Clinical Roundtable Monograph

Treatment of Chemotherapy-Induced Nausea and Vomiting: A Post-MASCC 2010 Discussion

Moderator

Mark G. Kris, MD
Chief, Thoracic Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

Discussants

Susan G. Urba, MD
Professor
Division of Hematology/Oncology
University of Michigan Health System
Ann Arbor, Michigan

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

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

Release Date: January 2011
Expiration Date: January 31, 2012
Estimated time to complete activity: 1 hour
Project ID: 7697

Abstract

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and troubling side effects of treatment, and the side effect cancer patients tend to fear most. An improved understanding of the pathophysiology underlying CINV, together with a clear definition of the risk for nausea and vomiting associated with specific chemotherapeutic agents, has for allowed the development of specific and effective antiemetic regimens. Antiemesis is most effective when used prophylactically, a principle shared among CINV management guidelines. Several antiemetic drug classes are available; among the most effective of these are serotonin ($5HT_3$) receptor antagonists, neurokinin 1 (NK_1) receptor antagonists, and steroids (primarily dexamethasone), although others are commonly used as well. When choosing an appropriate antiemetic regimen, clinicians should consider patient-specific factors such as sex and prior history of CINV, as well as treatment-specific factors such as the emetogenic potential of each chemotherapeutic agent. Using these factors, clinicians can follow the available algorithms included in guidelines from groups such as the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the Multinational Association for Supportive Care in Cancer. Ongoing and future clinical trials will be pivotal in helping to further delineate the optimal strategies to prevent and manage CINV in cancer patients.

Target Audience

This activity has been designed to meet the educational needs of practicing clinicians, medical oncologists, radiation oncologists, surgical oncologists, oncology nurses, and pharmacists who wish to review and update their knowledge of recent data presented in the management of chemotherapy-induced nausea and vomiting.

Statement of Need/Program Overview

Despite advances in pharmacologic and nonpharmacologic management, chemotherapy-induced nausea and vomiting (CINV) remains among the more distressing and feared side effects to cancer patients. CINV can result in significant metabolic derangements, nutritional depletion and anorexia, deterioration of patients' physical and mental status, and degeneration of self-care and functional ability. Advances in the treatment of CINV have dramatically improved response rates and quality of life outcomes. This monograph will discuss the impact of CINV on patient life and highlight the importance of prophylaxis. It will compare guidelines from the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the Multinational Association for Supportive Care in Cancer (MASCC). Current and future management approaches, with a focus on the latest trial data presented at the 2010 MASCC meeting, will be outlined.

Educational Objectives

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

- Describe the importance of new study findings and clinical trial data in the natural history of chemotherapy-induced nausea and vomiting (CINV)
- Assess the results of these new study findings, including updates on guidelines for highly and moderately emetogenic chemotherapy and radiotherapy
- Integrate into clinical practice updated guidelines and the latest knowledge and methods for treating cancer patients with CINV in an effort to improve current quality of life statistics
- Identify future research directions for all therapies in CINV

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Millennium Medical Publishing, Inc. PIM is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

PIM designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclosure of Conflicts of Interest

PIM assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of continuing medical education (CME) activities. All relevant conflicts of interest that are identified are thoroughly vetted by PIM for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. PIM is committed to providing its learners with high quality CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Disclosures

Mark G. Kris, MD—Consulting fees: Sanofi-aventis
Susan G. Urba, MD—No real or apparent conflicts of interest to report
Lee S. Schwartzberg, MD—Advisor or consultant: Merck; Speakers bureau: Eisai, Inc.

The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

The following PIM planners and managers, Jan Hixon, RN, BSN, MA, Trace Hutchison, PharmD, Julia Kimball, RN, BSN, Samantha Mattiucci, PharmD, Jan Schultz, RN, MSN, CCMEP, and Patricia Staples, MSN, NP-C, CCRN, hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months. Jacquelyn Matos: No real or apparent conflicts of interest to report.

Method of Participation

There are no fees for participating and receiving CME credit for this activity. During the period January 2011 through January 31, 2012, participants must read the learning objectives and faculty disclosures and study the educational activity.

PIM supports Green CE by offering your Request for Credit online. If you wish to receive acknowledgment for completing this activity, please complete the post-test and evaluation on www.cmeuniversity.com. On the navigation menu, click on "Find Post-test/Evaluation by Course" and search by course ID 7697. Upon registering and successfully completing the post-test with a score of 70% or better and the activity evaluation, your certificate will be made available immediately. Processing credit requests online will reduce the amount of paper used by nearly 100,000 sheets per year.

Media

Monograph

Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. PIM, Millennium Medical Publishing, Inc., and Eisai, Inc. do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of PIM, Millennium Medical Publishing, Inc., and Eisai, Inc. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Impact of CINV

Mark G. Kris, MD

One of the largest misconceptions in the field of oncology today is that the problem of chemotherapy-induced nausea and vomiting (CINV) has been solved. Although CINV no longer requires hospitalization—as it sometimes did 2 and 3 decades ago—it remains a significant health issue today. Noteworthy advancements in the management of CINV include the development of 5-hydroxytryptamine (5-HT$_3$) and neurokinin 1 (NK$_1$) receptor antagonists, as well as an improved understanding of the use of corticosteroids.[1] However, despite these improvements, CINV continues to affect a large number of cancer patients. Thus, healthcare professionals who care for cancer patients have a critical role in the prevention and management of CINV, and it is incumbent upon them to ensure that all patients treated with chemotherapy are treated appropriately according to current evidence-based guidelines.

CINV is the most significant side effect of chemotherapy from the patient's perspective, as was shown in a survey of 464 lung cancer patients who were asked about their treatment preferences and concerns about toxicity.[2] Nearly three-quarters of respondents (73%) reported that if they had the option, they would choose a chemotherapy regimen based on its side effect profile, assuming that the outcome was equivalent. Nausea/vomiting was considered the most important side effect by nearly half of the respondents (48%), followed by infection risk (20%), fatigue (13%), hair loss (9%), other (5%), and numbness/tingling (4%).

CINV is classified into 5 categories, according to when it transpires during the course of therapy.[3] Acute CINV begins within the first several hours following chemotherapy administration, whereas delayed CINV is defined as beginning following the first 24 hours after administration. Anticipatory CINV usually occurs before chemotherapy and is a conditioned response occurring as a result of a prior CINV experience. Breakthrough CINV occurs despite prophylactic treatment and/or requires rescue with antiemetic agents. Refractory CINV occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have previously failed.

Prevalence and Impact

CINV is highly prevalent, occurring in up to 80% of patients receiving chemotherapy.[1] In a study of 151 cancer patients from 10 community oncology centers who were scheduled for their first cycle of a new chemotherapy regimen, 67% experienced either acute or delayed CINV during their first chemotherapy cycle.[4] Delayed CINV was more common than acute CINV (59% vs 36%), although many patients experienced both types. Anticipatory CINV, although common, occurred less often (between 18% and 57%).[3] Nausea is more frequently experienced compared with vomiting, and it appears to be more clinically significant for patients.[5,6] In a prospective, observational study, more than 35% of patients experienced acute nausea, but only 13% experienced acute emesis.[7]

When uncontrolled, CINV can have a significant impact on daily activities. A survey of oncology patients found that reduced daily functioning occurs in approximately one-third of patients (37.2%), with up to 90% of patients with poorly managed CINV experiencing a significant impact on daily functioning.[8] The Functional Living Index-Emesis (FLIE) questionnaire is a patient-reported tool that was originally developed to assess the impact of CINV on a patient's daily life in the 3 days following chemotherapy. Since its development, it has also been validated to assess the 5 days after chemotherapy to ensure capture of the impact of both acute and delayed CINV.[9] Using the FLIE questionnaire, 67% of patients who had at least 1 emetic episode and 77% of patients who had at least mild nausea experienced an impact on their quality of life.[10] More than 90% of all patients who experienced both nausea and vomiting (either acute or delayed) experienced an impact on their quality of life. Patients perceive that CINV significantly affects their ability to complete household tasks, enjoy meals, spend time with family and friends, and maintain daily function and recreation.[11] Although it is not necessarily the most dangerous treatment-related adverse event, CINV causes a major disruption to a patient's lifestyle, severely limiting his or her ability to participate in social functions and employment, and hampering the ability to complete daily activities.[12]

