Review article

Chemotherapy-induced nausea and vomiting in an oncologist's practice. How can nausea and vomiting be prevented?

Agnieszka Jagiełło-Gruszfeld

Oncology Department, Mazovian Oncology Hospital, Warsaw
Head of Department: Agnieszka Jagiełło-Gruszfeld, MD, PhD

Correspondence:
Agnieszka Jagiełło-Gruszfeld, MD, PhD
Oncology Department, Mazovian Oncology Hospital
03-411 Warszawa, al. Solidarności 10/12
e-mail: agnieszka.jagiellogruszfeld@gmail.com

Received:
1.07.2025
Accepted:
30.07.2025

DOI: 10.24292/01.OR.152011025

ABSTRACT

Chemotherapy-induced nausea and vomiting (CINV) affects 70–80% of patients and significantly reduces quality of life and complicates treatment. Prevention is more effective than treatment – once symptoms develop, they are more difficult to control and can cause anticipatory nausea. The most important drug classes used for prophylaxis are: 5-HT_3-RAs (e.g., ondansetron, palonosetron), NK_1-RAs (aprepitant, netupitant), dexamethasone, and olanzapine. Modern regimens (e.g., NEPA, palonosetron) are more effective in preventing delayed and long-term CINV.

Key words: adverse events, chemotherapy-induced nausea and vomiting, CINV

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) are among the most common adverse effects of chemotherapy [1]. Approximately 70–80% of patients undergoing cancer treatment experience nausea and vomiting. CINV can significantly impair adherence to chemotherapy and reduce quality of life [2]. Appropriate preventive and therapeutic management can substantially reduce the incidence of CINV, thereby lowering healthcare costs and improving treatment effectiveness. Current antiemetic guidelines recommend four classes of drugs for CINV prophylaxis: neurokinin-1 receptor antagonists (NK_1-RAs), 5-hydroxytryptamine-3 receptor antagonists ($5\text{-}HT_3$-RAs), glucocorticosteroids (primarily dexamethasone), and atypical antipsychotics (primarily olanzapine) [3, 4].

WHY IS PREVENTION MORE IMPORTANT THAN TREATMENT?

Studies clearly demonstrate that once nausea or vomiting develops, it is more difficult to control than to prevent. The occurrence of CINV also leads to so-called anticipatory nausea, which appears before the next chemotherapy session due to conditioning and anxiety. Therefore, current guidelines (MASCC/ESMO, NCCN) emphasize the use of appropriate antiemetic regimens starting with the first cycle of chemotherapy. It is worth noting that patients who experience CINV during the first cycle of chemotherapy often develop more severe symptoms in subsequent cycles and may also develop refractory CINV [5].

TYPES

CINV is classified into the following types of nausea and vomiting [5]:

Acute: Occurs soon after the administration of chemotherapy and can last up to 24 h, primarily due to the release of serotonin (5-HT) from enterochromaffin cells.

Delayed (lasting more than 120 h): Occurs after 24 h, peaks at 2–3 days, and may last up to 5–7 days. The main mechanisms underlying these symptoms include substance P–mediated pathways, blood–brain barrier disruption, gastrointestinal motility disorders, and hormones produced by the adrenal glands.

Breakthrough: Refers to episodes of nausea or vomiting that occur despite the use of antiemetic therapy.

Anticipatory: Psychologically driven; nausea and vomiting may occur even before the next cycle of chemotherapy is administered [6]. These reactions may be triggered by taste, smell, sight, thoughts, or anxiety associated with previous experiences.

Refractory: Occurs despite appropriately administered antiemetic prophylaxis.

Distinguishing among the above types of CINV is crucial for selecting appropriate prophylaxis. It is also important to assess the emetogenic risk of specific chemotherapy regimens (list available at: https://www.mp.pl/interna/table/016_4865) and individual patient-related factors that may influence the onset and severity of CINV (tab. 1).

Table 1. Increased risk factors for CINV.

Vomiting after a previous cycle of chemotherapy
Female sex
Alcohol consumption
History of motion sickness or pregnancy-related nausea
Age <60 years
Receiving the first cycle of chemotherapy
History of nausea and vomiting due to other causes (e.g., drug-induced, postoperative, etc.)
Sleeping <7 h on the night before chemotherapy

PATHOGENESIS

The development of CINV results from the activation of multiple signaling pathways and neurotransmitters.

