Chemotherapy-Induced Nausea and Vomiting: Challenges and Opportunities for Improved Patient Outcomes

Rebecca Hawkins, MSN, ANP, AOCN®, and Steven Grunberg, MD

Oncology nurses play a pivotal role in the care of patients receiving chemotherapy and are in a prime position to facilitate better care of patients experiencing chemotherapy-induced nausea and vomiting (CINV). However, to do so, they must be kept well apprised of the most recent guidelines, the latest developments in CINV therapy, and the expanding knowledge of CINV pathophysiology. In April 2008, a roundtable meeting of experts in the field of CINV was convened after a detailed needs assessment revealed a knowledge gap in CINV management on the part of oncology nurses. The review found that many practitioners significantly underestimated the occurrence of CINV (particularly of delayed symptoms), and others failed to implement evidence-based guidelines. Presentations included CINV pathophysiology, the significance of CINV prophylaxis, evidence-based guidelines, current treatment options and future therapies, practical nursing considerations in CINV, and CINV learning gaps among oncology nurses, with the topics then discussed by the panel at large.

Chemotherapy has played an important role in improving patient outcomes in oncology and is a cornerstone of therapy for most patients with cancer. From the mid-1970s to 2002, the overall five-year cancer survival rate in the United States increased from 51% to 66% (American Cancer Society, 2007; Jemal et al., 2007). Advances in early diagnosis and better treatments made this improvement in survival possible. Although chemotherapy has enabled many patients to live longer, a high cost, in terms of adverse events and quality of life, is associated with it. Between 500,000 and 1 million Americans receive chemotherapy each year (Cell Therapeutics Inc., 1997; U.S. Food and Drug Administration [FDA], 2003), and a high proportion—as many as 80%—experience adverse effects (Khalifa, 2002; Smith & Toonen, 2007). Of the adverse effects, none is more feared than chemotherapy-induced nausea and vomiting (CINV) (Cohen, de Moor, Eisenberg, Ming, & Hu, 2007; Grunberg et al., 2004; Ihbe-Heffinger et al., 2004).

Despite the introduction of more effective antiemetics, beginning with the use of high-dose metoclopramide in the 1980s and followed by the introduction of the first-generation 5-HT_3 antagonists in the 1990s, the approval of the first second-generation 5-HT_3 antagonist in 2003, and the first NK1 antagonist in 2006, CINV remains an issue (Cohen et al., 2007; Grunberg et al., 2004; Ihbe-Heffinger et al., 2004) and continues to exact an unacceptable toll on patients with cancer and their families. Research indicates that at least some of the continuing burden of CINV may be attributed to failure on the part of healthcare practitioners to appreciate the incidence of CINV, to understand its complex pathophysiology, and to implement treatment guidelines (Grunberg et al., 2004; Ihbe-Heffinger et al.). Therefore, a first step toward improving patient outcomes is to ensure that healthcare professionals

At a Glance

- Chemotherapy-induced nausea and vomiting (CINV) remains an important adverse effect despite the introduction of new antiemetic medications, with delayed effects more common than acute symptoms.
- Failure to appreciate the scope of the issue and to implement established guidelines contributes to poorer patient outcomes; however, effective antiemetics can provide relief.
- Oncology nurses can play a critical role in decreasing the burden of CINV by providing more accurate assessments of patients before and during chemotherapy.

Rebecca Hawkins, MSN, ANP, AOCN®, is a nurse practitioner at St. Mary's Medical Center in Pendleton, OR, and Steven Grunberg, MD, is a professor of hematology/oncology at the University of Vermont in Burlington. Hawkins has no financial relationships to disclose. Grunberg is a consultant for Prostrakan; Merck & Co., Inc.; and GlaxoSmithKline, and has received honoraria from ProStrakan; Merck & Co., Inc.; and Eisai. Medical writing assistance was provided by Excellence in Medical Education through an educational grant from ProStrakan. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Clinical Journal of Oncology Nursing* or the Oncology Nursing Society. (Submitted September 2008. Accepted for publication October 5, 2008.)

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are well informed on the subject of CINV and aware of the evidence-based guidelines.

Impact and Incidence of Chemotherapy-Induced Nausea and Vomiting

The burden that CINV places on patients with cancer is considerable. Nausea and vomiting can adversely affect patients' quality of life and make it difficult for them to perform their activities of daily living (Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006). Uncontrolled CINV can give rise to medical complications, including poor nutrition, dehydration, electrolyte imbalances, and physical and mental deterioration (Hamadani et al., 2007). In some cases, patients may refuse to continue potentially beneficial treatment regimens because of treatment-associated nausea and vomiting (Hamadani et al.). Because poorly controlled or uncontrolled CINV requires the use of rescue medication and possible emergency department visits or visits to the healthcare practitioner's office, it can increase the cost of medical care (Shih, Xu, & Elting, 2007). A study found that uncontrolled CINV in a patient resulted in an additional $1,300 per month for direct medical costs (Shih et al.). CINV also may impede a patient's ability to work. Another study based on analysis of a large medical claims database found that occurrence of CINV was associated with greater absenteeism. Patients with cancer receiving chemotherapy with uncontrolled CINV averaged 6.23 lost work days per month; patients who did not experience uncontrolled CINV lost an average of 3.61 days per month (Shih et al.). The overall cost to the national economy in cumulative lost work days and decreased productivity because of CINV could be considerable.

The advent of highly emetogenic chemotherapy (HEC) occurred in the 1970s with the introduction of cisplatin. Patients treated with cisplatin would vomit 5–25 times during the first 24 hours (or an average of 10.5 times) (Gralla et al., 1981). The then-available antiemetic therapies—corticosteroids, antihistamines, and phenothiazines—were ineffective against cisplatin-associated nausea and vomiting (Herrstedt, 2004; Hesketh et al., 2003). Use of high-dose metoclopramide beginning in the 1980s decreased the occurrence of CINV; however, the risk of causing extrapyramidal effects made it a less-than-perfect antiemetic. Control was improved greatly with the introduction of the 5-HT_3 antagonists in the 1990s. NK1 inhibitors came into use with the approval of aprepitant by the FDA in 2006 and then fosaprepitant in 2008 (Waknine, 2008).