The impact of CINV is not limited to the patient's quality of life. One study has estimated that the direct medical costs incurred by working-age adults with uncontrolled CINV are 29.79% greater than those with controlled CINV ($10,720 vs $8,923; $P<.0001$).[13] Furthermore, patients with uncontrolled CINV had twice the number of work-loss days (6.23 vs 3.61 days/month). More recently, a survey of 178 patients who began chemotherapy during 2007–2008 reported that the total CINV-related costs from the day of chemotherapy administration through the 5 days following the first chemotherapy cycle averaged $778.58 per patient.[8]

Table 1. Classification Schemes for Intravenous and Oral Chemotherapeutic Agents According to Emetogenicity Risk[3,16,17]

Intravenous Agents		
Emetogenic potential* (ASCO, MASCC, and NCCN guidelines)	High	≥90% of patients
	Moderate	30–90% of patients
	Low	10–30% of patients
	Minimal	<10% of patients
Oral Agents		
Emetogenic potential* (MASCC guidelines only)	High	≥90% of patients
	Moderate	30–90% of patients
	Low	10–30% of patients
	Minimal	<10% of patients
Treatment requirement (NCCN guidelines only)		Antiemetic prophylaxis recommended
		Antiemetic treatment as needed

*Defined as the proportion of patients who will experience emesis after administration in the absence of effective antiemetic prophylaxis.

ASCO=American Society of Clinical Oncology; MASCC=Multinational Association for Supportive Care in Cancer; NCCN=National Comprehensive Cancer Network.

The impact of CINV on patients is underestimated by physicians and other healthcare providers. A prospective, observational study questioned 298 patients receiving chemotherapy for the first time and 24 of their physicians and nurses.[7] Although the clinicians accurately predicted the incidence of acute CINV, more than 75% underestimated the incidence of delayed CINV. In contrast, in another prospective, observational study of 95 patients receiving chemotherapy for the first time and 29 of their physicians and nurses, the clinicians underestimated the control of acute CINV, but accurately predicted the control of delayed CINV, in patients receiving a cisplatin-based regimen.[14]

Risk Classification of Chemotherapy Agents

The emetogenicity of a specific chemotherapy agent is the primary factor dictating whether a cancer patient will experience CINV and to what degree. According to recommendations from the Multinational Association of Supportive Care in Cancer (MASCC), the emetogenicity of a particular chemotherapeutic agent should be defined for 2 reasons: to be used as a framework when generating antiemetic treatment guidelines, and to achieve a more precise understanding of the CINV challenge.[15] Although emesis is measured by counting the number of vomiting episodes after therapy, nausea (defined as the perception that emesis may occur) is subjective and can be judged only by the patient.[16] Combination chemotherapy regimens often have a higher potential to induce CINV compared to most individual agents.

A variety of classification systems have been used to define the emetogenic potential of chemotherapy agents. To date, none of these have become standardized within clinical practice. However, several of the most widely used antiemesis guidelines (including those from MASCC,[17] the National Comprehensive Cancer Network [NCCN],[3] and the American Society of Clinical Oncology [ASCO][16]) have adopted a classification scheme (Table 1) that groups intravenous chemotherapeutic agents into 4 categories according to the proportion of patients likely to experience acute emesis when no prophylactic antiemetic therapy is administered: high (≥90% of patients); moderate (30%–90% of patients); low (10%–30% of patients); and minimal (<10% of patients). In contrast, oral chemotherapeutic agents are either grouped according to this same scheme (as in the MASCC guidelines), grouped according to whether antiemetic agents should be administered prophylactically or as needed (as in the NCCN guidelines), or not addressed (as in the ASCO guidelines).[3,16,17] Guidelines are regularly updated to reflect the introduction of new agents.

A major limitation to the classification of chemotherapeutic agents according to risk of emetogenicity is that this risk has been conclusively established for only a few agents. Additionally, the classification has been proposed based on the risk of acute emesis, and thus it potentially underestimates the potential for delayed emesis resulting from certain agents.[18] Despite this limitation, these risk classifications remain among the most widely used factors when clinicians consider the need for antiemetic therapy and the type of therapy.

Other Risk Factors

Several factors contribute to the occurrence and severity of CINV in an individual patient. Chief among these is the type of chemotherapy agent(s) used (discussed above). However, other factors must be weighed when considering if a patient is at risk of experiencing CINV and when designing an appropriate strategy to prevent and/or treat CINV. These factors can be largely divided into those relating directly to the patient and those relating directly to the treatment.

Several studies have evaluated risk factors in clinical settings.[4,19-21] For example, an analysis of 209 patients selected from multiple prospective randomized trials identified female sex (P=.0001), Eastern Cooperative Oncology Group (ECOG) performance status (P=.006), and age (P=.01) as significantly prognostic for the

Table 2. Predictive Model for CINV Risk[23]

Predictive Factors Significantly Associated With CINV (*P* values of significance)		
Factor	Post-Chemotherapy Nausea	Post-Chemotherapy Vomiting
Social functioning	.01	.0001
Nausea	.001	.008
Emetogenicity of chemotherapy	.06	.04
Maintenance antiemetics	.09	.04
Sex	.07	.06
Fatigue	.0001	N/A
ECOG performance status	.009	N/A
Alcohol consumption	N/A	.06
Combined Predictive Model (% likely to experience postchemotherapy nausea/vomiting)		
Number of Risk Factors	Post-Chemotherapy Nausea	Post-Chemotherapy Vomiting
0	66.7	20.0
1	60.8	41.7
2	70.7	57.7
3	74.5	53.2
4	76.0	75.7
5	81.7	N/A
6	96.2	N/A

CINV=chemotherapy-induced nausea and vomiting; ECOG=Eastern Cooperative Oncology Group; N/A=not available.

development of CINV, regardless of the type of antiemetic regimen used.[22]

In a larger study of 832 chemotherapy-naïve patients, a multivariate analysis revealed several factors.[23] Prechemotherapy nausea, female sex, and social functioning were significantly associated with both nausea and vomiting after chemotherapy, whereas fatigue and dyspnea were significantly associated with nausea, but not vomiting. ECOG performance status, emetogenicity of chemotherapy, maintenance antiemetics, and low alcohol consumption were significantly associated with postchemotherapy vomiting only. Using these variables in combination, a predictive model was developed to quantify the risk of developing CINV in patients with certain factors (Table 2). This model identified an approximate

30% increase in the incidence of postchemotherapy nausea among patients who had 6 of the 7 risk factors compared with patients who had no risk factors (96.2% vs 66.7%, respectively). Similarly, this same model demonstrated a 56% increase in the incidence of postchemotherapy vomiting among patients who possessed 4 of the 6 identified risk factors compared with patients who had no risk factors (75.7% vs 20.0%, respectively).

Overview of CINV Treatment Strategies

Each of the major antiemesis clinical guidelines include recommendations on the optimal CINV prevention and treatment strategies, according to the risk associated with a particular chemotherapy regimen. These treatment algorithms will be described in detail in a later section of this monograph.

