Chemotherapy-Induced Nausea and Vomiting (CINV): Perceptions, Mechanisms, and Treatment Guidelines

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Summary

Chemotherapy-induced nausea and vomiting (CINV) has a significant impact on quality of life and is a dreaded adverse effect of cancer treatment. As the understanding of the underlying pathophysiology of this process has evolved, so has treatment. There are numerous effective options for preventing both acute and delayed CINV. Following the evidence-based guidelines will significantly reduce the incidence of this feared adverse effect.

Key Points

- CINV can be acute, delayed, or anticipatory.
- In controlling CINV, the strategy is prevention rather than treatment.
- Therapy is guided by the emesis potential of the chemotherapy being given.
- The most effective combination for preventing acute CINV is serotonin receptor antagonists and dexamethasone.
- Guidelines provide specifics on agents to use that provide both acute and delayed coverage.

CHEMOTHERAPY-INDUCED NAUSEA AND vomiting (CINV) may be classified as acute (beginning within the first 24 hours after chemotherapy), delayed (beginning more than 24 hours after chemotherapy), or anticipatory (beginning before acute chemotherapy-related symptoms would be expected to occur). Some data suggest the delayed phase may begin as early as 16 hours after chemotherapy administration. Although mild nausea and vomiting may be discomfiting, more severe cases of nausea and vomiting may result in dehydration, malnutrition, and electrolyte imbalance. These conditions can affect quality of life, the desire to continue with antitumor therapy, and survival.1,2 Studies have demonstrated that nausea and vomiting secondary to chemotherapy impair a patient’s ability to complete household tasks, enjoy meals, and maintain activities of daily living and recreation.3,4

Patient- and treatment-related risk factors exist for developing chemotherapy-induced nausea and vomiting. Patient-related risk factors include younger age, female gender, and no prior history of alcohol use. Treatment-related risk factors include high emetogenicity (compared with moderate or low emetogenicity) of the chemotherapy agent and high drug dose.5,6 Exhibit 1 shows the definitions of the emetic risk groups for chemotherapy.7,8 Algorithms that account for these risks have been developed to classify the acute emetogenicity of chemotherapy agents. This classification system serves as a framework for the development of antiemetic treatment guidelines and the design of clinical trials.

Nausea and vomiting are two of the most concerning adverse effects of chemotherapy.9-12 Unfortunately, even in the era of modern antiemetic therapy, health care providers can underestimate the impact of CINV on patients. In an international prospective observational study of 298 patients from 14 oncology practices performed in 2001 to 2002, 97 percent of patients received a 5-HT3 receptor antagonist.
antagonist and 78 percent received a corticosteroid prior to receipt of moderately or highly emetogenic chemotherapy (78% received moderately emetogenic regimens). Given the emetogenic potential of the regimens, all the patients should have received both agents. Physicians and nurses overestimated the efficacy of antiemetic treatment for the majority of patients. The greatest discrepancy between predicted and actual nausea and emesis occurred for the delayed period, with physicians and nurses underestimating the incidence of delayed nausea/vomiting by nearly 30 percent. Of interest, even with treatment with antiemetics, 35 percent of patients experienced acute nausea and more than 50 percent experienced delayed nausea.\textsuperscript{13}

CINV appears to occur via two different mechanisms—one is located in the central nervous system (central) and the other is mediated in the GI tract (peripheral).\textsuperscript{14} The central mechanism is hypothesized to occur by activation of the chemotherapy trigger zone (CTZ) by a chemotherapeutic agent. The CTZ is found within the area postrema of the brain, which lacks a blood-brain barrier and can be accessed through either the blood or cerebrospinal fluid. Once activated, the CTZ releases multiple neurotransmitters, which in turn activate the brain stem vomiting center. The peripheral mechanism is postulated to occur by a chemotherapeutic agent causing local GI irritation and damage to the GI mucosa, which results in the release of neurotransmitters. This then activates receptors in the GI tract, which are mediated by afferent fibers of the vagus nerve. The activated vagal afferent fibers send signals to the brain stem vomiting centers. In both instances, the neurotransmitters may act independently or in combination to induce vomiting.