However, despite improvements in available antiemetics, the incidence of CINV in patients with cancer continues to be problematic. The results of a prospective multicenter study by Ihbe-Heffinger et al. (2004) found that 64.4% of patients receiving chemotherapy had one or more episodes of CINV. Delayed CINV occurred almost twice as often as acute episodes; 60.7% of patients experienced delayed episodes versus 32.8% of patients who experienced acute CINV (Ihbe-Heffinger et al.). The study also found that more than 50% of patients received an antiemetic regimen that was not in accordance with the American Society of Clinical Oncology (ASCO) guidelines. Among patients receiving antiemetic therapy according to guidelines, 49.5% experienced delayed CINV as compared with 71.6% of patients receiving inappropriate therapy, underscoring the importance of using guidelines to improve patient outcomes (Ihbe-Heffinger et al.). Nausea also occurred twice as often as vomiting (62.5% of the time as compared with 26.0%), and patients typically view nausea as more distressing than vomiting and as having a greater negative impact on their lives (Bloechl-Daum et al., 2006; Ihbe-Heffinger et al.). Other data confirm the findings. The incidence of acute CINV has ranged from 36% to almost 60% and the incidence of delayed CINV has ranged from 47.1%–75.4% (Cohen et al., 2007; Erazo Valle, Wisniewski, Figueroa Vadillo, Burke, & Martinez Corona, 2006; Molassiotis et al., 2008).

The issue of CINV is even greater in some types of cancer and with certain treatment modalities. Among patients receiving chemotherapy for acute myeloid leukemia, the percentage of patients remaining emesis-free 100 hours after initiation of chemotherapy was 47% (± 5%) but decreased to 20% (± 4%) among patients receiving a stem cell transplantation (Lopez-Jimenez et al., 2006). In addition, the absence of acute CINV does not imply good control. A study conducted with patients receiving chemotherapy (N = 151) found that 31% of patients experienced delayed CINV without prior acute symptoms. This represented 53% of patients reporting delayed CINV (Cohen et al., 2007). A study by Grunberg et al. (2004) (N = 67) found similar results. Thirty-eight percent of patients on an HEC regimen experienced delayed emesis and 33% experienced delayed nausea without acute symptoms. In the same study, 19% of 231 patients receiving moderately emetogenic chemotherapy (MEC) experienced delayed emesis and 21% experienced delayed nausea without acute symptoms.

However, the perceptions of medical practitioners—oncology nurses and oncologists—appear to be at odds with these findings (Grunberg et al., 2004). In a study involving 298 patients (67 receiving HEC and 231 receiving MEC), 13 medical oncologists and 11 oncology nurses were asked to estimate the incidence of acute and delayed CINV that would occur (Grunberg et al., 2004). For patients receiving HEC regimens, oncologists and oncology nurses accurately predicted the incidence of acute but not delayed CINV (see Figure 1), and although they were able to accurately predict acute emesis with MEC regimens, both groups underestimated acute nausea (see Figure 2). Delayed CINV was underestimated as well. When comparing oncology nurses and oncologists, the nurses' predictions were slightly more accurate than the oncologists'; however, in this study, healthcare professionals in general showed a failure to appreciate the degree of delayed nausea and vomiting (Grunberg et al., 2004).

Pathophysiology of Chemotherapy-Induced Nausea and Vomiting

CINV is classified as acute, delayed, anticipatory, breakthrough, or refractory. Acute CINV occurs less than 24 hours after chemotherapy (Jordan, Sippel, & Schmoll, 2007; Schwartzberg, 2006), whereas delayed CINV is defined as nausea and vomiting occurring 24 hours or more after chemotherapy. The designation of acute and delayed CINV as distinct is more than mere timing; physiologic differences exist in the pathways involved in these two forms of CINV (Jordan et al., 2007). Whereas acute CINV appears to be mediated primarily by serotonin pathways, delayed CINV is more substance P mediated (Jordan

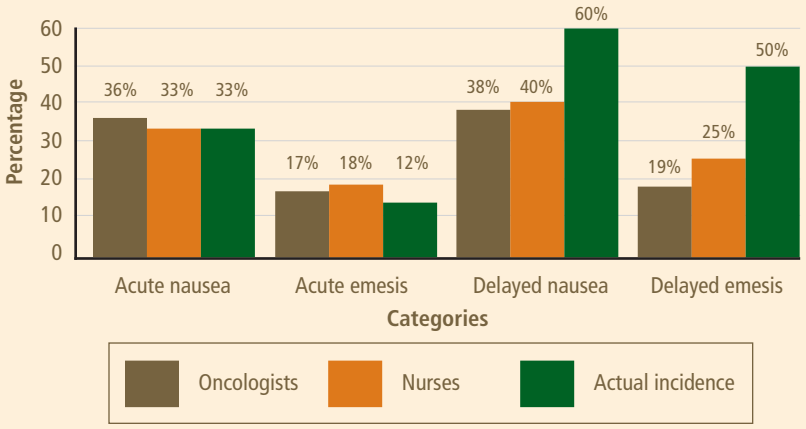


Figure 1. Oncologists' and Nurses' Predictions of the Incidence of Chemotherapy-Induced Nausea and Vomiting Versus Actual Incidence in Patients Receiving a Highly Emetogenic Chemotherapy Regimen for Cancer

Note. From "Incidence of Chemotherapy-Induced Nausea and Emesis After Modern Antiemetics," by S.M. Grunberg, R.R. Deuson, P. Mavros, O. Geling, M. Hansen, G. Cruciani, et al., 2004, *Cancer, 100*(10), p. 2266. Copyright 2004 by the American Cancer Society. This material is adapted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

et al.). Anticipatory CINV is a learned response that arises secondary to a history of poorly controlled CINV. It may be triggered by tastes, odors, sights, thoughts, or anxiety associated with chemotherapy (Jordan et al.; Schwartzberg). Anticipatory CINV is more difficult to control than acute or delayed CINV, and its treatment may include the use of behavioral therapy or benzodiazepines (Grunberg, 2007). Breakthrough CINV, as the name implies, is nausea and vomiting that occurs despite antiemetic therapy and requires rescue medication.