The Memorial Sloan-Kettering Cancer Center has a specific approach to CINV prevention and treatment that is followed in all oncology patients receiving chemotherapy. With this approach, the cancer patient receives the optimal antiemesis prevention or treatment, directed specifically against each individual chemotherapy agent as prescribed. Antiemesis strategies are chosen by a multidisciplinary team of the physicians, nurses, and pharmacists who are closely involved in the care of cancer patients. Quality assurance panels composed of healthcare professionals document that these specific plans of care are indeed followed. The strategy at this institution ensures that the vast majority of oncology patients receive antiemesis treatment as appropriate, and that the treatment has been chosen by those healthcare professionals with the most experience with that particular chemotherapy. Despite the implementation of this strategy, many patients still experience CINV despite prophylaxis; some of the most problematic regimens are those that are cisplatin-based and anthracycline/cyclophosphamide-based.

References

1. Nevidjon B, Chaudry R. Controlling emesis: evolving challenges, novel strategies. *Supportive Oncology*. 2010;8:1-10.
2. Dubey S, Brown RL, Esmond SL, Bowers BJ, Healy JM, Schiller JH. Patient preferences in choosing chemotherapy regimens for advanced non-small cell lung cancer. *J Support Oncol*. 2005;3:149-154.
3. National Comprehensive Cancer Network. Antiemesis. Clinical Practice Guidelines in Oncology. 2010;2.2010.
4. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. *Support Care Cancer*. 2007;15:497-503.
5. Kurin SE. Chemotherapy-induced nausea and vomiting: clinical updates. *Oncology Pharmacist*. 2010;3. www.theoncologypharmacist.com/article/chemotherapy-induced-nausea-and-vomiting-clinical-updates. Accessed January 14, 2010.
6. Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2008;358:2482-2494.
7. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer*. 2004;100:2261-2268.
8. Haiderali A, Menditto L, Good M, Teitelbaum A, Wegner J. Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a US population. *Support Care Cancer*. 2010 Jun 9. [Epub ahead of print]

9. Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindley C. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the Functional Living Index-Emesis (FLIE) with 5-day recall. *Support Care Cancer*. 2003;11:522-527.

10. Ballatori E, Roila F, Ruggeri B, et al. The impact of chemotherapy-induced nausea and vomiting on health-related quality of life. *Support Care Cancer*. 2007;15:179-185.

11. Lindley CM, Hirsch JD, O'Neill CV, Transau MC, Gilbert CS, Osterhaus JT. Quality of life consequences of chemotherapy-induced emesis. *Qual Life Res*. 1992;1:331-340.

12. Decker GM, DeMeyer ES, Kisko DL. Measuring the maintenance of daily life activities using the functional living index-emesis (FLIE) in patients receiving moderately emetogenic chemotherapy. *J Support Oncol*. 2006;4: 35-41, 52.

13. Tina Shih YC, Xu Y, Elting LS. Costs of uncontrolled chemotherapy-induced nausea and vomiting among working-age cancer patients receiving highly or moderately emetogenic chemotherapy. *Cancer*. 2007;110:678-685.

14. Majem M, Moreno ME, Calvo N, et al. Perception of healthcare providers versus patient reported incidence of chemotherapy-induced nausea and vomiting after the addition of NK-1 receptor antagonists. *Support Care Cancer*. 2010 Nov 18. [Epub ahead of print]

15. Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—an update. *Support Care Cancer*. 2005;13:80-84.

16. Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol*. 2006; 24:2932-2947.

17. Roila F, Hesketh PJ, Herrstedt J. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol*. 2006;17:20-28.

18. Hong WK, Bast RC HW, Hait N, et al. Antiemetic therapy. In: *Holland-Frei Cancer Medicine*. 8th ed. China: People's Medical Publishing House USA; Chapter 123.

19. Hesketh PJ, Grunberg SM, Herrstedt J, et al. Combined data from two phase III trials of the NK1 antagonist aprepitant plus a 5HT 3 antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. *Support Care Cancer*. 2006;14:354-360.

20. Herrstedt J. Antiemetics: an update and the MASCC guidelines applied in clinical practice. *Nat Clin Pract Oncol*. 2008;5:32-43.

21. Jordan K, Sippel C, Schmoll HJ. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. *Oncologist*. 2007;12:1143-1150.

22. Pollera CF, Giannarelli D. Prognostic factors influencing cisplatin-induced emesis. Definition and validation of a predictive logistic model. *Cancer*. 1989;64: 1117-1122.

23. Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L. Determinants of postchemotherapy nausea and vomiting in patients with cancer. Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1997;15:116-123.

Guidelines for CINV Management

Susan G. Urba, MD

Prevention and treatment of CINV are critical components of the overall management of oncology patients. An improved understanding of the pathophysiology underlying CINV, combined with the introduction of several antiemetic agents and a definition of the emetogenicity of multiple chemotherapy agents, has prompted the development of treatment recommendations that may be used by clinicians to help guide therapeutic decisions. Several guidelines have been issued by various groups, including MASCC, the National Comprehensive Cancer Network (NCCN), and ASCO.[1-3] Many of the recommendations included are common among the 3 guidelines, and several guiding principles are shared (Table 1).[4]

Importance of Prophylaxis

CINV prevention is the primary principle of emesis control in cancer patients, and a goal shared among all of the major antiemetic guidelines. CINV prophylaxis is critical, as it is generally easier to prevent the onset of CINV than to treat it once it has developed. Further, patients who experience an episode of CINV have an increased risk of developing CINV in a future chemotherapy cycle, thus emphasizing the need to aggressively prevent CINV.[5]

For optimal prevention of acute CINV, patients should receive antiemetic treatment prior to initiation of chemotherapy. This antiemetic therapy should then be continued through the first 24 hours after chemotherapy.

The choice of which antiemetic agent to use should be based primarily on the emetogenic risk classification of the chemotherapeutic agent, as well as existing patient-specific risk factors.

Choices for the prevention of delayed CINV are also highly dependent upon the emetogenic risk of the chemotherapy administered. For those agents with moderate or high emetogenic potential, antiemetic prophylaxis is continued throughout the period when delayed emesis may occur (typically 2–4 days after completion of the chemotherapy cycle).

Recommended Approaches for Intravenous Chemotherapy-Induced CINV

The guidelines from the NCCN include antiemetic regimens for prevention of CINV caused by either high-risk, moderate-risk, or low-risk intravenous chemotherapy agents.[2] Many of these recommendations are similar or identical to those provided in guidelines from ASCO and MASCC.

Prevention of CINV caused by intravenous chemotherapy agents with a high risk of emetogenicity should be initiated prior to the start of chemotherapy treatment (Table 2). Patients should receive a 3-pronged combination of antiemetic agents, composed of a serotonin ($5\text{-}HT_3$) antagonist, a steroid, and an NK_1 antagonist. There are currently 4 options when choosing a $5\text{-}HT_3$ antagonist: dolasetron, granisetron, ondansetron, and palonosetron.

Table 1. Common Guiding Principles Shared Among the 3 Antiemetic Guidelines[4]

Guidelines for Antiemesis and the Prevention and Treatment of CINV	Shared Principles
Multinational Association of Supportive Care in Cancer (MASCC) National Comprehensive Cancer Network (NCCN) American Society of Clinical Oncology (ASCO)	Prevention of CINV is the primary goal of antiemetic therapy
	Patients should receive CINV prophylaxis over the entire risk period, which for moderately and highly emetogenic chemotherapies is approximately 4 days
	Oral and intravenous antiemesis formulations are equally efficacious
	The antiemetic agent should be chosen based on the emetic risk classification of the chemotherapeutic agent, the patient's prior experience with CINV, and other patient factors
	Antiemetic prophylaxis should be implemented whenever the risk of CINV is ≥10%

CINV=chemotherapy-induced nausea and vomiting.