The evolution of antiemetic agents during the past 20 years parallels advances in understanding the neuropharmacology of emesis and which neurotransmitters are involved. In the early 1960s, phenothiazines became the first class of agents demonstrated to reduce emesis associated with fluorouracil by targeting the neurotransmitter dopamine and the D2 receptor. During the late 1970s, the introduction of cisplatin provided stimulus for further antiemetic research because the inevitable side effects of nausea and vomiting threatened the use of this effective agent. Beginning in the 1980s, high-dose metoclopramide provided a new antiemetic option. The value of combination regimens for improving antiemetic efficacy was recognized and our understanding of the pathophysiology of emesis significantly improved. In addition, predictive variables were identified, including such treatment-related factors as the inherent emetogenicity of the chemotherapeutic agent and patient-related factors as well. The first serotonin (5-HT3) receptor antagonist launched in 1991 and continued research led to its combined use with dexamethasone for improved results. This regimen became the standard of care. The extensive research regarding 5-HT3 receptor antagonists also clarified the existence and persistence of delayed nausea and vomiting following chemotherapy and helped fuel development of agents active on other neurotransmitter systems, such as substance P and neurokinin one (NK1) receptors.

Prior to the use of 5-HT3 receptor antagonists, dopamine antagonists (especially metoclopramide) were used to treat emesis from highly emetogenic chemotherapy regimens. Use of dopamine antagonists is limited by antidopaminergic side effects, including extrapyramidal reactions, anxiety, and depression. The effectiveness of metoclopramide, which is due to both antidopaminergic and anti-serotonergic actions, led to the development of 5-HT3 receptor antagonists specifically for the treatment of emesis. Cannabinoids (dronabinol) are effective in patients receiving moderately emetogenic chemotherapy, although serious side effects (including dysphoria, hallucinations, sedation, and disorientation) limit their use.

Steroids also have an antiemetic effect. A meta-analysis was performed to identify randomized evidence of the efficacy of dexamethasone in protecting against acute and delayed nausea and vomiting.

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### Exhibit 1: The Four Emetic Risk Groups of Chemotherapeutic Drugs (ASCO/MASCC/NCCN)\textsuperscript{7,8}

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>Risk in nearly all patients (&gt; 90%)</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Risk in 30% to 90% of patients</td>
</tr>
<tr>
<td>LOW</td>
<td>Risk in 10% to 30% of patients</td>
</tr>
<tr>
<td>MINIMAL</td>
<td>Fewer than 10% at risk</td>
</tr>
</tbody>
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in patients who received highly or moderately emet-
ic chemotherapy. A search of 1200 citations revealed
32 studies that included 42 pertinent comparisons
in a total population of 5,613 patients. Results of
the meta-analysis revealed that dexamethasone was
superior to placebo or to no treatment for complete
protection from acute and delayed emesis and nau-
sea. One in six patients treated with dexamethasone
avoided emesis completely.\(^{15}\)

Four 5-HT\(3\) receptor antagonists are approved for
use in the United States for chemotherapy-induced
emesis: palonosetron (Aloxi\(^{8}\)), ondansetron (Zo-
fran\(^{8}\)), dolasetron (Anzemet\(^{8}\)), and granisetron (Ky-
tril\(^{8}\)). Clinical studies have shown that a regimen
containing a 5-\(\text{hT3}\) receptor antagonist is highly
effective in preventing acute vomiting, but demon-
strates variable efficacy for delayed events. Based on
the vast accumulated literature to date, the primary
mechanism of action for 5-\(\text{HT3}\) receptor antagonists
is thought to be blockade of 5-\(\text{HT3}\) receptor activa-
tion mediated by serotonin release in the gut.\(^{16,17}\)
The 5-\(\text{HT3}\) agents are similar in efficacy with the
possible exception of palonosetron which appears to
have improved efficacy for delayed CINV. The ex-
tended plasma half-life of palonosetron, combined
with its high binding affinity for the serotonin recep-
tor, may contribute to its prolonged effect. During
the acute, delayed, and overall time intervals,
signifi-
cantly more patients treated with palonosetron 0.25
mg achieved a complete response (CR) compared
with those treated with ondansetron (\(\text{p}<0.025\)). CR
rates for palonosetron 0.75 mg were numerically
higher than ondansetron during the acute (73.5%),
delayed (64.6%), and overall (58.7%) time intervals
(Exhibit 2).\(^{18}\) Treatment with palonosetron 0.25 mg
resulted in significantly more patients nausea-free
on days three, four, and five compared with ondan-
setron. Nausea-free rates for palonosetron 0.75 mg
were significantly higher than ondansetron on days
four (70.9%) and five (81.0%).

