ABSTRACT

Despite recent advances in understanding chemotherapy-induced nausea and vomiting (CINV) and the growing number of newer antiemetic regimens, nausea and vomiting continue to be among the most significant adverse events following chemotherapy. Although most patients receiving chemotherapy experience at least some CINV, physicians and nurses often underestimate the scope of the problem. Recognizing the differences between acute, delayed, and anticipatory CINV is important to provide specific management strategies, which are based on the different underlying pathophysiologic processes for each form of CINV. Although the extent of CINV depends largely on the emetogenic potential of the administered chemotherapy agents, patient characteristics such as previous experience with chemotherapy, sex, age, and alcohol intake history also have an impact. The release of neurotransmitters from cells that are susceptible to the presence of toxic substances in the blood or cerebrospinal fluid may be responsible for the initiation of emesis following chemotherapy. Recently, focus has shifted from the role of dopamine and serotonin in emesis to the potential role of substance P and the use of neurokinin-1 (NK1) antagonists as antiemetics. NK1 antagonists have been shown to exhibit a broader spectrum of antiemetic activity than serotonin and dopamine receptor antagonists. Advances in the prevention and management of CINV depend on the development of new effective antiemetic treatments and an improved understanding of the impact that CINV continues to have on patients with cancer. (Adv Stud Nurs. 2005;3(1):9-15)

Although a great deal of progress has been made over the past 2 decades in understanding and preventing chemotherapy-induced nausea and vomiting (CINV), nausea and vomiting remain among the most feared adverse effects of cancer treatment. Most patients receiving chemotherapy experience at least some CINV.1 An accurate incidence level is difficult to determine because of the variety of drugs and doses and health conditions of patients who receive treatment for cancer.

In 1983, Coates et al reported that nausea and emesis were the adverse effects of chemotherapy most feared by patients with cancer.2 Patients’ perceptions of the most severe side effects gradually changed as new antiemetic agents became available and alterations in chemotherapy regimens were made. In a study published in 1993, patients reported nausea as the most severe
symptom and vomiting as the fifth most severe.³ More recently, Carelle et al reported that the impact of nausea and vomiting on a patient’s quality of life had decreased but did remain significant, and that the social impact of chemotherapy had assumed a more prominent role.⁴

There is some speculation that the presumed decrease in the impact of CINV on a patient’s quality of life may be because of a shift from acute CINV, which can be observed easily in the hospital or clinic, to delayed CINV, which often occurs after a patient is discharged. Healthcare professionals may assume that the improved efficacy of newer antiemetic protocols to manage acute CINV implies better control of delayed CINV, thus they may underestimate the actual experiences of patients.

This article provides an overview of recent advances in the understanding of the pathophysiology of CINV. In addition, nurses’ and physicians’ perceptions of the incidence of CINV are compared with actual observations of CINV in clinical practice.

ACUTE, DELAYED, AND ANTICIPATORY CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

There are 3 clinically distinct forms of CINV: acute, delayed, and anticipatory. Each form is primarily associated with a different phase of time surrounding chemotherapy administration. Recognizing the differences among the 3 forms of CINV is important in providing specific management strategies, which are based on the different underlying pathophysiologic processes for each form.

ACUTE

Acute nausea and vomiting typically occurs within the first 24 hours after chemotherapy administration.⁵ It can begin within 1 or 2 hours after the start of chemotherapy and last for a number of hours.⁶ Chemotherapy agents, such as cyclophosphamide and carboplatin, may cause acute CINV that begins 8 to 10 hours after administration.⁶

The use of antiemetic agents before chemotherapy can significantly lower the incidence of severe acute CINV. The essential tool for managing acute CINV is prevention, which is more effective than the treatment of established nausea and vomiting. In addition, the incidence and severity of delayed and anticipatory CINV can be lowered if acute CINV is prevented or minimized.⁶ Currently available antiemetic agents are most effective in the prevention of acute CINV.⁶

DELAYED

Delayed nausea and vomiting has been arbitrarily defined as CINV that occurs 24 hours after chemotherapy administration.⁶,⁷ Recent evidence suggests that delayed CINV may begin as early as 16 hours after chemotherapy administration and can persist for several days.⁶,⁷ Although delayed CINV may be less severe than acute CINV, it can cause significant nutrition and hydration problems.⁹ Patients with delayed CINV may require intravenous fluid replacement or even hospitalization.