Table 2. CINV Prevention Regimens for Emetogenic Intravenous Chemotherapy[1-3,6]

Emetic Risk	Choice of Antiemetic Therapy	
	Acute	Delayed
NCCN Guidelines		
High	5-HT$_3$ antagonist *and* steroid *and* NK$_1$ antagonist ± lorazepam ± H$_2$ blocker or proton pump inhibitor	Steroid *and* NK$_1$ antagonist ± lorazepam ± H$_2$ blocker or proton pump inhibitor
Moderate	5-HT$_3$ antagonist *and* steroid ±NK$_1$ antagonist* ± lorazepam ± H$_2$ blocker or proton pump inhibitor	5-HT$_3$ antagonist alone *or* steroid alone *or* NK$_1$ antagonist† *and* steroid ± lorazepam ± H$_2$ blocker or proton pump inhibitor
Low	Steroid *or* metoclopramide *or* prochlorperazine ± lorazepam ± H2 blocker or proton pump inhibitor	N/A
ASCO Guidelines		
High	5-HT$_3$ antagonist *and* steroid *and* NK$_1$ antagonist	Steroid *and* NK$_1$ antagonist
Moderate	5-HT$_3$ antagonist *and* steroid *and* NK$_1$ antagonist‡	5-HT$_3$ antagonist *or* steroid *or* NK$_1$ antagonist‡
Low	Steroid	N/A
MASCC Guidelines		
High	5-HT$_3$ antagonist *and* steroid *and* NK$_1$ antagonist	Steroid *and* NK$_1$ antagonist
Moderate	5-HT$_3$ antagonist *and* steroid *and* NK$_1$ antagonist‡	5-HT$_3$ antagonist *or* steroid *or* NK$_1$ antagonist‡
Low	Steroid	N/A

*In patients receiving other chemotherapy agents associated with moderate risk (eg, carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate).

†If an NK$_1$ antagonist was used on day 1.

‡In patients treated with an anthracycline/cyclophosphamide.
ASCO=American Society of Clinical Oncology; CINV=chemotherapy-induced nausea and vomiting; MASCC=Multinational Association for Supportive Care in Cancer; NA=not available; NCCN=National Comprehensive Cancer Network.

There are several formulations of 5-HT$_3$ antagonists, including oral, intravenous, and transdermal. In general, the 5-HT$_3$ antagonists are considered to be equivalent in efficacy. Dexamethasone, either orally or intravenously administered, is the only steroid recommended in this setting. Options for NK$_1$ antagonist therapy include oral aprepitant or intravenous fosaprepitant. The addition of an H$_2$ blocker or a proton pump inhibitor may help relieve dyspepsia, and the benzodiazepine lorazepam (oral or intravenous) may be added as needed. Prevention of CINV associated with high–emetic risk intravenous chemotherapy agents should occur during days 1–4 following chemotherapy administration.

Patients who receive intravenous chemotherapy agents with a moderate risk of emetogenicity should undergo a similar 3-pronged regimen of CINV prevention on day 1 of their chemotherapy regimen, with the exception that the NK$_1$ antagonist agent should be administered only in selected patients. Addition of an NK$_1$ antagonist should be considered in patients receiving multiple moderate-risk chemotherapy agents. Unlike patients who receive highly emetogenic chemotherapy, those patients receiving moderately emetogenic chemotherapy receive only the 5-HT$_3$ antagonist/steroid/NK$_1$ antagonist combination on day 1. Subsequently, patients

Table 3. CINV Prevention Regimens* for Emetogenic Oral Chemotherapy[2,3]

Emetic Risk		Choice of Antiemetic Therapy
Emetogenic potential (MASCC guidelines)	High, moderate, low, minimal	See regimens for high/moderate/low risk intravenous chemotherapeutic agents
Emetogenic potential (NCCN guidelines)	High to moderate: antiemetic prophylaxis recommended	5-HT$_3$ antagonist ± lorazepam ± H$_2$ blocker or proton pump inhibitor
	Low to minimal: antiemetic treatment as needed for CINV	Metoclopramide *or* prochlorperazine *or* haloperidol ± lorazepam ± H$_2$ blocker or proton pump inhibitor

*ASCO antiemesis guidelines do not include CINV prophylaxis regimens for oral chemotherapeutic agents.

CINV=chemotherapy-induced nausea and vomiting; MASCC=Multinational Association for Supportive Care in Cancer; NCCN=National Comprehensive Cancer Network.

are treated with either 5-HT$_3$ antagonist monotherapy, steroid monotherapy, or NK$_1$ antagonist with or without steroid therapy. The decision to add a steroid to the NK$_1$ antagonist is based upon whether the NK$_1$ antagonist was also administered on day 1. Again, lorazepam and an H$_2$ blocker or proton pump inhibitor may be used as needed.

Prevention of CINV caused by low-risk emetic intravenous chemotherapy is achieved with a simple regimen of either a steroid (dexamethasone), the dopamine D$_2$ receptor antagonist metoclopramide, or the phenothiazine dopamine D$_2$ receptor antagonist prochlorperazine. If an individual patient experiences CINV despite this single-agent prophylactic approach, a combination antiemetic agent, as described above, can be administered during the next round of chemotherapy. Lorazepam and an H$_2$ blocker or proton pump inhibitor are administered when needed. There are no routine prophylactic regimens for minimal emetic risk intravenous chemotherapy agents. Instead, these patients are treated for CINV as needed.

All 3 guidelines (NCCN, ASCO, and MASCC) recommend the 3-pronged combination strategy of a 5-HT$_3$ antagonist, a steroid, and an NK$_1$ antagonist within the first 24 hours to prevent acute CINV induced by highly emetogenic chemotherapy.[6] For the prevention of CINV

caused by moderately emetic intravenous chemotherapy, the ASCO and MASCC guidelines for antiemesis are largely comparable to those from the NCCN, with some slight differences (Table 3).[1,3] For example, the ASCO guidelines state that dexamethasone may be omitted on days 2 and 3 if aprepitant is given. Further, both ASCO and MASCC guidelines state that aprepitant is recommended for moderately emetic intravenous chemotherapy, primarily in patients receiving a combination of an anthracycline plus cyclophosphamide; in contrast, the NCCN guidelines expand this approach to include other moderate-risk emetogenic chemotherapies, including carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate.[2] Regarding CINV prevention for low-risk emetogenic chemotherapies, the ASCO and MASCC guidelines both recommend the use of single-agent dexamethasone for only the first 24 hours after chemotherapy, whereas the NCCN guidelines also include metoclopramide and prochlorperazine as options in this setting. Currently, only the MASCC and NCCN guidelines differentiate the emetic risk of oral chemotherapy agents.

Special Case: Prevention of CINV Induced By Anthracycline/Cyclophosphamide Chemotherapy

Recommendations for patients being treated with anthracycline/cyclophosphamide chemotherapy differ slightly among the antiemetic guidelines. This regimen is frequently used to treat a large group of cancer patients, most typically women with breast cancer. The anthracycline/cyclophosphamide regimen was initially considered to have a moderate emetogenic risk. However, over time it has been realized that this regimen is actually more appropriately considered as having a high emetogenic potential. Although the NCCN guidelines now include the anthracycline/cyclophosphamide combination in the high-risk group of chemotherapeutic agents,[2] the MASCC guidelines still label this regimen as having moderate-risk of emetogenicity.[3] However, the MASCC guidelines do separate this regimen from other moderate-risk agents, and actually recommend CINV prophylactic regimens that are similar to those for high-risk agents.

Treating Breakthrough CINV

Unfortunately, effective CINV prophylaxis is not achieved in all patients. Thus, antiemesis guidelines include recommendations for the treatment of breakthrough CINV. According to the NCCN guidelines, the general principle underlying the treatment of breakthrough CINV is to administer an additional agent from a drug class with a mechanism of action that has not yet been used for the patient (Table 4).[2] However, there is no consensus that one agent is better than another, and some patients may

Table 4. Management of Breakthrough CINV

Options and Alternative Drug Classes
• Antipsychotic
• Phenothiazine
• Benzodiazepine
• $5HT_3$ receptor antagonist
• Cannabinoid
• Steroid
• Dopamine D_2 receptor antagonist

require multiple additional agents. Scheduled dosing should be used as opposed to dosing as needed. Because these patients are likely to have ongoing nausea and vomiting, they may be unable to tolerate an oral antiemetic, thus making an intravenous or rectal formulation more desirable. Additionally, patients should be carefully monitored to ensure adequate hydration and electrolyte levels.