At a basic level, what we refer to as nausea and vomiting can really be divided into three categories: nausea, retching, and vomiting (Wilhelm, Dehoorne-Smith, & Kale-Pradhan, 2007). Whereas retching and vomiting are brainstem responses, nausea involves higher brain regions and is not well understood (Rahman & Beattie, 2004). Nausea is subjective and consists of an urge to vomit. It may be accompanied by autonomic symptoms such as pallor, tachycardia, diaphoresis, and salivation (Wilhelm et al.). Retching is the rhythmic contractions of the diaphragm, abdominal wall, and chest muscles that precede vomiting, although the latter is a reflexive, rapid, and powerful ejection of upper gastrointestinal tract contents resulting from vigorous and continuous contractions of the abdominal and thoracic muscles (Wilhelm et al.). The act of vomiting involves a reflex arc (Donnerer, 2003). Signals sent to the dorsal vagal complex activate somatic and visceral impulses to the effector organs: abdominal muscles, stomach, esophagus, and diaphragm (Bubalo, Bierman, & Yates, 2004). Once the vomiting center is stimulated, the airways close and respiration is markedly lowered. The upper esophagus relaxes and an increase in intra-abdominal pressure occurs, leading to the expulsion of the gastric contents (Girish & Manikandan, 2007). Activation of the vomiting center may occur as the result of afferent input from drugs, such as chemotherapeutic agents, motion, smells, sights, situations, and emotions, as well as from gastrointestinal input. The vomiting center has three main components (the area postrema, the nucleus tractus solitarius, and the dorsal vagal complex) that integrate the emetic responses (Girish & Manikandan). CINV may result from the presence of chemotherapeutic agents or their metabolites in the blood stream or the cerebrospinal fluid that acts directly on the chemoreceptor trigger zone in the area postrema. This area lies outside the blood-brain barrier and is, therefore, sensitive to blood-borne and cerebrospinal fluid–borne stimuli. Signals from the area postrema are then relayed to the nucleus tractus solitarius, which lies within the blood-brain barrier and relies on neurotransmitters to trigger emesis (Bubalo et al.). Cytotoxic agents also may induce release of serotonin and substance P from the enterochromaffin cells of the gastric mucosa, which then send signals to the nucleus tractus solitarius via vagal sensory fibers (Girish & Manikandan; Herrstedt, 2008). Following stimulation of the nucleus tractus solitarius, the vomiting response is mediated by efferent pathways, including the vagus and phrenic nerves (Girish & Manikandan). Current thinking is that, rather than a well-defined anatomic area, the vomiting center exists as interconnecting neural networks that penetrate into the nucleus tractus solitarius (Herrstedt, 2008). In addition to the serotonin (5-HT_3) and substance P (NK1) pathways, cannabinoid and dopamine (D2) pathways also are involved in CINV. Other pathways involved in nausea and vomiting include acetylcholine or muscarinic (M), histamine (H1), endorphin, and γ-aminobutyric acid, but these do not appear to be activated in CINV (Herrstedt, 2008). Figure 3 illustrates the metabolic pathways and receptors involved in the pathophysiology of emesis and CINV.

Risk Factors Involved in Chemotherapy-Induced Nausea and Vomiting

The patient and the chemotherapeutic regimen contribute to the overall risk of CINV (Jordan et al., 2007). Patients who are younger are more likely to experience CINV, as are those with a history of low alcohol consumption. CINV is more likely to occur in women, particularly in women with a history of morning sickness during pregnancy. Patients who are prone to motion sickness are at higher risk as well. Previous experience with chemotherapy also increases the risk of CINV.

Chemotherapy is stratified as HEC, MEC, low potential, or minimal risk regimens (see Figure 4). HEC regimens cause CINV more than 90% of the time and include, among others, cisplatin and cyclophosphamide ($\geq$ 1,500 mg/m^2). MEC regimens cause CINV 30%–90% of the time and include oxaliplatin, the anthracyclines, cyclophosphamide ($<$ 1,500 mg/m^2), and irinotecan. Low-risk regimens cause CINV 10%–30% of the time and include the taxanes, mitoxantrone, gemcitabine, and 5-fluorouracil (Grunberg, 2007; Herrstedt, 2008). The targeted biologics bortezomib, cetuximab, and trastuzumab also are considered low-risk regimens (Grunberg; Herrstedt, 2008). Minimal risk regimens cause

CINV less than 10% of the time and include bleomycin, busulfan, 2-chlorodeoxyadenosine, fludarabine, the vinca alkaloids, and bevacizumab (Grunberg; Herrstedt, 2008).

Treatment of Chemotherapy-Induced Nausea and Vomiting

In light of the multiple pathways involved in CINV, the fact that combination therapy is the most effective is not surprising. Prophylaxis of acute CINV targets the serotonin emetic pathway using the 5-HT_3 antagonists and a corticosteroid; prophylaxis of delayed CINV targets the substance P pathway with an NK1 antagonist and a corticosteroid. Rescue medication for breakthrough episodes include dopamine receptor antagonists such as metoclopramide, prochlorperazine, or haloperidol; benzodiazepines such as lorazepam; 5-HT_3 antagonists; the cannabinoids dronabinol or nabilone; or novel agents such as olanzapine (commonly known as an atypical antipsychotic) (National Comprehensive Cancer Network [NCCN], 2008).