Key neurotransmitters and their associated receptors involved in CINV include dopamine and its receptors, substance P and neurokinin-1 (NK_1) receptors, and serotonin (5-HT) and its receptors. The medulla oblongata, which contains the vomiting center in the medulla oblongata, regulates the emetic response. This center integrates signals from peripheral gastrointestinal and central pathways to initiate the vomiting reflex appropriately.

Through the peripheral pathway, stimuli from the pharynx, stomach, or duodenum are transmitted via afferent fibers of the vagus nerve. This pathway is primarily associated with acute vomiting. In contrast, the central pathway directly stimulates the vomiting center, leading to vomiting in response to pain, vestibular dysfunction, or emotional stimuli. The chemoreceptor trigger zone, located in the fourth ventricle, sends signals to the vomiting center in response to endogenous toxins and chemical stimuli, such as chemotherapy or other drugs. The neurochemical mediators involved in this signaling pathway include 5-HT and its receptors, dopamine and its receptors, as well as substance P and NK_1 receptors.

Because this area is not protected by the blood–brain barrier, certain drugs (such as opioids and dopamine agonists) can act directly on receptors in this region. The exact mechanisms underlying nausea and its triggers remain unclear. Although nausea is a subjective sensation that is difficult to quantify, it typically

originates in the stomach and is believed to precede vomiting. It remains uncertain whether the neurotransmitters and receptors that mediate vomiting, such as substance P and serotonin, also play a role in nausea. However, dopaminergic, muscarinic, and histaminergic receptors may be involved in this mechanism [7].

PREVENTION

Antiemetic prophylaxis of acute nausea and vomiting

Preventive antiemetic treatment of acute and delayed nausea and vomiting is essential before the initiation of chemotherapy, as symptom-directed interventions at later stages often prove ineffective. This is particularly important for the prevention of delayed vomiting. Preliminary assessment of the emetogenic potential of a chemotherapy regimen is critical for developing an effective antiemetic treatment strategy. In addition, for patients receiving outpatient chemotherapy, it is important to establish a comprehensive plan to prevent delayed vomiting and to provide appropriate patient education [8].

Details of the current guidelines for the prevention of CINV are presented in table 2.

How to make the optimal choice of antiemetic drugs?

Among the 5-HT_3 receptor antagonists (5-HT_3-RAs), ondansetron is the most commonly used. It is metabolized by CYP2D6 and therefore may have reduced efficacy in patients with an ultra-rapid metabolizer genotype. In contrast, no clinically significant interaction has been observed between palonosetron and CYP2D6. Palonosetron may also be more effective in delayed CINV because of its longer half-life.

Regarding the choice of NK_1 receptor antagonists (NK_1-RAs), there is a lack of studies directly comparing aprepitant and netupitant. However, it has been shown that the combination of netupitant and palonosetron (NEPA), administered only on day 1, was not inferior to a 3-day regimen of aprepitant in preventing nausea and vomiting during treatment with cisplatin-based regimens. Similarly, a single dose of NEPA was at least as effective as a 3-day regimen of aprepitant in patients receiving an AC (doxorubicin and cyclophosphamide) regimen [8, 9].

If a patient receiving AC-based chemotherapy develops nausea and vomiting after day 1, extending the duration of dexamethasone administration may be considered. In addition, if the patient has been receiving olanzapine at a dose of 5 mg, the dose may need to be increased to 10 mg. Metoclopramide is unlikely to provide additional benefit, as it also acts on D_2 receptors, which are already antagonized by olanzapine [8].

Management of nausea and anticipatory vomiting

Anticipatory nausea and vomiting is an acquired, conditioned response that typically responds poorly to pharmacologic interventions. Initiating the first cycle of chemotherapy with appro-

Table 2. Guidelines applicable to the prevention of CINV

MASCC-ESMO guidelines		
CINV risk level	Acute phase of antiemetic treatment	Delayed phase of antiemetic treatment
High	NK_1-RA in combination with 5-HT_3-RA and dexamethasone	dexamethasone and aprepitant
Moderate	palonosetron in combination with dexamethasone	dexamethasone
Low	dexamethasone or a dopamine or 5-HT_3-RA receptor agonist	no routine treatment is recommended
ASCO guidelines		
High	A treatment regimen consisting of: • dexamethasone and aprepitant or • NEPA and 5-HT_3 receptor antagonist	dexamethasone in combination with aprepitant
Moderate	• palonosetron with dexamethasone or • aprepitant with dexamethasone	dexamethasone
Low	dexamethasone	5-HT_3-RA or dexamethasone, or aprepitant
NCCN guidelines		
High	• NEPA and dexamethasone or • dexamethasone with NK_1-RA and 5-HT_3-RA	dexamethasone and NEPA
Moderate	dexamethasone, palonosetron and olanzapine	dexamethasone, palonosetron and olanzapine
Low	dexamethasone in combination with aprepitant or 5-HT_3-RA	dexamethasone, palonosetron and olanzapine