Prevention of Anticipatory CINV

Anticipatory CINV is most effectively avoided by preventing CINV from occurring in initial chemotherapy cycles.[2] Behavioral therapy, including systematic desensitization hypnosis and music therapy, are nonpharmacologic prophylactic options for prevention of anticipatory CINV. Acupuncture or acupressure may also be useful. Pharmacologic options to prevent anticipatory CINV generally revolve around antianxiety agents. The most frequently used antianxiety agents in this setting are lorazepam and alprazolam. These agents may be given the day before chemotherapy administration.

Prevention of CINV in Patients Treated With Multidrug Regimens

The prevention and management of CINV in patients treated with multidrug chemotherapy regimens is complicated by the fact that these patients are at risk for both acute and delayed CINV dependent upon the emetogenic potential of each individual agent, as well as the sequence in which these agents are administered. The general principle underlying CINV prevention in this setting is to choose antiemetic therapy according to the chemotherapeutic agent with the highest antiemetic risk.[2] A $5HT_3$ receptor antagonist should be given each day prior to the administration of the first dose of moderate or high emetogenic risk chemotherapeutics, and dexamethasone should be administered each day of treatment and the following 2 to 3 days after chemotherapy. NK_1 receptor antagonists may also be useful in this setting, especially for multidrug regimens that contain high emetogenic risk chemotherapeutic agents.

References

1. Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol.* 2006;24:2932-2947.
2. National Comprehensive Cancer Network. Antiemesis. Clinical Practice Guidelines in Oncology. 2010;2.2010.
3. Roila F, Hesketh PJ, Herrstedt J. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol.* 2006;17:20-28.
4. Wickham R. Best practice management of CINV in oncology patients: II. Antiemetic guidelines and rationale for use. *J Support Oncol.* 2010;8(2 suppl 1):10-15.
5. Nevidjon B, Chaudry R. Controlling emesis: evolving challenges, novel strategies. *Supportive Oncology.* 2010;8:1-10.
6. Jordan K, Sippel C, Schmoll HJ. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. *Oncologist.* 2007;12:1143-1150.

Overview of CINV Agents

Lee S. Schwartzberg, MD

Agents from several different drug classes are now available for the prevention and treatment of CINV. Antiemetic agents are available in numerous formulations, including oral, rectal, intravenous, intramuscular, and transdermal. The use of these medications in this setting is a result of an increased knowledge of the underlying pathophysiologic processes that cause nausea and vomiting in response to noxious substances, such as chemotherapeutic agents.

Pathophysiology of CINV

Nausea and the emesis reflex are controlled via a multistep process that is initiated when afferent (sensory) neurons transmit impulses from the pharynx and gastrointestinal tract (especially the small intestine) in what is referred to as the *peripheral mechanism* of CINV.[1,2] Chemotherapeutic agents can trigger these afferent impulses by causing irritation or damage to the enteroendocrine cells of the gastrointestinal mucosa, resulting in the release of neurotransmitters that activate receptors located on the terminal ends of the vagal afferent nerve fibers. The afferent impulses are transmitted to the brainstem vomiting center that is located within the medulla oblongata, the lower portion of the brainstem that controls autonomic functions.[3] The brainstem vomiting center is composed of loosely organized and interconnected regions within

the medulla, including the area postrema, the nucleus tractus solitarius, and the dorsal motor nucleus of the vagus nerve.[2,4] The chemoreceptor trigger zone, located within the area postrema, receives and transmits the afferent nerve impulses within the other structures of the brainstem vomiting center. Emesis may also be triggered via a central mechanism in which the chemotherapeutic agent directly activates the chemoreceptor trigger zone via the bloodstream or cerebral spinal fluid. Once the afferent impulses are received and processed, the brainstem vomiting center releases efferent impulses to the salivation center, abdominal muscles, respiratory center, and cranial nerves, leading to the process of vomiting.[5]

A number of neurotransmitters have been established as important mediators of CINV, including dopamine, serotonin (5-hydroxytryptamine, 5-HT), and substance P.[6,7] Dopamine was first thought to be the primary neurotransmitter responsible for CINV.[8] However, the high degree of variability associated with the use of dopamine antagonists as antiemetic agents, as well as the inability of dopamine antagonists to prevent the CINV caused by certain chemotherapeutic agents, suggested the importance of other neurotransmitters.[9] It is now understood that no single neurotransmitter is responsible for all forms of CINV. Several antagonists to these neurotransmitter receptors have been developed. However, because a single common pathway for emesis is not yet defined, no single agent is able to provide complete prophylactic protection against all forms of CINV.

Corticosteroids

Corticosteroids, themselves a component of many chemotherapy regimens, were first found to have antiemetic characteristics approximately 30 years ago.[10] The mechanism by which they are effective in preventing CINV is not well understood, but they are active against both acute and delayed emesis. A meta-analysis of 32 studies containing 5,613 patients found that the corticosteroid dexamethasone increased the likelihood that patients would avoid acute or delayed CINV symptoms (odds ratio, 2.22; 95% confidence interval [CI], 1.89–2.60; and odds ratio, 2.04; 95% CI, 1.63–2.56, respectively).[11] The majority of studies evaluating corticosteroids as antiemetic agents are limited to dexamethasone and methylprednisolone. Corticosteroids are now a mainstay of antiemetic regimens for the prevention of CINV.

Dopamine (D$_2$) Receptor Antagonists

Dopamine receptor antagonists such as high-dose metoclopramide have been shown to have a beneficial effect in CINV prophylaxis. Although they can be utilized in this setting, they are generally not given because of the availability of more effective regimens, as well as the substantial toxicity—particularly extrapyramidal side effects—

associated with the use of high-dose metoclopramide. Thus, metoclopramide is predominantly of historical use, although occasionally it may be administered in the rare case of a patient who cannot tolerate the other more common and more useful classes that are available.

Serotonin (5HT$_3$) Receptor Antagonists

In vitro studies demonstrated that cisplatin treatment of gastrointestinal enterochromaffin cells resulted in calcium-dependent 5-HT release, a process possibly mediated by free radical generation.[12-14] The importance of 5-HT in CINV was further supported with evidence showing that cisplatin results in a large increase in the amount of 5-HT metabolite excreted.[15] Among the many 5-HT receptors, the 5-HT$_3$ receptor appears to be the most critical for CINV. The 5-HT$_3$ receptors that are located in the vagal afferent nerve fibers are involved in the peripherally-mediated CINV, whereas the 5-HT$_3$ receptors in the area postrema and nucleus tractus solitarius are involved in centrally mediated CINV.[16,17]

The prevention and management of CINV were dramatically revolutionized with the introduction of the use of 5-HT$_3$ antagonists in the 1990s. First-generation 5-HT$_3$ antagonists include ondansetron, granisetron, dolasetron, and tropisetron. Meta-analyses of multiple randomized trials demonstrated that these agents are largely therapeutically equivalent and are associated with relatively few and mild adverse events.[18-20] These agents are effective in preventing acute emesis, but their effect on delayed emesis is minimal.[21]

In 2003, the second-generation 5-HT$_3$ antagonist palonosetron was approved for CINV. Palonosetron offers the advantages of a prolonged half-life and an approximate 100-fold greater affinity for the 5-HT$_3$ receptor compared with the first-generation 5-HT$_3$ antagonists.[22,23] In several prospective, randomized phase III clinical trials, palonosetron was demonstrated to be either noninferior or significantly superior to the first-generation agents ondansetron and dolasetron. At the 2010 MASCC meeting, Morrow and colleagues presented a retrospective subgroup analysis of 2 phase III studies of palonosetron versus ondansetron and dolasetron.[24] Patients received either a single intravenous dose of palonosetron (0.25 mg), ondansetron (32 mg), or dolasetron (100 mg). Higher rates of complete response, defined as no emetic episodes and no need for rescue therapy, were achieved by patients who received palonosetron compared with either ondansetron or dolasetron over both acute and delayed CINV intervals. Overall, a higher proportion of patients in the palonosetron arm experienced no nausea and no vomiting during the entire 120 hours postchemotherapy.

