Delayed Chemotherapy-Induced Nausea and Vomiting in the Hematology Population: A Review of the Literature

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Background: Chemotherapy-induced nausea and vomiting (CINV) is one of the most bothersome problems experienced by patients with cancer and results in serious complications. Considerable progress has been made in the management of acute CINV, but many patients receiving chemotherapy still complain of delayed nausea. In particular, delayed CINV affects patients in the hematology population who typically undergo several frontline chemotherapy regimens, multiday conditioning regimens, and salvage treatments. However, no international guidelines exist for the prevention of CINV in this population.

Objectives: This article provides a literature review of the pathophysiologic mechanisms of delayed CINV as well as the etiologies, assessment strategies, and potential therapies in this population.

Methods: A narrative review of the literature was performed.

Findings: Nurses fulfill an important role in the assessment of delayed symptoms by ensuring adequate measurement of the duration, frequency, severity, and distress caused by nausea, vomiting, and retching. A systematic assessment of retching, in addition to nausea and vomiting, that involves patients’ assessment of their own symptoms may enhance the accuracy of clinical reports, leading to improved tolerability of chemotherapy and patient quality of life. In addition, nurses may actively contribute to the development of specific guidelines for hematologic malignancies and a patient risk factor algorithm for optimizing the tolerability of chemotherapy.

Cancer treatments may cause a wide range of side effects that negatively affect quality of life (QOL) (Ballatori & Roila, 2003) and, occasionally, survival. In particular, chemotherapy-induced nausea and vomiting (CINV) is a bothersome and common problem associated with cancer treatment and may cause complications such as electrolyte imbalance, dehydration, and malnourishment (Navari, 2013). Chemotherapy is better tolerated by well-nourished patients who have fewer episodes of low blood counts and infection, experience fewer treatment delays, are able to tolerate higher doses of chemotherapy, and have better QOL (Bozzetti, 2001). Therefore, the management of nausea and vomiting (NV) should be considered in all phases of treatment.

Despite treatment progress and the introduction of new drugs like palonosetron, a second-generation 5-hydroxytryptamine 3 (5-HT3) receptor antagonist, and aprepitant, a neurokinin-1 receptor (NK-1R) antagonist, delayed CINV still affects about half of all patients undergoing moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) (Aapro et al., 2012). Poor management of CINV may lengthen the hospital stay, increase medical costs, and contribute to a patient’s physical and mental deterioration.

The incidence of delayed CINV is often underestimated by healthcare professionals. A study by Grunberg et al. (2004) showed that, although physicians and nurses accurately predicted the incidence of acute CINV, more than 75% underestimated...
the occurrence of delayed CINV. A gap of more than 30% has been observed between patients' reports of CINV and the predictions of healthcare professionals (Erazo Valle, Wisniewski, Figueroa Vadillo, Burke, & Martinez Corona, 2006).

The aim of this literature review is to describe the pathophysiological mechanisms of delayed CINV, as well as the etiologies, assessment strategies, and potential therapies for patients with hematologic cancer.

**Epidemiology**

More than half of all patients undergoing autologous hematopoietic stem cell transplantation (HCT) complained of uncontrolled NV related to the conditioning regimen on the day of the transplantation (Gonella, Berchialla, Bruno, & Di Giulio, 2014). Before the introduction of aprepitant, only 10% of patients had no nausea or emesis at the end of the chemotherapy, demonstrating some progress in prophylaxis; however, delayed nausea remains a significant issue (Fox-Geiman et al., 2001).

In the delayed phase, symptom control was poorer than in the acute phase, not only for patients undergoing transplantation and highly myelosuppressive conditioning, but also in patients with hematologic malignancies treated with MEC or HEC regimens. During the 24 hours following chemotherapy, 52% of the patients undergoing autologous or allogeneic HCT and 24% of patients with acute leukemia treated with multiple-day chemotherapy complained of nausea, compared with almost 90% and 55%, respectively, in the delayed phase (Lopez-Jiménez et al., 2006). In the five days following treatment, 38% of patients with leukemia and only 10% of patients undergoing HCT were completely protected from NV without rescue therapy (Lopez-Jiménez et al., 2006).

