Delayed Chemotherapy-Induced Nausea and Vomiting in Hematological Patients: a Review of the Literature on an Unmet Problem

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) are two of the most bothersome problems experienced by cancer patients and result in serious complications. In the last twenty years, considerable progress has been made in the management of acute CINV, although approximately 80% of patients receiving chemotherapy still complain of delayed nausea.

In particular, delayed CINV affects hematological patients who typically undergo several front-line chemotherapy regimens, multi-day conditioning regimens and salvage treatments. However, there are no international guidelines for the prevention of CINV in this population. This paper provides a literature review of the pathophysiological mechanisms of delayed CINV as well as the etiologies, assessment strategies and potential therapies in this population.

Nurses may fulfil an important role in the assessment of delayed symptoms, 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. Moreover, nurses may actively contribute to the development of specific guidelines for hematological malignancies and a patient risk factor algorithm for optimizing the tolerability of chemotherapy.

Keywords: nausea, vomiting, antiemetics, antineoplastic agents, guidelines, hematology

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Introduction

Cancer treatments often cause a wide range of side effects that may negatively affect quality of life (QoL) (Ballatori & Roila, 2003) and, occasionally, survival. In particular, chemotherapy-induced nausea and vomiting (CINV) are two of the most bothersome and common problems associated with cancer treatment and may cause complications such as electrolyte imbalance, dehydration and malnourishment (Navari, 2013). Treatment is better tolerated by well-nourished patients who experience fewer episodes of low blood count and infection, have fewer treatment delays, experience better QoL and are able to tolerate higher doses of chemotherapy (Bozzetti, 2001). Therefore, the management of nausea and vomiting (NV) should be considered in all phases of treatment. Despite the progress in treatment and the introduction of new drugs, such as palonosetron, a second-generation 5-hydroxytryptamine-3 receptor antagonist ($5HT_3$-RA), and aprepitant, a neurokinin-1 receptor antagonist (NK1-RA), delayed CINV still affects approximately half of all patients undergoing moderate (MEC) or high (HEC) emetogenic chemotherapy (Aapro et al., 2012). Poor management of NV may lengthen the hospital stay and increase medical costs, and it may contribute to a patient's physical and mental deterioration.

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

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

Epidemiology

More than half of all patients undergoing autologous hematopoietic cell transplant (auto-HCT) complained of uncontrolled nausea or vomiting on the day of the transplant, associated with the conditioning regimen (Gonella, Bruno, Berchialla, Di Giulio, 2014). Before the introduction of aprepitant, only 10% of patients had no nausea or emesis at the end of the chemotherapy, demonstrating that there has been some progress in prophylaxis, although 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 transplant patients undergoing highly myeloablative conditioning, but also in patients with hematological malignancies treated with MEC or HEC. During the 24 hours following chemotherapy, approximately half of the patients undergoing autologous or allogenic HCT and more than 20% of acute leukemia patients treated with multiple-day chemotherapy complained of nausea compared with almost 90% and 55%, respectively, in the delayed phase (Lopez-Jimenez et al., 2006). In the five days following treatment, approximately 35% of leukemia and only 10% of HCT patients were completely protected from NV without rescue therapy (Lopez-Jimenez 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 known as chemoreceptor trigger zone (CTZ), vomiting centre (VC) and gastrointestinal (GI) tract. It is still unknown whether different chemotherapeutic drugs trigger different pathways and/or the release of different neurotransmitters.

The vomiting center can be directly activated by various signaling pathways: 1) originating in the cerebral cortex (fear, anticipation, or memory); 2) sensory organ signals responding to pain, disturbing smells and sights; 3) and vestibular signals associated with motion sickness. This center can also 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 the neurokinin-NK1) in the CTZ identify potentially harmful substances and relay impulses to the VC to initiate the vomiting cascade (Garret et al., 2003).