In a study comparing ondansetron and palonosetron in 563 cancer patients, palonosetron resulted in significantly higher rates of complete response during the acute

period, defined as having no emetic response and requiring no antiemetic rescue therapies (68.6% vs 81.0%; *P*<.01).[25] Palonosetron therapy also resulted in significantly higher rates of complete response during the delayed period (74.1% vs 55.1%; *P*<.01), as well as overall, up to 120 hours postchemotherapy (69.3% vs 50.3%; *P*<.01). Comparatively, a second study of 569 patients found palonosetron to be as effective as dolasetron,[26] and a trial of 667 patients showed that palonosetron was as effective as ondansetron.[27] Interestingly, this same study showed that dexamethasone, which was administered at the investigators' discretion, significantly increased the efficacy of palonosetron but not ondansetron during the delayed phase and overall.

In a recent randomized study, palonosetron plus dexamethasone was overall superior to granisetron plus dexamethasone for prevention of CINV.[28] This study included 1,114 patients receiving highly emetogenic chemotherapy. Although a similar proportion of patients in each group had a complete response during the acute phase (75.3% vs 73.3%), more patients in the palonosetron group had a complete response during the delayed phase (56.8% vs 44.5%; *P*<.0001). However, these conclusions have been questioned because of potentially inadequate dosing in the granisetron arm and the use of a high (nonapproved) dose of palonosetron.[22] The superiority of palonosetron compared with first-generation 5-HT$_3$ antagonists remains to be established in prospective trials incorporating the latest evidence-based guidelines and other antiemetic agents, as appropriate.[2]

Unfortunately, 5-HT$_3$ antagonists with corticosteroids do not adequately prevent all CINV cases, and a number of patients still suffer from CINV. This is especially true for highly emetogenic chemotherapeutic agents.

NK$_1$ Receptor Antagonists

The neurotransmitter substance P is a member of the tachykinin peptides, a family of peptides involved in a number of regulatory processes through interaction with the NK receptors.[29] Specifically, substance P binds to NK$_1$ receptors, which are located throughout the central nervous system, including the area postrema and the nucleus tractus solitarius, as well as in peripheral sites in the gastrointestinal tract. However, because experiments in animal models show that NK$_1$ antagonists that are unable to cross the blood-brain barrier are ineffective antiemetic agents, it is believed that the involvement of substance P and NK$_1$ receptors is limited to the central mechanism of CINV.[30] Substance P was first demonstrated to be involved in the emetic process when it was shown that administration of the peptide to dogs induced emesis.[31,32]

As the importance of the NK$_1$ receptor became apparent in the centrally-driven mechanism of CINV—the main mechanism responsible for delayed emesis—NK$_1$ antagonists have been investigated as potential antiemetic

agents. In 2003, aprepitant, the first NK$_1$ antagonist, was approved as an orally available antiemetic agent. This was followed in 2008 by the approval of fosaprepitant, an intravenously administered aprepitant pro-drug. Aprepitant was approved based on 2 identically-designed, pivotal phase III trials.[33] Both trials compared the safety and efficacy of a 3-drug combination consisting of ondansetron, dexamethasone, and aprepitant with the 2-drug combination of ondansetron and dexamethasone. All agents were administered prior to use of the emetic chemotherapeutic agent, and dexamethasone and aprepitant were also subsequently continued. The trials evaluated the antiemetic therapy over a 5-day period, and in both, the addition of aprepitant reduced the risk of CINV or the need for rescue therapy by approximately half. In one study, the rate of complete response was significantly higher in patients who received aprepitant compared with those who did not (72.7% vs 52.3%; *P*<.001), a difference that became especially apparent on days 2–5 following cisplatin treatment.[34] Similarly, the rate of complete response in the second trial was 62.7% versus 43.3%, respectively (*P*<.001).[35] Interestingly, pooled data from these trials suggested that aprepitant negated the increased risk for CINV associated with female sex.[36] A subsequent phase III study in breast cancer patients further showed that a regimen consisting of a prophylactic combination of aprepitant, ondansetron, and dexamethasone prior to moderately emetogenic chemotherapy (anthracycline plus cyclophosphamide) followed by aprepitant alone on days 2 and 3 was significantly superior to a prophylactic combination of ondansetron and dexamethasone followed by ondansetron and dexamethasone on days 2 and 3.[37]

At the 2010 MASCC meeting, Grunberg and coworkers presented results from a double-blind randomized phase III clinical trial that compared aprepitant at the approved 3-day oral schedule with a single intravenous dose of fosaprepitant.[38] The study was designed to determine whether fosaprepitant was noninferior to aprepitant with regard to the primary endpoint, complete response (no vomiting and no use of rescue medications). The 2,247 evaluable patients received cisplatin (70 mg/m^2) for the first time and also received ondansetron and dexamethasone; patients were randomized to receive either aprepitant (125 mg day 1, 80 mg days 2–3; n=1,138) or fosaprepitant (150 mg day 1; n=1,109). A similar proportion of patients in both arms required antiemetic rescue medication, indicating that fosaprepitant was indeed noninferior during the overall risk period. Most adverse events were similar in both arms, with aprepitant and fosaprepitant considered to be well tolerated. Infusion site pain/erythema/phlebitis was more frequent in the fosaprepitant arm (0.6% vs 2.4%).

Aprepitant both induces and inhibits the activity of the drug metabolizing enzyme cytochrome P450 enzyme 3A4 (CYP3A4).[39] Therefore, aprepitant may interact

significantly with the metabolism of coadministered drugs that are metabolized in a CYP3A4-mediated pathway. Because of the risk of life-threatening reactions, the combination of aprepitant with pimozide, terfenadine, astemizole, and cisapride is contraindicated.[22] Coadministration with chemotherapeutic agents metabolized by CYP3A4 is generally allowed without dose modification, but caution should be used. Dexamethasone should be reduced when combined with aprepitant. Typically, the dose is reduced from a maximum of 20 mg without aprepitant to 12 mg on day 1 with aprepitant. When dexamethasone is combined with aprepitant on days 2 and 3, a regimen of 8 mg/day in a single dose or divided doses is commonly used for highly emetogenic chemotherapy.

Other Agents for CINV

The benzodiazepine lorazepam can be used in conjunction with the standard 3-drug antiemetic regimen in the prophylactic setting. This approach is especially useful in patients who experience anticipatory CINV or in patients who exhibit moderate or extreme anxiety prior to receiving chemotherapy.

There is a growing realization that many patients who receive chemotherapy are at an increased risk for developing symptoms of gastroesophageal reflux. This condition may exacerbate pre-existing nausea, or it can even be misinterpreted as nausea. Therefore, acid reduction strategies such as a proton pump inhibitor or an H_2 antagonist can be used, especially in patients with a history of gastroesophageal reflux or heartburn.