**Pathophysiology of Emesis and Delayed Emesis**

The emetic process is regulated by several neurotransmitters, but 5-HT, dopamine, and substance P (SP) appear to play the most important roles (Hesketh, 2008). Chemotherapeutic agents are thought to cause vomiting by activating neurotransmitter receptors in the area postrema (a circumventricular structure located at the caudal end of the fourth ventricle, known as the chemoreceptor trigger zone [CTZ]), vomiting center (VC), and gastrointestinal (GI) tract. Whether different chemotherapeutic drugs trigger different pathways or the release of different neurotransmitters is still unknown.

The VC can be directly activated by various signaling pathways from the cerebral cortex (fear, anticipation, or memory); sensory organ signals responding to pain, disturbing smells, and sights; and vestibular signals associated with motion sickness. The VC also can be indirectly activated by stimuli acting on the CTZ. The CTZ responds indirectly to vagal afferent nerve signals from the stomach and small intestine and, lacking a true blood-brain barrier, it responds directly to emetogenic compounds in the blood (Garret, Tsuruta, Walker, Jackson, & Sweat, 2003). Specific neurotransmitters (serotonin, dopamine, acetylcholine, histamine, and NK-1R) in the CTZ identify poten-

**Chemotherapy can trigger the vomiting reflex, directly affecting the CTZ or indirectly stimulating enterochromaffin cells (ECs) in the GI tract to release mediators, which bind to the appropriate receptors on the terminal side of vagal nerve afferents that lie in close proximity to ECs. This leads to an afferent stimulus that terminates in the nucleus tractus solitarius (NTS), activating the central pattern generator.**

Serotonin released by ECs plays the most important role, and the vagal-dependent pathway is the primary mechanism by which chemotherapeutic drugs induce acute emesis. At elevated levels, serotonin binds to 5-HT3 receptors on the terminal side of vagal nerve afferents that project to the NTS (Hesketh, 2008). Briefly, acute vomiting is mediated by serotonin, primarily through a peripheral pathway.

The mechanisms of delayed vomiting are less understood, but a main central pathway has been proposed (Hesketh, 2008). SP, an undecapeptide tachykinin present in the central and peripheral nervous systems and in the immune system, has several biologic effects, including the stimulation of secretion (pulmonary and gastrointestinal), smooth muscle contraction, and inflammatory responses. SP functions as a sensory neurotransmitter and neuromodulator related to the nociceptive pain pathways (Douglas & Leeman, 2011). SP binds to the NK-1R receptors that are widespread throughout several major sites in the central nervous system, including the area postrema and the NTS; they are less frequent in peripheral sites (Douglas & Leeman, 2011). Gut-derived peptides and metabolites of chemotherapeutic agents are thought to induce vomiting by binding to NK-1R in the CTZ, which is highly accessible by the blood or the cerebrospinal fluid because it lacks a blood-brain barrier (Hesketh, 2008). The NK-1R antagonists activate a main central pathway, although they may have a peripheral site of action and may prevent emesis by binding to SP-containing afferent nerve fibers that innervate the NTS (Hesketh, 2008).

In summary, acute CINV refers to NV in the first 24 hours after chemotherapy with a maximal intensity after 5–6 hours; it usually is caused by a peripheral mechanism mediated by serotonin. Delayed CINV occurs 24 hours post-treatment and can persist up to seven days with a maximal intensity occurring 48–72 hours after drug administration. Delayed CINV is largely associated with the activation of NK-1Rs that are centrally located, and it most likely is caused by cytotoxic therapy-induced mucosal damage. Studies have suggested that crosstalk occurs between 5-HT3 and NK-1R signaling, which may improve the control of acute and delayed CINV (Darmani, Chebolu, Amos, & Alkam, 2011; Stathis, Pietra, Rojas, & Slusher, 2012).

**Etiologies**

The inhibition of some of the previously described pathways results in a reduction in vomiting and, to a lesser extent, nausea. This suggests that the induction of NV may involve different mediators that act through different pathways. In addition, nausea is accompanied by the patient’s aware perception and the involvement of the upper cortical centers. Nausea typically precedes vomiting, but NV are not necessarily on a continuum;
patients undergoing auto-HCT receiving MEC or HEC experienced nausea with or without emesis in the five days following the transplantation (Gonella & Di Giulio, 2015).