Chemotherapy can trigger the vomiting reflex, directly affecting the CTZ or indirectly stimulating enterochromaffin cells (ECs) in the gastrointestinal 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-HT_3 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 biological effects, including the stimulation of secretion (pulmonary, 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 neurokinin-1 (NK-1R) receptors that are widespread throughout several major sites in the central nervous system, including the area postrema and the NTS, and 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 either 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 nausea and/or vomiting in the first 24 hours after chemotherapy with a maximal intensity after 5-6 hours; it is usually caused by a peripheral mechanism mediated by serotonin. Delayed CINV occurs 24 hours post-treatment and can persist up to 7 days with a maximal intensity occurring 48-72 hours after drug administration. Delayed CINV is largely associated with the activation of NK-1 receptors that are centrally located, and it is most likely caused by cytotoxic therapy-induced mucosal damage (CIMD). Recent studies have suggested that crosstalk occurs between 5-HT_3 and NK-1 receptor signaling, which may improve the control of acute and delayed CINV (Stathis, Pietra, Rojas, & Slusher, 2012; Darmani, Chebolu, Amos, & Alkam, 2011).

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. Moreover, 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: auto-HCT patients undergoing MEC or HEC experienced nausea with or without emesis in the 5 days following the transplant (Gonella & Di Giulio, 2014).

The most important factor influencing the severity of CINV is the emetogenic potential of the chemotherapy (Janelsins, 2013; Navari, 2013; Sekine, Segawa, Kubota, & Saeki, 2013). Antiemetic guidelines classified chemotherapeutic agents as having high, moderate, low and minimal emetogenicity. A category of "high/moderate" emetogenicity has been recently 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 to drugs with a high emetogenic risk.

The emetogenicity of the most frequently used chemotherapeutic agents is reported in Table 1 (Ettinger et al., 2012). Other patient-related risk factors associated with the development of CINV are shown in Table 2, but most of these refer to the acute phase, while less attention has been paid to delayed CINV.

High cisplatin doses (Italian Group for Antiemetic Research, 1994; Du Bois et al., 1992; Roila et al., 1991) as well as a high emetogenic potential (Sekine et al., 2013; Du Bois et al., 1992) and the 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 (Janelsins et al., 2013; Navari et al., 2013; Ettinger et al., 2012).

Female gender is another independent risk factor for delayed vomiting (Sekine et al., 2013; Du Bois et al., 1992; Roila et al., 1991) and nausea (Sekine et al., 2013), but no mechanism has yet been described. Future 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) separately assessed NV in the acute and delayed phases, and they showed that female gender and low alcohol consumption remained risk factors for nausea in the delayed phase.

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 under 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 5th day of chemotherapy, confirming the important role of the cycle emetogenicity (Sekine et al., 2013).

In a hematological setting, delayed CINV is a major problem because the emetogenic potential of chemotherapeutic agents, which are often 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 pre-transplant conditioning regimens are delivered over multiple days and multiple lines of chemotherapy (Schwartzberg et al., 2012). In particular, patients undergoing HCT have usually 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, and both of these conditions promote emesis (Janelsins et al., 2013; Schwartzberg et al., 2012).

Assessment Strategies

Emesis is a well-defined and easily measured event, while nausea may be more subjective, difficult to assess, and more distressing (Navari, 2013): a baseline assessment must be provided and symptoms should be monitored over time.

Currently, 24 tools are available to assess nausea in the oncology population: 13 of these include a separate assessment of vomiting, and three of retching (Wood, Chapman, & Eilers, 2011). Only the MASCC Antiemesis Tool (MAT) (Multinational Association of Supportive Care in Cancer, 2004) assesses both acute and delayed NV. The MAT evaluates duration and severity of nausea and duration and frequency of vomiting without considering intensity or patient distress, both important for assessing the impact of symptoms on QoL.