The dopaminergic D_2 antagonists metoclopramide and the butyrophenones effectively prevent CINV in a dose-dependent manner, and metoclopramide plus dexamethasone is as effective as single-agent ondansetron to prevent acute and delayed CINV.[40] Interestingly, the atypical antipsychotic agent olanzapine, an antagonist of both dopamine and 5-HT receptors, has also been found in 2 phase II trials to effectively prevent both acute and delayed CINV, and it is also active in the breakthrough setting.[41,42] At the 2010 MASCC meeting, Navari and Gray presented results from a randomized trial comparing the ability of olanzapine versus aprepitant to prevent CINV when either agent was combined with palonosetron and dexamethasone.[43] A total of 53 patients were included; all patients were chemotherapy-naïve and received either cisplatin or cyclophosphamide plus doxorubicin. Patients in the olanzapine arm received olanzapine at 10 mg on day 1 combined with 0.25 mg palonosetron and 20 mg dexamethasone, followed by 10 mg/day olanzapine alone on days 2–4 after chemotherapy. Patients in the aprepitant arm received aprepitant at 125 mg on day 1 combined with 0.25 mg palonosetron and 12 mg dexamethasone,

followed by 80 mg aprepitant plus 4 mg dexamethasone twice daily on days 2 and 3. Both regimens were found to be similar overall, resulting in a 75% and 70% rate of CINV prevention for the olanzapine and aprepitant regimens, respectively, during the overall period (0–120 hours) following chemotherapy. A higher proportion of patients achieved complete response during the acute period with the olanzapine regimen compared with the aprepitant regimen (100% vs 87%), but the proportions were similar in the delayed period (75% vs 70%). However, it was demonstrated that the olanzapine regimen resulted in improved nausea control in both the delayed (65% vs 38%) and overall (65% vs 38%) periods.

Management of breakthrough CINV remains problematic. Although several pharmacologic options are available, they are generally of lesser or undefined efficacy. Furthermore, in general these agents have not been formally studied in great detail against one another. The phenothiazines, particularly prochlorperazine, are probably the most commonly used agents in the breakthrough CINV setting. In one study, prochlorperazine was actually shown to be more effective than 5-HT$_3$ antagonists in the treatment of breakthrough CINV resulting from anthracycline plus cyclophosphamide chemotherapy.

Other pharmacologic agents have been investigated for their antiemetic potential. Several of them have a low therapeutic index and are associated with a lower efficacy and higher risk of adverse events. The synthetic cannabinoids nabilone and dronabinol have antiemetic efficacy, but they are associated with significant adverse events such as postural hypotension and dysphoria.[44] One recent review of several clinical studies found that although nabilone was superior to placebo in the treatment of CINV, it did not add to the benefits of 5-HT$_3$ antagonists.[45]

Conclusion

Our expanded knowledge of the pathophysiology of CINV has resulted in several classes of agents—including the 5-HT$_3$ receptor antagonists, NK$_1$ antagonists, dopamine receptor antagonists, and corticosteroids—which when utilized in combination, are effective in prevention of this toxicity. Nonetheless, the problem still exists for a significant fraction of patients. Further improvement in preventing CINV will likely come from a better understanding of the complex interaction of neurotransmitters involved in this reflex and the concurrent development of both more effective agents and novel inhibitory drugs.

References

1. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer*. 2004;100:2261-2268.
2. Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2008;358:2482-2494.
3. Miller AD. Central mechanisms of vomiting. *Dig Dis Sci*. 1999;44:39S-43S.

4. Hornby PJ. Central neurocircuitry associated with emesis. *Am J Med.* 2001;111;(suppl 8A):106S-112S.

5. Sanger GJ, Andrews PL. Treatment of nausea and vomiting: gaps in our knowledge. *Auton Neurosci.* 2006;129:3-16.

6. Endo T, Minami M, Hirafuji M, et al. Neurochemistry and neuropharmacology of emesis—the role of serotonin. *Toxicology.* 2000;153:189-201.

7. Leslie RA, Shah Y, Thejomayen M, Murphy KM, Robertson HA. The neuropharmacology of emesis: the role of receptors in neuromodulation of nausea and vomiting. *Can J Physiol Pharmacol.* 1990;68:279-288.

8. Berger AM, RA C-S. Adverse events of treatment. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology.* Philadelphia, Pennsylvania: Lippincott Williams & Wilkins. 2001:2869-2880.

9. Ison PJ, Peroutka SJ. Neurotransmitter receptor binding studies predict antiemetic efficacy and side effects. *Cancer Treat Rep.* 1986;70:637-641.

10. Aapro MS, Alberts DS. High-dose dexamethasone for prevention of cisplatin-induced vomiting. *Cancer Chemother Pharmacol.* 1981;7:11-14.

11. Ioannidis JP, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. *J Clin Oncol.* 2000;18:3409-3422.

12. Andrews PL, Naylor RJ, Joss RA. Neuropharmacology of emesis and its relevance to anti-emetic therapy. Consensus and controversies. *Support Care Cancer.* 1998;6:197-203.

13. Torii Y, Mutoh M, Saito H, Matsuki N. Involvement of free radicals in cisplatin-induced emesis in Suncus murinus. *Eur J Pharmacol.* 1993;248:131-135.

14. Minami M, Endo T, Nemoto M, et al. How do toxic emetic stimuli cause 5-HT release in the gut and brain? In: Reynolds DJM, Andrews PLR, Davis CJ, eds. *Serotonin and the Scientific Basis of Anti-Emetic Therapy.* Oxford, UK: Oxford Clinical Communications. 1995:68-76.

15. Cubeddu LX. Serotonin mechanisms in chemotherapy-induced emesis in cancer patients. *Oncology.* 1996;53(suppl 1):18-25.

16. Fozard JR. Neuronal 5-HT receptors in the periphery. *Neuropharmacology.* 1984;23:1473-1486.

17. Kilpatrick GJ, Jones BJ, Tyers MB. Binding of the 5-HT3 ligand, [3H] GR65630, to rat area postrema, vagus nerve and the brains of several species. *Eur J Pharmacol.* 1989;159:157-164.

18. del Giglio A, Soares HP, Caparroz C, Castro PC. Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting: results of a meta-analysis of randomized controlled trials. *Cancer.* 2000;89:2301-2308.

19. Jordan K, Hinke A, Grothey A, Schmoll HJ. Granisetron versus tropisetron for prophylaxis of acute chemotherapy-induced emesis: a pooled analysis. *Support Care Cancer.* 2005;13:26-31.

20. Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. *Support Care Cancer.* 2007;15:1023-1033.

21. Geling O, Eichler HG. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. *J Clin Oncol.* 2005;23:1289-1294.

22. National Comprehensive Cancer Network. Antiemesis. Clinical Practice Guidelines in Oncology 2010;2.2010.

23. Tonini G, Vincenzi B, Santini D. New drugs for chemotherapy-induced nausea and vomiting: focus on palonosetron. *Expert Opin Drug Metab Toxicol.* 2005;1:143-149.

24. Morrow G, Ballinari G, Moresino C, Chen K, Cox D. Palonosetron (Palo) versus ondansetron (Ond) and dolasetron (Dol) for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy: a subgroup analysis of two phase III studies. Paper presented at: Multinational Association for Supportive Care in Cancer 2010 International Symposium; July 24–26, 2010; Vancouver, British Columbia. Abstract 02-009.

25. Gralla R, Lichinitser M, Van Der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol.* 2003;14:1570-1577.

26. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: results of a phase III, single-dose trial versus dolasetron. *Cancer.* 2003;98:2473-2482.

27. Aapro MS, Grunberg SM, Manikhas GM, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Ann Oncol.* 2006;17:1441-1449.

28. Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. *Lancet Oncol.* 2009;10:115-124.

29. Severini C, Improta G, Falconieri-Erspamer G, Salvadori S, Erspamer V. The tachykinin peptide family. *Pharmacol Rev.* 2002;54:285-322.

30. Tattersall FD, Rycroft W, Francis B, et al. Tachykinin NK1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. *Neuropharmacology.* 1996;35:1121-1129.

31. Carpenter DO, Briggs DB, Strominger N. Responses of neurons of canine area postrema to neurotransmitters and peptides. *Cell Mol Neurobiol.* 1983;3:113-126.

32. Saito R, Takano Y, Kamiya HO. Roles of substance P and NK(1) receptor in the brainstem in the development of emesis. *J Pharmacol Sci.* 2003;91:87-94.