Delayed emesis is observed in as many as 80% of patients, usually occurring 24 to 72 hours after high-dose cisplatin (>100 mg/m²) has been administered.¹⁰ Delayed CINV can also occur in patients who receive as little as 50 mg/m² of cisplatin or a chemotherapy combination such as cyclophosphamide and an anthracycline.⁹ Historically, antiemetic agents have been less successful in the prevention of delayed CINV than in the prevention of acute CINV.⁶

According to the American Society of Clinical Oncology, poor control of acute CINV is the most important characteristic used to predict which patients are at greater risk for delayed CINV.¹¹ Patients who have had acute CINV with chemotherapy are more likely to experience delayed CINV. Therefore, an important part of an effective strategy to prevent delayed CINV may be to prevent acute symptoms.

ANTICIPATORY

Anticipatory CINV is a learned or conditioned response and can occur before, during, or after the administration of chemotherapy. It is a response to environmental stimuli, such as tastes, sensations, smells, sights, or psychological factors associated with the chemotherapy experience. Approximately 10% to 44% of patients who receive chemotherapy experience anticipatory CINV.¹²,¹³

Manifestations of anticipatory emesis can range from mild to severe. Patients may experience insomnia or anxiety in the days before treatment, or they may experience intense nausea and vomiting before chemotherapy is administered. Anticipatory CINV is most likely to occur in patients who have had poor control of acute or delayed emesis with prior chemotherapy.⁶,¹¹

Treatments for anticipatory CINV include the use of antianxiety medications and behavioral interventions, such as guided imagery, hypnosis, and thermal biofeedback. Early screening and recognition of patients at risk
for anticipatory CINV are essential for optimal treatment. Prevention of CINV is more likely to be successful than the modification of established negative behavioral responses to chemotherapy.

**TREATMENT-RELATED AND PATIENT-RELATED FACTORS**

The potential for CINV may be influenced by 2 major categories of risk factors: chemotherapy agents and patient characteristics.\textsuperscript{11,16-18}

**CHEMOTHERAPY AGENTS**

The primary risk factor for CINV is the intrinsic emetogenicity of the chemotherapy agent.\textsuperscript{17,18} Table 1 lists chemotherapy agents according to their emetic risk. Varying emetic risk may result because different agents act at different sites or even multiple sites within the patient’s system.\textsuperscript{3}

The administration dose and schedule of a chemotherapy agent also are important treatment-related factors that affect risk for CINV.\textsuperscript{5} Administration of a low-risk emetic drug in high doses over a short period of time may dramatically increase the risk for CINV. In addition, concomitant administration of chemotherapy agents and repeated cycles of chemotherapy also increase the potential for CINV.\textsuperscript{5,11,16,18} Although an agent may be associated with low emetic risk, the combined emetogenicity of individual agents can lead to an increased risk of nausea and vomiting that requires aggressive antiemetic therapy.\textsuperscript{18} Most patients with cancer receive combination chemotherapy, and the emetogenic potential of the combined drugs and individual drug doses must be considered.\textsuperscript{7}

**PATIENT CHARACTERISTICS**

Although the extent of CINV depends largely on the emetogenic potential of the administered chemotherapy agents, patient characteristics such as previous experience with chemotherapy, sex, age, and alcohol intake history also have an impact.\textsuperscript{6,11} Patients who are at increased risk for CINV include women, patients younger than 50 years, patients prone to motion sickness, and patients with pre-existing anxiety and nausea.\textsuperscript{11,17,18} The degree of CINV also may be influenced by taste changes induced by chemotherapy.\textsuperscript{16}

A patient’s history of low alcohol consumption may indicate increased susceptibility to CINV.\textsuperscript{11} Chronic heavy alcohol usage, which can be defined as 100 g of alcohol per day for a period of a few years, has been associated with improved control of emesis.\textsuperscript{11} In general, the higher the alcohol intake history, the lower the risk of CINV.\textsuperscript{11}

Fewer women achieve complete emetic control than men, with differences as great as 20% to 30% between the sexes.\textsuperscript{18} One reason for this result may be that women often receive combination chemotherapy regimens containing agents, such as cyclophosphamide, which result in an extended risk of emesis.\textsuperscript{9} Women also are less likely than men to have a history of high alcohol intake.\textsuperscript{9}

**ADVANCES IN UNDERSTANDING THE PATHOPHYSIOLOGY OF EMESSION**

In recent years, progress has been made in understanding the neurophysiologic mechanisms that control nausea and vomiting. Nausea and vomiting are mediated through the central nervous system (CNS) but by different mechanisms. Nausea is mediated through the autonomic nervous system. Vomiting results from the stimulation of a complex reflex mediated by the “vomit-
ing center” in the brain stem, which integrates afferent stimulation from a number of neurologic pathways.