The most important factor influencing the severity of CINV is the emetogenic potential of the chemotherapy (Janelins et al., 2013; Navari, 2013; Sekine, Segawa, Kubota, & Saeki, 2013). Antiemetic guidelines classified chemotherapy agents as having high, moderate, low, and minimal emetogenicity. A category of “high/moderate” emetogenicity has been introduced (Basch et al., 2011) for regimens based on a two-drug chemotherapeutic combination (cyclophosphamide/anthracycline) that is more emetogenic than either drug alone, asking for an antiemetic prophylaxis reserved for drugs with a high emetogenic risk.

The emetogenicity of antineoplastic drugs has been defined on the proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis (Hesketh, 2008). Agents with high emetogenic potential lead to emesis in 91% of patients or more, whereas 31%–90% of those undergoing MEC experience emesis (Hesketh, 2008). Agents with low and minimal emetogenic potential cause emesis in 10%–30% and in 9% or less of the patients, respectively (Hesketh, 2008). Other patient-related risk factors associated with the development of CINV are shown in Figure 1, but most of these refer to the acute phase, while less attention has been paid to delayed CINV.

High cisplatin doses (Du Bois et al., 1992; Italian Group for Antiemetic Research, 1994; Roila et al., 1991), high emetogenic potential (Du Bois et al., 1992; Sekine et al., 2013), and poor control of acute emesis (Roila et al., 1991) are the most important prognostic factors of delayed emesis. The control of acute and delayed emesis in the previous cycles seems to influence the risk for delayed vomiting (Italian Group for Antiemetic Research, 1994). Delayed emesis has been studied mainly in patients treated with cisplatin, but it also occurs with the anthracycline/cyclophosphamide combination and with moderately emetogenic chemotherapies, particularly carboplatin and cyclophosphamide (Ettinger et al., 2012; Janelins et al., 2013; Navari, Nagy, & Gray, 2013).

Female gender is another independent risk factor for delayed vomiting (Du Bois et al., 1992; Roila et al., 1991; Sekine et al., 2013) and nausea (Sekine et al., 2013), but no mechanism has yet been described. Additional studies may explore whether women express higher levels of NK-1R compared to men, which is a possible explanation for the discrepancy. Sekine et al. (2013) also observed an association between the number of risk factors and the incidence of delayed CINV, which was higher in patients with three risk factors; women younger than 55 years with no habitual alcohol intake had a higher risk of CINV. However, the incidence of emetic episodes, the use of rescue medications, and nausea of any grade were higher in the delayed phase regardless of the number of risk factors. Even among patients without associated risk factors, 40% experienced vomiting or were treated with a rescue therapy by the fifth day of chemotherapy, confirming the important role of the cycle emetogenicity (Sekine et al., 2013).

In a hematologic setting, delayed CINV is a major problem because the emetogenic potential of chemotherapeutic agents, which often are used at higher doses than in solid neoplasm, is increased by the schedule of administration (Schwartzberg, Jacobs, Matsouka, Azevedo, & Pinto, 2012) and platinum-based rescue regimens. Several pretransplantation conditioning regimens are delivered during multiple days and through multiple lines of chemotherapy (Schwartzberg et al., 2012). In particular, patients undergoing HCT typically have been treated with at least two lines of HEC or MEC and will receive other consolidation cycles. The concomitant antibiotic and antifungal prophylaxis and the use of opioids for mucositis may increase the risk of CINV (Schwartzberg et al., 2012). During the period of aplasia, isolation and dietary limitations may increase anxiety and depression; both of these conditions promote emesis (Janelins et al., 2013; Schwartzberg et al., 2012).

**Assessment Strategies**

Emesis is a well-defined and easily measured event; nausea may be more subjective, difficult to assess, and distressing (Navari, 2013). A baseline assessment must be provided, and symptoms should be monitored over time. Twenty-four tools are available to assess nausea in the oncology population; 13 of these include a separate assessment of vomiting and 3 of retching (Wood, Chapman, & Eilers, 2011). Only the MultinationalAssociation of Supportive Care in Cancer (MASCC) Antiemesis Tool (MAT) (MASCC, 2004) assesses acute and delayed NV. MAT is used to evaluate the duration and severity of nausea and the duration and frequency of vomiting without considering intensity or patient distress, which are important for assessing the effect of symptoms on QOL.