The drug classes effective in CINV operate through a variety of mechanisms. Of the dopamine receptor antagonists, metoclopramide is the most extensively studied as an antiemetic. It has been used at conventional doses for mild to moderate CINV and at high doses for delayed cisplatin-induced CINV (Herrstedt, 2004). Adverse effects of the dopamine antagonists include sedation, orthostatic hypotension, and increased risk of extrapyramidal effect (Herrstedt, 2004). Corticosteroids are widely used in combination with other classes of antiemetics for the prophylaxis of CINV. The mechanism of action is not known, but it has been speculated that it may involve modification of capillary permeability of the chemoreceptor trigger zone, reduction in inflammatory changes in the gut after chemotherapy, and participation in the release of endorphins (Herrstedt, 2004). Dexamethasone is the most commonly used corticosteroid in antiemetic regimens, but methylprednisolone is used as well. Adverse effects include insomnia, euphoria, anxiety, facial flushing, and pharyngeal or perineal itching (Herrstedt, 2004). The 5-HT_3 receptor antagonists are the most important agents in acute CINV, and approval of the agents dramatically improves the situation for patients receiving HEC (Herrstedt, 2004). Granisetron, ondansetron, palonosetron, and dolasetron are all 5-HT_3 receptor antagonists. The adverse effects of this class are generally mild and include headache and constipation (Herrstedt, 2004). The NK1 receptor antagonist class, which targets substance P and is more effective for delayed CINV, now includes aprepitant and fosaprepitant as agents approved by the FDA. Another NK1 antagonist, casopitant, is in phase III trials (Herrstedt, 2004). The cannabinoids have agonist activity at the CB1 receptor. This class, which includes nabilone, dronabinol, and levonantradol, has some efficacy against mild to moderate CINV but is not effective in patients receiving HEC regimens (Herrstedt, 2004). Adverse effects include dry mouth, ataxia, dizziness, sedation, confusion, distortion of perception, and mood changes (euphoria/dysphoria) (Herrstedt, 2004) (see Table 1).

Clinical Trial Data

Clinical trials have demonstrated comparable efficacy in controlling CINV for the 5-HT_3 antagonists. Data have shown that granisetron, ondansetron, dolasetron, and palonosetron are comparable for acute CINV (Aapro et al., 2006; Dempsey et al., 2004; Eisenberg et al., 2003). However, a head-to-head comparison of palonosetron plus dexamethasone versus ondansetron plus dexamethasone in 667 patients receiving HEC found that the regimen containing palonosetron was more effective for delayed CINV than ondansetron, with a complete response of 42% versus 28.6% for those agents, respectively (Aapro et al.). Palonosetron also proved to be more effective than dolasetron for delayed CINV in a trial conducted in 592 patients receiving MEC (Eisenberg et al., 2003). In addition, a double-blind trial of palonosetron versus ondansetron in 570 patients receiving MEC found that palonosetron was not only significantly superior to ondansetron for prevention of delayed CINV but also for acute CINV. Complete responses occurred in 81% of palonosetron-treated patients versus 68.6% of ondansetron-treated patients for acute CINV and in 74.1% and 55.1% of those patients, respectively, for delayed CINV ($p < 0.01$) (Gralla et al., 2003).

The NK1 antagonist aprepitant has demonstrated efficacy for delayed CINV in clinical trials. In a study comparing ondansetron plus dexamethasone versus aprepitant plus ondansetron and dexamethasone in 523 patients receiving HEC, the addition of aprepitant to the regimen proved to be significantly more effective than standard therapy (5-HT_3 antagonist plus corticosteroid) alone (Poli-Bigelli et al., 2003). Forty-four percent of patients in the aprepitant group achieved total control (no emesis and no nausea on days 1–5) compared to 32% of patients on standard antiemetic therapy. Not surprisingly, the differences were more dramatic for delayed than acute

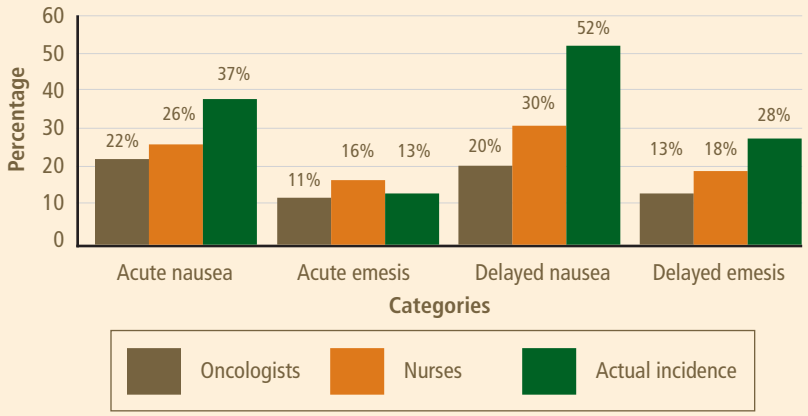
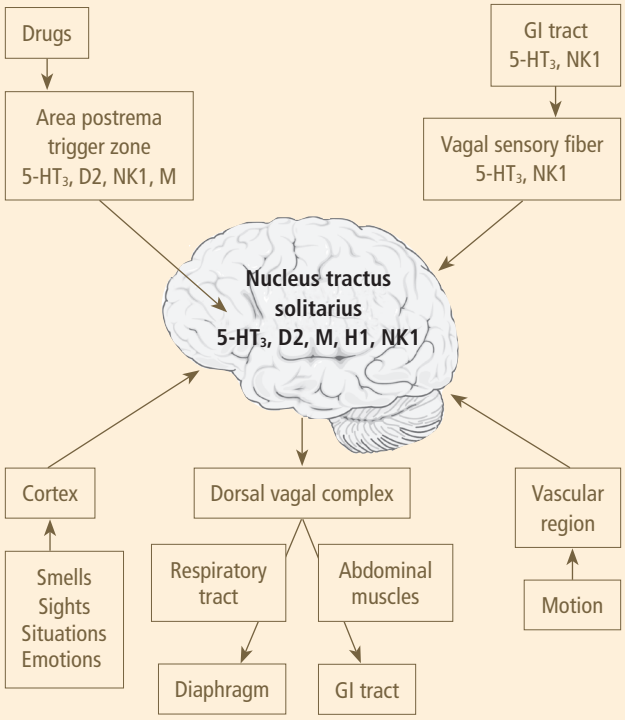


Figure 2. Oncologists' and Nurses' Predictions of the Incidence of Chemotherapy-Induced Nausea and Vomiting Versus Actual Incidence in Patients Receiving a Moderately Emetogenic Chemotherapy Regimen for Cancer

Note. From "Incidence of Chemotherapy-Induced Nausea and Emesis After Modern Antiemetics," by S.M. Grunberg, R.R. Deuson, P. Mavros, O. Geling, M. Hansen, G. Cruciani, et al., 2004, *Cancer, 100*(10), p. 2266. Copyright 2004 by the American Cancer Society. This material is adapted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.