Vomiting is a fundamental protective reflex to prevent the harmful effects of ingested, potentially toxic, substances. Mechanisms of CINV are listed in Table 2. The activation of the chemoreceptor trigger zone (CTZ) is thought to be the most common mechanism of CINV for most chemotherapy agents.9

Studies have reported that emesis after chemotherapy is initiated by the release of neurotransmitters, such as dopamine, acetylcholine, histamine, opiates, serotonin, and substance P.20 These neurotransmitters are released from cells that are susceptible to the presence of toxic substances in the blood or cerebrospinal fluid. Until recently, dopamine was the neurotransmitter that appeared to be most responsible for CINV.9 Although several effective antiemetics are dopamine antagonists, there is a high degree of variability in the dopamine-receptor binding affinity of these drugs,21 and some chemotherapy agents that cause CINV are affected very little or not at all by dopamine antagonists.

No single neurotransmitter appears to be responsible for all CINV. However, serotonin (5-hydroxytryptamine [5-HT]) receptors may be particularly important in the pathophysiology of early or acute vomiting.22 Studies in humans have shown that cisplatin administration results in a large increase in urinary output of the serotonin metabolite 5-hydroxyindoleacetic acid within 24 hours, indicating the release of intracellular serotonin.20 The release of serotonin activates receptors of the 5-HT3 subtype, which stimulate the CNS centers mediating the emetic response. Although serotonin plays an important role in the acute phase of CINV, it is a less significant mediator of delayed emesis. Patients with delayed CINV respond poorly to 5-HT3 antagonists, which indicates that other neurotransmitters may be involved in the pathogenesis of this phenomenon.20

Recent data have become available regarding the potential role of substance P in emesis and the use of neurokinin-1 (NK1) antagonists as antiemetics. Substance P is a neuropeptide found in the CTZ and gastrointestinal tract, where it is colocalized with serotonin in the enterochromaffin cells.20-23 The emetic effects of substance P result from binding to the NK1 receptor.24 Substance P levels in the peripheral circulation may become elevated after administration of cisplatin.20 In animal models, substance P has been shown to cross the blood-brain barrier,20 presenting the possibility that substance P of peripheral origin may act centrally to induce emesis.20 CNS penetration by NK1 antagonists is essential for the prevention of vomiting in the first 4 hours after cisplatin-based chemotherapy.25

Neurokinin-1 antagonists have exhibited a broad spectrum of antiemetic activity, including antagonism of several emetic stimuli not affected by serotonin and dopamine receptor antagonists.9 Hesketh et al also have examined the time course of antiemetic effect of an NK1 antagonist, a 5-HT3 antagonist, and a combination of both.20 They used data obtained in 2 phase II clinical trials of aprepitant in patients receiving cisplatin, a highly emetogenic chemotherapy agent. Post hoc analysis revealed that over a period of 7 days after cisplatin, emetic control was better in patients who received the NK1 antagonist than in patients who received the 5-HT3 antagonist. However, in the first several hours after cisplatin administration, emesis occurred in fewer patients who received the 5-HT3 antagonist. In addition, most treatment failures occurred within the first 8 to 12 hours of administering chemotherapy in patients who received the NK1 antagonist, as compared with a more even distribution of failures over time for patients who received the 5-HT3 antagonist. Patients who received a combination of drugs had superior control of symptoms, as compared with patients who received either drug as a single agent. Hesketh et al concluded that serotonin mediates the early vomiting process occurring within 8 to 12 hours after cisplatin-based chemotherapy and that sub-

<table>
<thead>
<tr>
<th>Table 2. Mechanisms of Chemotherapy-Induced Nausea and Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stimulation of chemoreceptor trigger zone of the area postrema</td>
</tr>
<tr>
<td>• Peripheral mechanisms</td>
</tr>
<tr>
<td>– Damage of GI mucosa</td>
</tr>
<tr>
<td>– Stimulation of GI neurotransmitter receptors</td>
</tr>
<tr>
<td>• Cortical mechanisms</td>
</tr>
<tr>
<td>– Direct cerebral activation</td>
</tr>
<tr>
<td>– Indirect (psychogenic) mechanisms</td>
</tr>
<tr>
<td>• Vestibular mechanisms</td>
</tr>
<tr>
<td>• Alterations of taste and smell</td>
</tr>
</tbody>
</table>

GI = gastrointestinal.
stance P, acting as NK1 receptors, becomes the dominant mediator of vomiting after this time.20

ARE PHYSICIANS AND NURSES ACCURATELY RECOGNIZING CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING?