Another meta-analysis evaluated 30 randomized
studies comparing 5-\(\text{HT3}\) antagonists with conven-
tional antiemetics in patients receiving moderately
and highly emetogenic chemotherapy. In 11 of these
trials, 5-\(\text{HT3}\) antagonists used as single agents were
compared to combination therapy with 5-\(\text{HT3}\) an-
tagonists plus dexamethasone. Combination therapy
with dexamethasone was superior to treatment with
a 5-\(\text{HT3}\) antagonist alone in 10 of 11 trials.\(^{19}\) Based
on extensive research and as reflected in guidelines,
5-\(\text{HT3}\) antagonists are first-line treatments for em-
esis associated with chemotherapy and are most ef-
tective when combined with dexamethasone.

Relatively new treatment options for CINV are
the NK-1 antagonists, with aprepitant (Emend\(^{8}\))
as the only agent in this class with FDA approval.
As single agents, NK-1 antagonists are less effective
than serotonin receptor antagonists in preventing
acute emesis. However, when combined with sero-
tonin receptor antagonists, they appear to be effec-
tive in delayed emesis.\(^{20}\)

The discovery of substance P was first reported in
1931. This neurotransmitter plays an integral role in
relaying noxious sensory information to the brain.
As a modulator of nociception, it is involved in sev-
eral physiologic activities, including the vomiting
reflex. Substance P, which belongs to the group of
peptides known as neurokinins, exerts its effect by

![Exhibit 2: Palonosetron vs Ondansetron in MEC – Complete Response: Acute and Delayed Emesis\(^{18}\)](image)
binding to the NK1 receptor. High concentrations of substance P/NK1 receptors are located in brain regions implicated in the emetic reflex, such as the nucleus tractus solitarius and area postrema. Unlike 5-HT3 receptor antagonists that work primarily at a peripheral site, the primary mechanism of NK1 receptor antagonists appears to be central. Several clinical trials have demonstrated that the most effective use of a NK1 receptor antagonist is with a 5-HT3 receptor antagonist and a corticosteroid.

Exhibit 3 shows the combined efficacy data from two studies of aprepitant. The combination of a 5-HT3 receptor antagonist plus dexamethasone is the cornerstone of therapy, and aprepitant adds to symptom control in the acute and delayed phases after highly emetic chemotherapy.

Fosaprepitant (Emend®) is an intravenous form of aprepitant that can be given as a single dose, which produces equivalent results to a three-day oral regimen of aprepitant. The only differences between these two regimens are the possible adverse effects of the intravenous injection and possibly a lower cost with the injectable form. Phlebitis can occur in addition to pain on infusion.
In controlling emesis, the strategy is prevention rather than treatment. Thus, the goal is to prevent CINV from occurring if at all possible. Evidence-based guidelines are available to guide therapy.2,3,24

Exhibit 4 shows the recommended regimens by emetogenic type of chemotherapy from the updated ASCO guidelines.23 The Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology (MASCO/ESMO) guidelines are very similar.24 The only difference between these two guidelines are for acute prevention with low emetogenic risk. The MASCO/ESMO guidelines recommend dexamethasone, a 5-HT3 receptor antagonist, or a dopamine receptor antagonist (metoclopramide).

Conclusion
The key to treating CINV is to prevent it from ever occurring. Preventive regimens are selected based on the emetogenic potential of the chemotherapy being given and patient-related factors. The available evidence-based guidelines should be used to select therapy.

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References
1. ASHP Commission on Therapeutics. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm. 1999;56:729–64.