D2—dopamine; GI—gastrointestinal; H1—histamine; M—muscarinic; NK1—neurokinin-1

Figure 3. The Pathophysiology of Chemotherapy-Induced Nausea and Vomiting: Emetic Pathways and the Vomiting Center

Note. From "Relieving Patients' Fear of Chemotherapy-Induced Nausea and Vomiting," by J. Bubalo, B. Bierman, & M. Yates, 2004. Retrieved March 20, 2008, from http://www.uspharmacist.com/index.asp?show=article&page=8_1186.htm. Copyright 2004 by Jobson Publication. Adapted with permission.

CINV. Total control of delayed CINV was achieved by 50% in the aprepitant group and 34% in the standard therapy group; total control of acute CINV was achieved by 64% and 57%, respectively (Poli-Bigelli et al.).

The results from two phase III trials evaluating casopitant, a new NK1 antagonist, are now available. Casopitant has shown efficacy when used in combination with ondansetron and dexamethasone in patients receiving HEC and MEC regimens. Patients in the active treatment groups received ondansetron and dexamethasone plus casopitant; patients in the control groups received only ondansetron and dexamethasone. Of the 531 patients receiving an HEC regimen, the complete response rate in the first cycle was 86% for casopitant compared with 66% for the control arm ($p < 0.0001$) (Herrstedt et al., 2008). Similar rates of control were found in 1,438 patients receiving an MEC regimen and treated with ondansetron and dexamethasone with or without casopitant (a single 150 mg dose of casopitant on day 1 or a 150 mg dose of casopitant on day 1 and 50 mg of casopitant on days 2 and 3). During the first cycle, the control group had a complete response rate of 59% compared with 73% for both casopitant groups ($p < 0.0001$) (Grunberg et al., 2008). Complete control rates were maintained over six cycles of HEC and four cycles of MEC (Grunberg et al., 2008; Herrstedt et al.). A regimen involving casopitant 90 mg IV followed by casopitant 50 mg orally on days 2 and 3 was evaluated in HEC and MEC patients. Of the 534 patients receiving HEC, a complete response occurred in 80% of the casopitant cohort and 66% of the control during the first cycle of chemotherapy ($p = 0.0004$) (Strausz et al., 2008). In the 958 patients receiving MEC, complete response during the first cycle occurred in 74% of the casopitant group and 59% of the control ($p < 0.0001$) (Aziz et al., 2008).

Palonosetron also was investigated in combination with dexamethasone and olanzapine in 40 patients receiving either HEC or MEC regimens. Palonosetron, dexamethasone, and olanzapine were given on day 1, and olanzapine was given on days 2–4 as well. A complete response for acute CINV occurred in 100% of patients receiving HEC and 97% of patients receiving MEC; a complete response for delayed CINV occurred in 75% of patients receiving HEC and 75% receiving MEC (Navari et al., 2007). Overall complete response was 75% for HEC, 72% for MEC (Navari et al.).

New Delivery Options for Antiemetics

New delivery mechanisms also may play an important role in antiemetic therapy. A randomized, active control, double-dummy, parallel-group, phase III trial compared a granisetron patch with oral granisetron in patients receiving three- to five-day regimens of MEC or HEC. In this noninferiority study, patients received a patch (granisetron or placebo) 24–48 hours before the first dose of chemotherapy and a capsule (granisetron or placebo) one hour before therapy. Patients were followed up to 14 days (Grunberg, Gabrial, & Clark, 2007). Of the 582 patients treated in the study, 60.2% in the transdermal patch group and 64.8% in the oral granisetron group achieved complete control of CINV, defined as control from the first administration of the chemotherapeutic regimen to 24 hours after the last dose ($p > 0.05$ [not significant]). Complete control was considered to be no vomiting and/or retching and no more than mild nausea, as well as no use of rescue medication. Safety analysis found no significant differences between the two groups, with the most commonly reported adverse effects being headache and constipation (Grunberg et al., 2007).

Intranasal delivery of antiemetics also is being investigated. This mechanism may be a viable approach for rapid, high systemic drug absorption during emergency treatment of severe emesis. Early-stage testing of intranasal delivery of metoclopramide has been initiated (Zaki, Mortada, Awad, & Abed El-Hady, 2006). Other antiemetics under investigation for intranasal delivery include ondansetron and granisetron, both of which have been tested in rats and appear to be feasible (Cho, Gwak, & Chun, 2008; Woo, 2007).

Current Guidelines

A number of guidelines and evidence-based treatment approaches exist for CINV, including recommendations from the Multinational Association of Supportive Care in Cancer (MASCC), ASCO, NCCN, and Oncology Nursing Society (ONS) (see Table 2). Despite the fact that implementation of CINV guidelines results in better patient outcomes, they often are not adhered to by oncology healthcare professionals (Grunberg et al., 2004; Ihbe-Heffinger et al., 2004); this is particularly true of prophylaxis of delayed CINV because symptoms occur after

High-Risk Regimens or Highly Emetogenic Chemotherapy (> 90% incidence)

- Cisplatin
- Mechlorethamine
- Streptozotocin
- Cyclophosphamide (≥ 1,500 mg/m^2)
- Carmustine
- Dacarbazine

Moderate-Risk Regimens or Moderately Emetogenic Chemotherapy (30%–90% incidence)

- Oxaliplatin
- Cytarabine (> 1 g/m^2)
- Carboplatin
- Ifosfamide
- Doxorubicin
- Daunorubicin
- Epirubicin
- Idarubicin
- Irinotecan

Low-Risk Regimens (10%–30% incidence)

- Paclitaxel
- Docetaxel
- Mitoxantrone
- Etoposide
- Pemetrexed
- Methotrexate
- Mitomycin C
- Gemcitabine
- Cytarabine (≤ 100 mg/m^2)
- 5-fluorouracil
- Bortezomib
- Cetuximab
- Trastuzumab

Figure 4. Emetogenic Potential of Common Chemotherapies

Note. From "Antiemetic Activity of Corticosteroids in Patients Receiving Cancer Chemotherapy: Dosing, Efficacy, and Tolerability Analysis," by S.M. Grunberg, 2007, *Annals of Oncology, 18*(2), p. 234. Copyright 2007 by Oxford University Press. This material is adapted with permission from Oxford University Press.

the patient leaves the treatment center. A study found that more than 50% of patients were not treated adequately for delayed CINV and that this was associated with a higher incidence of this adverse event (Ihbe-Heffinger et al.).