Objective measures, such as the number of emetic episodes after chemotherapy, have shown that the control of CINV has improved in recent years. The introduction of less emetogenic chemotherapy agents and the development of 5-HT3 antagonists (potentiated by concomitant use of steroids) in the early 1990s have contributed to the decline in emetic episodes.

Despite improvements, antiemetic control is not yet optimal. Further progress will depend not only on the development of new effective antiemetic treatments but also on the clinician’s accurate understanding of the continuing frequency of CINV. Delayed CINV often occurs after the patient is discharged from the hospital and is not available for direct observation by a healthcare provider, which makes a true assessment of the problem difficult.

In a recent study, Grunberg et al examined the incidence of acute and delayed nausea and emesis after high emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) when appropriate antiemetic therapy was administered.26 In addition, the study investigators evaluated the accuracy with which physicians and nurses perceive the incidence of CINV within their own practice settings. The prospective observational study enrolled 198 adult patients receiving HEC or MEC for the first time and recruited 24 physicians and nurses from 14 oncology practices in 6 countries.

Although all of the patients in the study received antiemetic therapy, more than 35% of all patients experienced acute nausea; 13%, acute emesis.26 Delayed CINV was more commonly observed than acute CINV. Among patients who received HEC, 60% experienced delayed nausea; 50%, delayed emesis. Among patients who received MEC, 52% experienced delayed nausea; 28%, delayed emesis.

Figure IA. Incidence of Nausea and Emesis with HEC

Comparison of physician (MD), nurse (RN), and combined physician/nurse (MD + RN) estimates with observations of the incidence of nausea and emesis in patients who received HEC (95% confidence interval).

HEC = high emetogenic chemotherapy.


Figure IB. Incidence of Nausea and Emesis with MEC

Comparison of physician (MD), nurse (RN), and combined physician/nurse (MD + RN) estimates with observations of the incidence of nausea and emesis in patients who received MEC (95% confidence interval).

MEC = moderately emetogenic chemotherapy.

Before the patients were surveyed, oncologists and oncology nurses were asked to estimate the incidence of acute (day 1) and delayed (days 2–5) CINV after the first administration of HEC or MEC. Figures 1A and 1B show the comparison of physician, nurse, and combined physician/nurse estimates with observations of the incidence of CINV after HEC and MEC. Although physicians and nurses accurately estimated the incidence of acute CINV, they underestimated the incidence of delayed CINV in their own practices. For patients who received HEC, the predicted incidence of delayed nausea was 39% (95% confidence interval [CI], 30%–48%), and the observed incidence was 60% (95% CI, 48%–72%); the predicted incidence of delayed emesis was 22% (95% CI, 12%–31%), and the observed incidence was 50% (95% CI, 37%–63%). The incidence rates of delayed nausea and vomiting were also underestimated for patients who received MEC. The incidence rate of delayed nausea was predicted to be 24% (95% CI, 15%–34%), but the observed incidence rate was 52% (95% CI, 46%–59%); the incidence rate of delayed emesis was predicted to be 15% (95% CI, 6%–24%), but the observed rate was 28% (95% CI, 22%–34%). More than 75% of doctors and nurses underestimated the incidence of delayed CINV associated with HEC and MEC.

Chemotherapy-induced nausea and vomiting, particularly delayed CINV, continues to be a significant problem for patients with cancer. To provide effective treatment, healthcare providers must recognize that a problem exists. Physician and nurse education and structured reporting by patients of their experiences during chemotherapy may help to increase appreciation of the incidence and duration of delayed CINV.

**Conclusions**

Although newer antiemetic protocols have broadened the number of effective management options for CINV, antiemetic control is not yet optimal; nausea and vomiting remain among the most severe effects of cancer treatment. To provide optimal care for patients, physicians and nurses must recognize the differences between the forms of CINV resulting from chemotherapy administration. Risk for CINV is affected by the chemotherapy agent’s emetogenicity and individual patient characteristics, such as sex, age, alcohol intake history, and previous experience with chemotherapy. Advances in the understanding of the pathophysiology of emesis have shifted focus from the role of neurotransmitters, such as dopamine and serotonin, to the potential role of substance P, which binds to the NK1 receptor. NK1 antagonists exhibit a broader spectrum of antiemetic activity than serotonin and dopamine receptor antagonists. Further progress in the prevention and management of CINV depends not only on the development of new effective antiemetic treatments but also on an accurate understanding of the impact that CINV continues to have on patients with cancer.

**References**