5-HT_3-RA – 5-hydroxytryptamine 3 receptor antagonists; ASCO – American Society of Clinical Oncology; ESMO – European Society for Medical Oncology; MASCC – Multinational Association for Supportive Care in Cancer; NCCN – National Comprehensive Cancer Network; NEPA – combination of netupitant and palonosetron; NK_1-RA – neurokinin 1 receptor antagonists.

priate antiemetic prophylaxis is the most effective strategy to prevent anticipatory nausea and vomiting. In such cases, psychological interventions combined with the use of benzodiazepines prior to subsequent cycles of chemotherapy may be beneficial. Other potential treatment approaches include hypnosis, systematic desensitization, and muscle relaxation; however, their effectiveness varies [5].

Nausea and vomiting during treatment with conjugates

New anticancer preparations entering clinical practice are also associated with emetogenic potential. The most relevant appear to be antibody drug conjugates (ADCs), which consist of three main components: a monoclonal antibody targeting a specific tumor-associated antigen, a potent cytotoxic cargo, and a linker that binds the two together. Initially, ADCs were not expected to cause nausea and vomiting due to the targeted release of the cytostatic into tumor cells. However, the release of even a small portion of the cytostat into the bloodstream can lead to various toxicities, including nausea and vomiting [10]. ADCs are suspected of inducing nausea and vomiting in a mechanism similar to classic cytostatics, although the exact mechanism remains unclear [11]. Antibody–drug conjugates with the highest emetogenic potential include trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) [12]. However, guidelines for prophylactic management during ADC treatment remain unclear [3, 4]. Nevertheless, effective antiemetic prophylaxis is required in patients receiving T-DXd or SG and should follow the recommendations for cytotoxic agents with high or moderate emetogenic potential.

Nausea and vomiting beyond the delayed phase

Most studies evaluating antiemetic agents for the prevention of CINV have assessed their efficacy up to 120 h after chemotherapy administration (i.e., through the end of the conventionally defined delayed phase). However, nausea and vomiting may persist beyond 120 h [13], a phenomenon that is relatively poorly characterized in the literature but recognized in routine clinical practice. The NCCN guidelines emphasize, for example, that cisplatin-related vomiting reaches peak intensity 48–72 h after administration but may persist for 6–7 days [3]. Patients who experience nausea and vomiting on Days 4 and 5 after chemotherapy appear to be at increased risk of CINV beyond the delayed phase [13]. Several studies have evaluated the efficacy of NEPA beyond 120 h after chemotherapy. In a prospective study of patients receiving MEC (mitoxantrone, etoposide, cytarabine), covering a 144-hour period after chemotherapy, a single dose of NEPA was compared with a 3-day aprepitant regimen. Outcomes were significantly better in patients receiving NEPA [14].

Optimizing the role of glucocorticosteroids in the treatment of CINV in combination with immunotherapy

In cancers for which immunotherapy has demonstrated efficacy, glucocorticosteroid-induced immunosuppression may affect treatment response and prognosis. With the availability of new antiemetic agents, dexamethasone-free regimens are being explored because of concerns regarding the potentially reduced efficacy of immunotherapy. Several randomized trials have demonstrated greater antiemetic efficacy with dexamethasone-free regimens (olanzapine, NK_1-RA, 5-HT_3-RA) [15, 16]. Therefore, a shift in recommendations toward reducing the role of glucocorticosteroids and emphasizing greater use of NEPA and olanzapine in regimens that include immunotherapy may be anticipated [17].

CONCLUSIONS

Despite significant progress in the prevention of CINV, this symptom remains one of the most serious challenges for oncologists and a major burden for patients with cancer. Appropriate management of CINV is often a fundamental component of successful chemotherapy and requires continually expanding knowledge of pharmacotherapy and pathophysiology. Implementing adequate CINV prophylaxis from the first cycle of chemotherapy is essential, as it may protect patients from serious treatment-related complications.

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Conflict of interests:
The authors declare no conflict of interest

Financial support:
None.

Ethics:
The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.