Duration may be measured by asking patients if they experienced nausea or vomiting 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 scale, a visual analogue

scale (VAS) or a numerical rating scale 0-10 or 0-100 (NRS) (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 Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) (National Cancer Institute, 2009), introduced in 2009. This instrument examines NV separately and investigates their influence on the oral intake or the need for intravenous fluid replacement. However, this scale does not consider the time between the treatment and the onset of symptoms. An overall assessment of acute and delayed adverse events is given (table 3). Other examples of CINV assessment tools are presented in table 4.

While the assessment of NV improved over time, retching is seldom 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 patient's experience and pattern of chemotherapy-associated disorders.

Patients' Experience

Nausea, vomiting and retching can severely affect QoL, and treatment should include the management of all these symptoms (Olver, Elliot, & Koczwara, 2014). Basch et al. (2009) observed 163 lung cancer patients and their clinicians' independent assessments of their symptoms over 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, they may also improve safety.

Quinten et al. (2011) analyzed data from 14 EORTC randomized controlled trials on 2279 cancer patients. 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 (k=0.07, 95% Confidence Interval=0.09-0.10), nausea (k=0.14, 95% CI=0.10-0.18) and diarrhea (k=0.14, 95% CI=0.07-0.20). The overall survival was more accurately predicted when considering both the patients' and the 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 116/124 PRO-CTCAE items with the QLQ-C30 global health scale (r=-0.21; range 0.08 to -0.57). Fatigue, nausea, vomiting, pain and insomnia were most strongly correlated with the corresponding QLQ-C30 symptom scale (0.69 to 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 to 0.96) (Dueck et al., 2012).

Another strategy is the use of a daily diary to record the pattern of NV, duration, frequency, and the associated distress. These strategies may offer health care 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 sub-populations (co-morbidities, older adults). Integrating the patients' 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. Moreover, 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.

Challenges in the Treatment of CINV

The prophylaxis for acute CINV should start 24 hours before the administration of chemotherapy

and should cover the first 24 hours after treatment, while the prevention of delayed CINV requires an antiemetic therapy for 2 to 4 days after the completion of HEC and MEC cycles (Ettinger et al., 2012).

In contrast to solid tumors, there are no international guidelines for the prevention and management of CINV in hematological malignancies. Thus, formal recommendations are urgently required.

The best management for delayed CINV is prevention. Poor control of acute and delayed emesis in the 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, while NCCN, MASCC and ASCO guidelines recommend aprepitant with anthracycline-cyclophosphamide regimens. For MEC, the post-treatment strategy depends on the antiemetics used before chemotherapy. Three possible regimens can be used: if used on day one, aprepitant is continued on days 2 and 3; alternatively, dexamethasone or a $5HT_3$ antagonist may be used. The doses of both drugs are decreased on days 2-3 (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 and/or a proton pump inhibitor or H_2 blockers may be added. Antacid therapy should be considered in patients with dyspepsia because they may not discriminate heartburn from nausea, while benzodiazepines are recommended for anxious patients (Ettinger et al., 2012).

Approximately 30% of patients receive rescue antiemetic therapy in the 120 hours following chemotherapy (Gonella et al., 2014; Aapro et al., 2012). 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).

Current prophylaxis is often not effective in preventing delayed and breakthrough nausea. Further studies, particular on HEC regimens and HCT patients, should assess new uses for drugs, such as olanzapine for emesis (Navari, Nagy, & Gray, 2013) because of its action on dopamine D2, 5-HT_{2c}, histamic and muscarinic receptors that may mediate chemotherapy-induced nausea. In addition, new combinations of second-generation $5HT_3$RA, aprepitant, olanzapine and gabapentin warrant further exploration (Navari, 2013).

Conclusion

Several studies have shown progress in the management of CINV, but NV in patients with hematological malignancies continue to be a significant challenge with a profound impact on QoL. This may be due to a lack of specific guidelines and prophylaxis based on the emetic potential of chemotherapy. A formal consensus on antiemetic prophylaxis in hematological 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 nausea and vomiting, 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.

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