A key principle of all guidelines and treatment approaches is that effective management of delayed or anticipatory CINV requires adequate control of acute CINV (Grunberg, 2007). The recommendations of MASCC and ASCO differ little; however, for the prophylaxis of delayed emesis in patients receiving cyclophosphamide plus an anthracycline, MASCC recommends the use of dexamethasone or aprepitant whereas ASCO recommends only aprepitant (Herrstedt, 2008).

The NCCN guidelines and ONS evidence-based treatment approaches are similar. Unlike MASCC or ASCO guidelines, NCCN guidelines suggest the use of the benzodiazepine lorazepam with most emetogenic regimens in addition to corticosteroids, aprepitant, and 5-HT$_3$ antagonists. With MEC regimens, aprepitant, dexamethasone, or a 5-HT$_3$ antagonist is suggested for delayed CINV, whereas MASCC and ASCO guidelines do not recommend aprepitant with MEC regimens for either acute or delayed CINV in patients not receiving cyclophosphamide plus an anthracycline. NCCN and ONS guidelines recommend aprepitant for acute CINV in MEC regimens (Herrstedt, 2008; Kris et al., 2006; NCCN, 2008).

Discussions and Observations

An expert panel of oncology healthcare practitioners was formed for this roundtable through interviews with key opinion leaders and a review of their involvement with top clinical practice societies. Once chosen, the expert panel reviewed and discussed the content of the presentations, which have been summarized to this point, on the pathophysiology of CINV, the significance of CINV prophylaxis, evidence-based guidelines, current treatment options and future therapies, practical nursing considerations in CINV, and CINV learning gaps among healthcare providers. The comments of the panel amplified the data presented and placed them within the context of key oncology nursing issues.

Pathophysiology

The pathophysiology of CINV was considered to be of great importance by the roundtable participants. Panel members felt that it is essential for oncology nurses to understand the pathophysiology of CINV and the different mechanisms of action used by the various antiemetics so that they recognize the need for medications targeting different CINV pathways and can communicate this effectively to patients. A study of noncompliance among patients found that lack of confidence in the efficacy of a drug on the part of the patient can contribute to failure to adhere to the regimen (Cerveny et al., 2007). Therefore, patients who understand why they are taking multiple agents and have been given some insight into the way these drugs work may have more confidence in their effectiveness and may be more likely to comply with the regimen. The panel also suggested that a good understanding of the pathophysiology of CINV may enable oncology nurses to do the critical thinking necessary for providing the best possible patient care.

One issue touched on briefly during the roundtable discussion was whether there might be any difference in the pathophysiology of nausea as compared with emesis and if this could be of clinical relevance. Members of the panel suggested that the mechanisms involved in nausea warranted investigation to determine whether nausea pathways differ from vomiting pathways in any way. It was suggested that such a difference might explain why vomiting is better controlled than nausea (Grunberg et al., 2004; Ihbe-Heffinger et al., 2004).

Another issue discussed in brief was the definition of acute CINV. Standard definitions state that any nausea or vomiting that occurs within 24 hours of chemotherapy constitutes acute CINV (Jordan et al., 2007; Schwartzberg, 2006). However, it was pointed out during the meeting that this is a somewhat arbitrary cutoff based more on hospital schedules than human physiology. The actual delineation between acute and delayed CINV may occur earlier, about 16 hours after chemotherapy (Riley & DeRuiter, 2004).

Practical Nursing Issues—Assessment

Assessment of and communication with the patient were major topics of discussion. Patient assessment is a primary responsibility of oncology nurses, and an accurate assessment of patient response to medication and the occurrence of adverse events is a foundation for better patient outcomes. Participants discussed the importance of an accurate assessment and communicating that assessment to the oncologist in the most concise and timely fashion. A careful initial patient history can identify risk factors for CINV and may suggest a more or less aggressive approach

Table 1. Agents Commonly Prescribed as Antiemetics in Chemotherapy-Induced Nausea and Vomiting

GENERIC NAME	BRAND NAME	DOSAGE FORMS
5-HT_3 RECEPTOR ANTAGONISTS		
Dolasetron	Anzemet® (sanofis-aventis, U.S.)	PO, IV
Granisetron	Kytril®, Sancuso® (Pro-Straken Inc.)	PO, IV, transdermal
Ondansetron	Zofran® (GlaxoSmithKline)	PO, IV, IM
Palonosetron	Aloxi® (Eisai Inc.)	PO, IV
NEUROKININ-1 RECEPTOR ANTAGONISTS		
Aprepitant	Emend® (Merck & Co., Inc.)	PO
Fosaprepitant	Emend for injection (Merck & Co., Inc.)	IV
CORTICOSTEROIDS		
Dexamethasone	Decadron® (Merck & Co., Inc.)	PO, IV, IM
Methylprednisolone	Medrol® (Pfizer, Inc.)	PO, IV, IM
CANNABINOIDS		
Dronabinol	Marinol® (Solvay Pharmaceuticals, Inc.)	PO
Nabilone	Cesamet® (Valent Pharmaceuticals International)	PO
DOPAMINE RECEPTOR ANTAGONISTS		
Substituted benzamides		
Metoclopramide	Reglan® (Baxter Pharmaceuticals)	PO, IV, IM
Phenothiazines		
Perphenazine	Trilafon® (Schering Corp.)	PO
Prochlorperazine	Compazine® (GlaxoSmithKline)	PO, IV, IM, PR
Thiethylperazine	Torecan® (Novartis)	PO, IV, IM
Butyrophenones		
Haloperidol	Haldol® (Ortho-McNeil Pharmaceuticals)	PO, IM
BENZODIAZEPINES		
Lorazepam	Ativan® (Biovail Pharmaceuticals, Inc.)	PO

depending on the chemotherapy regimen being used. An assessment of current concomitant medications also is critical, and patients should be asked to bring in their medications because recall may not be accurate. If this is not recorded properly the first time, the error often is perpetuated and may lead to issues down the line. It was stated that the "brown bag approach" is the best way to ensure that such errors and issues are avoided. The patient is simply asked to bring in all their medications in a brown paper bag (Caskie, Willis, Schaie, & Zanjani, 2006). A study of this approach found that asking the patient to bring in all medication in a bag is at least as accurate as pharmacy prescription records and may even be more so because of the use of samples (Caskie et al.). Keep in mind that chemotherapy may not be the only medication contributing to nausea and vomiting, and an accurate assessment of concomitant drugs can help determine this.