Duration may be measured by asking patients if they experienced NV and/or the number of hours these symptoms lasted. Frequency may be measured as the number of episodes during the timeframe addressed. Severity may be measured using a Likert-type scale, visual analog scale, or numeric rating scale of 0–10 or 0–100 (Stern, Koch, & Andrews, 2011; Wood et al., 2011). Distress may be measured using a Likert-type scale or by asking about the distress caused by a vomiting episode in the past week (Wood et al., 2011).

The most complete and widely used scale to classify the adverse effects of chemotherapy and radiotherapy is the Common

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**FIGURE 1. Patient-Related Risk Factors Associated With Chemotherapy-Induced Nausea and Vomiting Onset**

Note. Based on information from Janelins et al., 2013; Navari, 2013.
Oral intake decreased with... 

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Vomiting Inadequate oral caloric or

Nausea Life-threatening consequences; need for IV fluid replacement. However, this scale does not consider the time from the treatment to the onset of symptoms. An overall assessment of acute and delayed adverse events is provided in Table 1. Of the 24 available tools in the oncology population, severity (n = 15) and distress (n = 11) of nausea are the features assessed more frequently, whereas its duration (n = 7) and frequency (n = 4) are less addressed. Six tools explore vomiting in frequency and distress, five tools focus on duration, and only four focus on distress (Wood et al., 2011).

Although the assessment of NV has improved over time, retching seldom is assessed on its own, and no instrument measures its duration and severity. Monitoring of retching is not a routine practice, possibly because patients are unlikely to report it because nothing is expelled.

An adequate individual measurement of the duration, frequency, severity, and distress related to nausea, vomiting, and retching during the acute and delayed phases may provide healthcare professionals a more complete understanding of patients’ experiences and the pattern of chemotherapy-associated disorders.

**Patients’ Experience**

NV and retching can severely affect QOL, and treatment should include the management of all of these symptoms (Olver, Elliot, & Koczvara, 2014). Basch et al. (2009) observed 163 patients with lung cancer and their clinicians’ independent assessments of their symptoms during 28 months. The severity threshold of each symptom was reached earlier and more frequently in patients’ reports compared with those of clinicians. Patient reports may not only enhance the accuracy of clinicians’ CTCAE reports, but they also may improve safety.

Quinten et al. (2011) analyzed data from 14 randomized, controlled trials of 2,279 patients with cancer from the European Organisation for Research and Treatment of Cancer (EORTC). The authors investigated the agreement between the patients and their clinicians on six symptoms: pain, fatigue, vomiting, nausea, diarrhea, and constipation. Low to fair agreement was found for all symptoms, with the poorest agreement for fatigue (kappa coefficient [k] = 0.07; 95% CI [0.09, 0.1]), nausea (k = 0.14; 95% CI [0.1, 0.18]), and diarrhea (k = 0.14; 95% CI [0.07, 0.2]). The overall survival was more accurately predicted when considering the patients’ and clinicians’ scores.

In 2008, the National Cancer Institute launched the Patient Reported Outcomes (PRO) version of the CTCAE (PRO-CTCAE), a web-based platform to collect and integrate patients’ ratings of their symptoms during treatment (National Cancer Institute, 2014). PRO-CTCAE has acceptable validity and reliability in a large, heterogeneous sample of patients. Correlations in the expected direction were observed for 116 of 124 PRO-CTCAE items with the EORTC QOL Questionnaire–Core 30 (QLC–C30) global health scale (r = -0.21, range = 0.08 to -0.57). Fatigue, NV, pain, and insomnia were most strongly correlated with the corresponding QLC–C30 symptom scale (0.69–0.79, p < 0.001), indicating their negative impact on patients’ QOL. The test-retest reliability was observed across all tested items (intraclass correlation coefficient = 0.77, range = 0.53–0.96) (Dueck et al., 2012).

Another strategy is the use of a daily diary to record the pattern of NV, duration, frequency, and associated distress. These strategies may offer healthcare professionals a more complete understanding of their patients’ symptoms, particularly their severity and impact on patients’ daily activities and QOL. These strategies would allow clinicians to assess and optimize the tolerability of chemotherapy and to tailor regimens for vulnerable subpopulations (e.g., patients with comorbidities, older adults). Integrating the patient’s perspective may reduce the loss of information, helping healthcare professionals to understand the pattern of CINV, particularly anticipatory and delayed CINV, which have been less studied. In addition, this new type of reporting will change the patients’ role in clinical practice and research, making them active and central figures in the assessment and management of symptoms.

