moderately emetogenic chemotherapy, the addition was associated with:

   a. Small improvements in acute CINV, delayed CINV, and overall CINV
   b. A small improvement in acute CINV, no improvement in delayed CINV, and a small improvement overall in CINV
   c. No improvement in acute CINV, a small improvement in delayed CINV, and a small improvement overall in CINV
   d. No improvements in acute CINV, delayed CINV, or overall CINV

7. In a phase 3 trial comparing olanzapine and aprepitant (each with dexamethasone and palonosetron), what was the overall complete response rate associated with olanzapine?

   a. 55%
   b. 66%
   c. 77%
   d. 88%

8. Which organization updates its CINV guidelines annually?

   a. American Society of Clinical Oncology
   b. European Society of Medical Oncology
   c. Multinational Association of Supportive Care in Cancer
   d. National Comprehensive Cancer Network

9. In a prospective observational study of patients in the Southeastern United States receiving single-day highly or moderately emetogenic chemotherapy, how many patients were receiving CINV prophylaxis that was consistent with guideline recommendations?

   a. 57%
   b. 61%
   c. 73%
   d. 81%

10. In general, the difference between the approaches for moderately emetogenic regimens and highly emetogenic regimens lies in:

    a. The use of the corticosteroid
    b. The use of the dopamine receptor antagonist
    c. The use of the 5-HT_3 receptor antagonist
    d. The use of the NK_1 antagonist

Project ID: 9607

Evaluation Form: New Data in Emerging Treatment Options for Chemotherapy-Induced Nausea and Vomiting

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 9607**. 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 with cancer?

❒ 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:

Identify patient-related and/or treatment-related factors that heighten the risk of developing CINV
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Manage the impact of CINV on general patient functioning
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Implement evidence-based treatment strategies to incorporate antiemetic agents as CINV prophylaxis for patients with cancer in clinical practice
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Discuss with patients and colleagues the efficacy and safety data of novel and emerging antiemetic agents to improve CINV outcomes for patients with cancer
❒ 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:

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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 1.00 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: **9607**