33. Warr DG, Grunberg SM, Gralla RJ, et al. The oral NK(1) antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials. *Eur J Cancer.* 2005;41:1278-1285.

34. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J Clin Oncol.* 2003;21:4112-4119.

35. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer.* 2003;97:3090-3098.

36. Hesketh PJ, Grunberg SM, Herrstedt J, et al. Combined data from two phase III trials of the NK1 antagonist aprepitant plus a 5HT 3 antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. *Support Care Cancer.* 2006;14:354-360.

37. Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol.* 2005;23:2822-2830.

38. Grunberg S, Chua D, DeVandry S, Hardwick J, Taylor A, Herrstedt J. Evaluation of fosaprepitant in a single dose schedule for prevention of chemotherapy-induced nausea and vomiting: a phase III randomized double-blind study. Paper presented at: Multinational Association for Supportive Care in Cancer/International Society of Oral Oncology 2010 International Symposium; July 24–26, 2010; Vancouver, British Columbia. Abstract 02-006.

39. Shadle CR, Lee Y, Majumdar AK, et al. Evaluation of potential inductive effects of aprepitant on cytochrome P450 3A4 and 2C9 activity. *J Clin Pharmacol.* 2004;44:215-223.

40. Bhatia A, Tripathi KD, Sharma M. Efficacy & tolerability of ondansetron compared to metoclopramide in dose dependent cisplatin-induced delayed emesis. *Indian J Med Res.* 2004;120:183-193.

41. Navari RM, Einhorn LH, Loehrer PJ Sr, et al. A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier oncology group study. *Support Care Cancer.* 2007;15:1285-1291.

42. Navari RM, Einhorn LH, Passik SD, et al. A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier Oncology Group study. *Support Care Cancer.* 2005;13:529-534.

43. Navari R, Gray G. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV): a randomized trial. Paper presented at: Multinational Association for Supportive Care in Cancer/International Society of Oral Oncology 2010 International Symposium; July 24–26, 2010; Vancouver, British Columbia. Abstract 02-010.

44. Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ.* 2001;323:16-21.

45. Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opin Investig Drugs.* 2008;17:85-95.
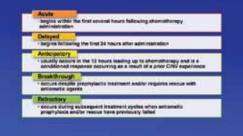
Slide Library

Advancements in the Management of CINV

- 5-hydroxytryptamine (5-HT$_3$) receptor antagonists
- Neurokinin-1 (NK$_1$) receptor antagonists
- Improved understanding of the use of corticosteroids

CINV=chemotherapy-induced nausea and vomiting.

Classification of CINV

Acute
- begins within the first several hours following chemotherapy administration

Delayed
- begins following the first 24 hours after administration

Anticipatory
- usually occurs in the 12 hours leading up to chemotherapy and is a conditioned response occurring as a result of a prior CINV experience

Breakthrough
- occurs despite prophylactic treatment and/or requires rescue with antiemetic agents

Refractory
- occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have previously failed

Impact of CINV: Quality of Life

- Reduced daily functioning occurred in 37.2%, with up to 90% of patients with poorly managed CINV experiencing a significant impact on daily functioning[1]
- Using the FLIE questionnaire, 67% of patients who had at least 1 emetic episode and 77% of patients who had at least mild nausea experienced an impact on their quality of life.[2] More than 90% of all patients who experienced both nausea and vomiting (either acute or delayed) experienced an impact on their quality of life
- Patients perceive that CINV significantly affects their ability to complete household tasks, enjoy meals, spend time with family and friends, and maintain daily function and recreation[2]

FLIE=Functional Living Index-Emesis.
1. Haiderali A et al. Support Care Cancer. 2010 Jun 9. 2. Ballatori E et al. Support Care Cancer. 2007;15(2):179-185. 3. Lindley CM et al. Qual Life Res. 1992;1(5):331-340.

CINV: Prevalence

- Occurs in up to 80% of patients receiving chemotherapy[1]
- In a study of 151 cancer patients from 10 community oncology centers who were scheduled for their first cycle of a new chemotherapy regimen, 67% experienced either acute or delayed CINV during their first chemotherapy cycle.[2] Delayed CINV was more common than acute CINV (59% vs 36%), although many patients experienced both types
- Anticipatory CINV occurs in 18–57%[3]
- Nausea is more frequently experienced compared with vomiting, and it appears to be more clinically significant for patients[4,5]
- In a prospective, observational study, more than 35% of patients experienced acute nausea, but only 13% experienced acute emesis[6]

1. Navári R, Chawla R. Supportive Oncology. 2010;6:1-10. 2. Grunberg SM et al. Support Care Cancer. 2007;15:497-503. 3. National Comprehensive Cancer Network. Antiemesis. Clinical Practice Guidelines in Oncology. 2011. 4. Sun CC. Oncology Pharmacist. 2010;3. 5. Hesketh PJ. N Engl J Med. 2008;358:2482-2494. 6. Grunberg SM et al. Cancer. 2004;100:2261-2268.

Impact of CINV: Financial Costs

- The direct medical costs incurred by working-age adults with uncontrolled CINV are 29.79% greater than those with controlled CINV ($10,720 vs $8,923; P<.0001).[1] Furthermore, patients with uncontrolled CINV had twice the number of work-loss days (6.23 vs 3.61 days/month)
- A survey of 178 patients who began chemotherapy during 2007–2008 reported that the total CINV-related costs from the day of chemotherapy administration through the 5 days following the first chemotherapy cycle averaged $778.58 per patient[2]

1. The Shih YC et al. Cancer. 2007;110:678-685. 2. Haiderali A et al. Support Care Cancer. 2010 Jun 9.

CINV Risk Factors

Patient-specific Factors
- Female sex
- Age
- History of low alcohol intake
- History of chemotherapy-induced nausea and vomiting
- Performance status
- Pretreatment expectations
- History of motion sickness
- History of emesis during pregnancy

Treatment-specific Factors
- Emetogenic risk of particular agent(s)
- Dosage and schedule
- Rate of administration
- Route of administration

Antiemetic Guidelines

- Multinational Association of Supportive Care in Cancer (MASCC)
- National Comprehensive Cancer Network (NCCN)
- American Society of Clinical Oncology (ASCO)

CINV Prevention

- CINV prevention is the primary principle of emesis control in cancer patients
- Patients who experience an episode of CINV have an increased risk of developing CINV in a future chemotherapy cycle, thus emphasizing the need to aggressively prevent CINV[1]
- For optimal prevention of acute CINV, antiemetics should be administered prior to the initiation of chemotherapy and through the first 24 hours after chemotherapy

1. Navidson R, Chaudry R. Supportive Oncology. 2010;8:1-10.

General Principles in CINV Treatment

- Breakthrough CINV: administer an additional agent from a drug class with a mechanism of action that has not yet been used for the patient. Use scheduled dosing as opposed to dosing as needed
- Anticipatory CINV: prevent CINV from occurring in initial chemotherapy cycles
- In multidrug chemotherapy regimens: choose antiemetic therapy according to the chemotherapeutic agent with the highest antiemetic risk

Antiemetic Agent Formulations

- Oral
- Rectal
- Intravenous
- Intramuscular
- Transdermal

Neurotransmitters Established as Important Mediators of CINV

- Dopamine
- Serotonin (5-hydroxytryptamine, 5-HT)
- Substance P

CINV Treatment Options

- Corticosteroids
- Dopamine receptor antagonists (eg, high-dose metoclopramide)
- Serotonin (5HT3) receptor antagonists
- Neurokinin 1 (NK1) receptor antagonists
- Other agents: lorazepam, proton pump inhibitors or aH2 antagonists, dopaminergic D_2 antagonists, olanzapine

For a free electronic download of these slides, please direct your browser
to the following web address:

http://www.clinicaladvances.com/index.php/our_publications/hem_onc-issue/ho_january_2011/