**Treatment Challenges**

The prophylaxis for acute CINV should start 24 hours before the administration of chemotherapy and should cover the first 24 hours after treatment; the prevention of delayed CINV requires an antiemetic therapy for two to four days after the completion of HEC and MEC cycles (Ettinger et al., 2012). In contrast to solid tumors, no international guidelines exist for the prevention and management of CINV in hematologic malignancies. Therefore, formal recommendations are urgently required. The best management for delayed CINV is prevention. Poor control of acute and delayed emesis in previous cycles is a prognostic factor of delayed vomiting (Italian Group for Antiemetic Research, 1994).

For patients with solid tumors treated with HEC regimens, an aprepitant/dexamethasone combination therapy is recommended; the National Comprehensive Cancer Network, MASCC, and American Society of Clinical Oncology guidelines recommend aprepitant with anthracycline/cyclophosphamide regimens.

**TABLE 1. Nausea and Vomiting Grades**

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<thead>
<tr>
<th>Grade</th>
<th>Nausea</th>
<th>Vomiting</th>
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<tbody>
<tr>
<td>1</td>
<td>Loss of appetite without alteration in eating habits</td>
<td>1–2 episodes (separated by 5 minutes) in 24 hours</td>
</tr>
<tr>
<td>2</td>
<td>Oral intake decreased without significant weight loss, dehydration, or malnutrition</td>
<td>3–5 episodes (separated by 5 minutes) in 24 hours</td>
</tr>
<tr>
<td>3</td>
<td>Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition, or hospitalization indicated</td>
<td>6 or more episodes (separated by 5 minutes) in 24 hours; tube feeding, total parenteral nutrition, or hospitalization indicated</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>Death</td>
</tr>
</tbody>
</table>

Implications for Practice

- Involve patients in assessing their own symptoms to enhance the accuracy of clinical reports.
- Assess nausea, vomiting, and retching as separate symptoms.
- Provide an adequate measurement of the duration, frequency, severity, and distress related to nausea, vomiting, and retching during the acute and delayed phases after chemotherapy administration.

For MEC, the post-treatment strategy depends on the antiemetics used before chemotherapy. Three possible regimens can be used. If used on Day 1, aprepitant is continued on Days 2 and 3; alternatively, dexamethasone or a 5-HT3 antagonist may be used. The doses of both drugs are decreased on Days 2 and 3 (aprepitant is decreased from 125 mg to 80 mg, and dexamethasone is decreased from 12 mg to 8 mg). Finally, no routine prophylaxis is recommended for chemotherapy with low or minimal emetogenic potential (Roila et al., 2010).

Lorazepam, a proton pump inhibitor, or H2 blockers may be added. Antacid therapy should be considered in patients with dyspepsia because they may not discriminate heartburn from nausea; benzodiazepines are recommended for anxious patients (Ettinger et al., 2012). About 30% of patients receive rescue antiemetic therapy in the 120 hours following chemotherapy (Aapro et al., 2012; Gonella et al., 2014). When breakthrough CINV appears, an additional agent from a different drug class should be administered, and several agents with different mechanisms of action may be required (Ettinger et al., 2012).

Prophylaxis is often not effective in preventing delayed and breakthrough nausea. Additional studies, particularly on HEC regimens and patients undergoing HCT, should assess new uses for drugs, such as olanzapine for emesis (Navari et al., 2013) because of its action on dopamine D2, 5-HT3, and histaminic and muscarinic receptors that may mediate chemotherapy-induced nausea. In addition, new combinations of second-generation 5-HT3 receptor antagonist, aprepitant, olanzapine, and gabapentin warrant further exploration (Navari, 2013).

Conclusion

Studies have shown progress in the management of CINV, but NV in patients with hematologic malignancies continue to be a significant challenge with a profound effect on QOL. This may be because of a lack of specific guidelines and prophylaxis based on the emetic potential of chemotherapy. A formal consensus on antiemetic prophylaxis in hematologic malignancies, as well as the validation of a patient risk factor algorithm based on prognostic risk factors, could support the choice of the most suitable antiemetic prophylaxis during the acute and delayed phases. A systematic assessment of retching, in addition to NV, with patients’ involvement in judging their own symptoms, may enhance the accuracy of clinicians’ reports, leading to an improvement in the tolerability of chemotherapy and patient QOL.