Participants also suggested that, although assessments are more or less mandated by documentation requirements, taking that next step—ensuring that the information is acted on—is not always done. Panel members noted that nurses may not choose to take that next step or may not have the power to impact treatment. Therefore, better, more effective communication should exist between the oncology nurse and the oncologist. Too often, it was said, a nurse may simply report that the patient is vomiting rather than give a concise, detailed summary of the assessment that was performed. However, good communication requires participation from both sides. A study of nursing issues conducted in Sweden (N = 18) found that 71% of oncology nurses reported lack of communication with other oncology professionals as an issue (Wengstom & Haggmark, 1998).

Practical Nursing Issues—Time Constraints and Mentoring

The participants talked about the difficulty of finding enough time to properly address assessment and documentation as well as patient follow-up. This area also was explored in the Swedish study. When asked to rank major issues experienced in the care of patients with cancer, 76% of nurses ranked poor follow-up of patients as a top 10 issue, and 65% stated that finding time to document nursing care and talk to patients was a major issue (Wengstom & Haggmark, 1998).

The importance of mentoring novice nurses was brought up. Several panel members mentioned that they are teaching the Situation-Background-Assessment-Recommendation (SBAR) technique in their institutions as a method for improving communication between healthcare professionals about a patient's condition. The SBAR tool can be downloaded from the Internet and contains two documents. The first, "SBAR Report to Physician About a Critical Situation" (www.ahrq.gov/qual nurseshdbk/docs/O%27DanielM_TWC.pdf), is a worksheet for organizing information to communicate to a physician about a critically ill patient. The second document, "Guidelines for Communicating With Physicians Using the SBAR Process" (www.Ihi.org), explains the SBAR technique in detail (Institute for Healthcare Improvement, n.d.).

Barriers to Communicating With the Patient

Effective communication with the patient is part of the art of oncology nursing. Oncology nurses play a key role in educating patients about what to expect and how to handle chemotherapy. Successful interaction is essential. A number of panel participants spoke to the difficulty of educating patients who speak English as a second language or who are not literate or well educated (Harmsen, Bernsen, Bruijnzeels, & Meeuwesen, 2008; Osborn, Paasche-Orlow, Davis, & Wolf, 2007). The level of health literacy also is relevant, and studies have found that limited health literacy is associated with poorer adherence (Osborn et al.). Even patients who are literate often receive stacks of information that are difficult to comprehend regarding their cancer and its treatment, which can be overwhelming.

Cultural and ethnic differences also may impede effective communication because patients' expectations and coping styles may differ (Mardby, Akerlind, & Jogensen, 2007; Meddings & Haith-Cooper, 2008; Pagano & Gotay, 2005). For

Table 2. Treatment Recommendations for Prophylaxis of Chemotherapy-Induced Nausea and Vomiting

REGIMEN	ONS TREATMENT APPROACHES	NCCN GUIDELINES	ASCO GUIDELINES	MASCC GUIDELINES
HEC	Day 1: 5-HT_3 antagonist plus dexamethasone plus aprepitant and/or lorazepam Days 2–4: dexamethasone plus aprepitant (days 2–3) and/or lorazepam	Day 1: aprepitant plus dexamethasone plus 5-HT_3 antagonist and/or lorazepam Days 2–3: aprepitant and dexamethasone and/or lorazepam Day 4: dexamethasone and/or lorazepam	Acute CINV: pretreatment with 5-HT_3 antagonist plus dexamethasone plus aprepitant Delayed CINV: dexamethasone (days 2–4) plus aprepitant (days 2–3)	Acute CINV: serotonin antagonist plus dexamethasone plus aprepitant Delayed CINV: aprepitant (days 2–3) plus dexamethasone (days 2–3 or 2–4)
MEC	Day 1: 5-HT_3 antagonist plus dexamethasone plus aprepitant and/or lorazepam Days 2–4: aprepitant or any of the following: dexamethasone, 5-HT_3 antagonist, metoclopramide, and/or diphenhydramine	Day 1: aprepitant plus dexamethasone plus 5-HT_3 antagonist with or without lorazepam Days 2–3: aprepitant or any of the following: dexamethasone, 5-HT_3 antagonist, and/or lorazepam	Acute CINV: 5-HT_3 antagonist plus dexamethasone Delayed CINV: dexamethasone or 5-HT_3 antagonist (days 2–3) Patients receiving cyclophosphamide plus anthracycline should receive acute emesis protection as recommended for HEC group and delayed emesis protection with aprepitant (days 2–3).	Acute CINV: serotonin antagonist plus dexamethasone Delayed CINV: dexamethasone (days 2–3), if risk of delayed CINV If corticosteroid contraindicated, serotonin antagonist can be used. Patients receiving cyclophosphamide plus anthracycline should receive acute emesis protection as recommended for HEC group and delayed emesis protection with aprepitant or dexamethasone (days 2–3).
Low risk	Day 1: no antiemetic agent or any of the following: dexamethasone, prochlorperazine, metoclopramide, or lorazepam	Before chemotherapy: dexamethasone or any of the following: prochlorperazine, metoclopramide, and/or diphenhydramine, and/or lorazepam	Acute CINV: low dose of dexamethasone Delayed CINV: no routine prophylaxis	Acute CINV: low dose of dexamethasone Delayed CINV: no routine prophylaxis
Minimal risk	Not applicable	No routine prophylaxis	No routine prophylaxis	No routine prophylaxis
Other recommendations	Dexamethasone or any of the following: 5-HT_3 antagonist, prochlorperazine, metoclopramide, haloperidol, lorazepam, dronabinol, or olanzapine	Not applicable	General recommendation on adjunctive medication: Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs but not recommended as single agents.	Not applicable

ASCO—American Society of Clinical Oncology; CINV—chemotherapy-induced nausea and vomiting; HEC—highly emetogenic chemotherapy; MASCC—Multinational Association of Supportive Care in Cancer; MEC—moderately emetogenic chemotherapy; NCCN—National Comprehensive Cancer Network; ONS—Oncology Nursing Society

Note. Based on information from Herrstedt, 2008; Kris et al., 2006; NCCN, 2008; Tipton et al., 2007b.

example, in some cultures, stoicism is highly valued, and patients from that cultural setting may be reluctant to report side effects. Personal expectations about therapy also may color responses. For example, panel experts suggested that patients who expect to experience nausea and vomiting with chemotherapy may not want to bother the nurse with their symptoms, or they may fear that by reporting such symptoms, the dose of a valuable and potentially curative treatment may be reduced. Other patients may believe that their suffering is a sign that the drug is potent and really working. Although vomiting is an objective symptom and easier to assess, nausea is subjective and may be perceived or reported differently depending on the patient. Participants noted that patients may report heartburn rather than nausea or may say that they feel "off" or queasy. To solve this issue, some panel members suggested asking about eating habits to ascertain whether patients have any degree of anorexia, but others noted that patients may eat when they are mildly nauseous, and women who have had morning sickness may have been taught that eating something alleviates nausea or heartburn. Therefore, eating habits alone do not provide an accurate assessment of nausea. Older patients may require a slightly different approach because their expectations may differ from younger patients, they often have comorbidities, and some may have cognitive difficulties (Miller, 2008). Overall, the consensus was that a blanket approach does not produce the best clinical outcomes and that each patient has to be considered as an individual.

The panel had a number of suggestions for patients that might help improve outcomes. For example, patient journaling was suggested as a method for keeping an accurate record of the incidence and intensity of CINV. Members also mentioned that with the first chemotherapy session, educating the patient

about possible adjunctive strategies, such as avoiding spicy or fatty foods, strong food odors, and large meals, might be helpful (Tipton et al., 2007b).

Guidelines

The use of guidelines was discussed. Panel members mentioned that NCCN and ONS recommendations were most likely to be used by oncology nurses and ASCO and NCCN recommendations by oncologists. The MASCC guidelines were thought to be the least well known. Panel members expressed the opinion that, overall, guidelines are not used that often, particularly in rural settings and private practice. In contrast, panel members believed that the bigger institutions—cancer centers and academic institutions—are more likely to use guidelines. It was suggested that guidelines could be expanded to include nonpharmacologic therapies, such as acupuncture, relaxation therapy, and guided imagery, to provide some relief to patients (Tipton et al., 2007a). It also was suggested that, in settings in which guidelines are not being used, oncology nurses should take a proactive stance and approach oncologists and nurse practitioners to establish the use of a set of guidelines. Interestingly, it was noted that many oncologists expect oncology nurses to handle symptom management, underscoring the importance of nurses being up-to-date on both guidelines and the most recent data on antiemetics.

Treatment

Alternative delivery mechanisms were discussed by panel members. The transdermal patch was thought to offer the advantage of convenience to the patient and better adherence. Although prophylaxis of CINV is much more effective than trying to treat active nausea or vomiting, patients may forget to take their medication until they experience symptoms. That issue does not occur with a patch that is applied 24–48 hours before the start of chemotherapy. Some panel members questioned whether it would stay on patients who live in humid climates. However, research has shown that the patch adheres well in humid weather and remains effective for a week after application (Grunberg et al., 2007). Disadvantages of this particular delivery system include the need to apply it up to two days before chemotherapy. If therapy is cancelled at the last minute, the patch has been given unnecessarily. Another factor to consider is that the drug remains active within the body for a day and a half after the patch is removed. Although this may be an advantage in continuing to control CINV, if the patient develops a granisetron-related side effect such as a headache, this effect might last after the patch has been removed.

Consensus Statements

The CINV roundtable thoroughly discussed most of the major issues in CINV. Given the discussions that occurred, a number of statements regarding CINV can be made.

- Knowledge of the pathophysiology of CINV is essential for oncology nurses.
- Nurses should question patients carefully to determine whether antiemetic therapy is effective and follow-up with patients in the days after chemotherapy to ascertain if delayed CINV is occurring.
- Patient differences in age, background, and primary language can affect communication.
- CINV guidelines are not used often enough and need to be consistently implemented.
- Although guidelines should continue to be the cornerstone of treatment, patient treatment should be approached on an individual basis.

Summary

CINV remains an important adverse effect despite the introduction of new antiemetic medications. Delayed CINV is more common than acute symptoms, and nausea is more common than emesis. Failure to appreciate the scope of the issue and to implement guidelines on the part of healthcare professionals contributes to poorer patient outcomes and appears to play a part in the problem. However, effective antiemetics are available and can provide relief and improvement in quality of life for many patients. Because CINV involves multiple emetic pathways, including serotonin, substance P, dopamine, and cannabinoid pathways, combination therapy is necessary to prevent acute and delayed symptoms, as suggested by the existing guidelines. Medications such as the 5-HT_3 antagonists and NK1 inhibitors improve CINV because they target acute and delayed symptoms. Newer delivery mechanisms, such as the transdermal patch, may improve CINV control through more consistent delivery of medication and increased compliance, and they may be more convenient to patients as well. Other possibilities, such as an intranasal spray, are being investigated.

Oncology nurses can play a critical role in decreasing the burden of this most dreaded of chemotherapy-associated adverse effects. More accurate assessments of patients before and during chemotherapy can ensure that the most appropriate antiemetic therapy is received. More effective communication with patients can improve adherence. Taking the time to address patients as individuals and accounting for differences in education level, language skills, age, cultural background, and expectations will improve communication and, ultimately, patient outcomes. Guidelines are essential. In institutions or settings in which guidelines for CINV have not been established, oncology nurses should initiate the process. In addition, more education of oncology nurses, particularly of nurses new to oncology, is an important step toward decreasing the burden of CINV.

Author Contact: Steven Grunberg, MD, can be reached at steven.grunberg@uvm.edu, with copy to editor at CJONEditor@ons.org.

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