Review article

Modern CINV prevention: fewer medications, greater comfort for the patient and the therapeutic team

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ABSTRACT

Nausea and vomiting are among the most frequently reported adverse effects of systemic oncological treatment. Effective prevention is key to improving patients' quality of life. Nausea and vomiting can be early, late, or preemptive. Both the mechanism of their onset and the therapeutic methods vary. Treatment primarily involves 5-HT_3 antagonists, glucocorticosteroids, NK_1 antagonists, and olanzapine. Modern antiemetic therapy is safe and effective in most cases. The most common side effects include headache, constipation, and sedation.

Key words: CINV, antiemetic treatment, nausea and vomiting

INTRODUCTION

Nausea and vomiting are among the most common gastrointestinal symptoms reported by oncology patients. Although they often occur together, they are distinct entities. Nausea is a subjective and unpleasant sensation characterized by the urge to vomit. Vomiting is the forceful expulsion of gastric contents through the mouth resulting from coordinated contractions of the abdominal and thoracic muscles. These symptoms may be caused by gastrointestinal diseases; however, activation of the vomiting reflex often originates outside the gastrointestinal tract. An example is chemotherapy-related vomiting (CINV) [1].

Before initiating oncologic treatment, patients frequently express concerns about potential adverse effects, particularly persistent nausea and vomiting associated with chemotherapy. CINV may lead to postponement, interruption, or even discontinuation of systemic therapy. With the introduction of modern antiemetic agents, chemotherapy-related adverse effects have been significantly reduced. Patients' quality of life during treatment has improved, which has translated not only into better adherence to anticancer therapy but also into improved daily functioning. Patients are less likely to experience weight loss, the risk of fluid and electrolyte disturbances is reduced (facilitating the prevention of cancer-related cachexia), they are able to maintain daily activities, and they experience less anxiety regarding subsequent treatment cycles [2]. Vomiting associated with drug administration may trigger anticipatory vomiting during subsequent cycles of therapy. In such cases, patients may experience discomfort even before the next drug administration, sometimes merely at the thought of treatment. Therefore, it is important to prevent any episode of CINV [3].

GUIDELINES

Although the emetogenic potential of modern targeted therapies, monoclonal antibodies, and immunotherapies is generally lower than that of traditional cytotoxic chemotherapeutic agents, and despite the availability of a broad range of antiemetic drugs, nausea and vomiting continue to occur in many oncology patients. In the late 1990s, several organizations began developing international guidelines for antiemetic therapy. One of the key conferences in this field was held in Perugia in 1997, where a consensus was established under the auspices of the Multinational Association of Supportive Care in Cancer (MASCC) [4].

Since 2009, subsequent MASCC guidelines have been co-authored with panelists from the European Society for Medical Oncology (ESMO) [5]. The most recent MASCC/ESMO guidelines were published in 2023 [6] and represent an update of the 2016 version, incorporating new clinical trial data, including revisions to the emetogenicity classification of 107 regimens currently used in oncology. In Poland, guidelines based on these recommendations are published and regularly updated by the Polish Society of Clinical Oncology (PTOK) [7].

CLASSIFICATION AND MECHANISMS

Nausea and vomiting can be classified as follows:

- Early – occurring within the first 24 h after drug administration.
- Delayed – occurring after this period.
- Anticipatory – occurring before treatment [8].

As with other treatment-related toxicities, their severity is classified using the CTCAE (Common Terminology Criteria for Adverse Events) scale [9]. The mechanism of nausea and vomiting in CINV is complex and is usually a consequence of activation of the vomiting center in the floor of the fourth ventricle (area postrema) via direct or indirect pathways from receptors located in various regions. This process involves multiple neurotransmitters, which forms the basis for preventive management. Among the most important are serotonin (5-hydroxytryptamine, 5-HT) and its type 3 (5-HT_3) receptors, as well as dopamine and its type 2 (D_2) receptor. The neurokinin-1 (NK_1) receptor plays a major role in delayed vomiting [8]. Drugs such as olanzapine also act through additional receptor pathways that complement those mentioned above.

The emetogenic potential of individual drugs and systemic cancer treatment regimens varies and is generally divided into four categories: high (>90% incidence), moderate (30–90%), low (10–30%), and minimal (<10%). Regimens with the highest emetogenic potential include those based on high-dose cisplatin and combinations of cyclophosphamide and doxorubicin [10]. High-dose chemotherapy regimens and combined chemoradiotherapy, particularly those based on cisplatin, are generally classified as highly emetogenic [6]. Due to limited data, oral regimens are more difficult to classify and are stratified into only two risk categories: minimal–low and moderate–high. This also limits the ability to provide specific prophylactic recommendations during their administration; antiemetics should be used as needed [6].

PROPHYLAXIS

When highly emetogenic chemotherapy is administered, a four-drug regimen is recommended for the prevention of acute nausea and vomiting. This regimen includes a 5-HT_3 receptor antagonist (e.g., ondansetron or palonosetron), a glucocorticosteroid (GCS, usually dexamethasone), an NK_1 receptor antagonist (e.g.

aprepitant or netupitant), and olanzapine. Ondansetron is administered at a dose of 8–16 mg, palonosetron at 0.5 mg, dexamethasone at 12 mg, aprepitant at 125 mg, and netupitant at 300 mg. Netupitant is administered only in combination with palonosetron as part of the NEPA regimen [6].

Olanzapine is typically administered at a dose of 10 mg; however, particularly in older patients, a 5 mg dose may be considered effective due to its potential sedative effects. The addition of olanzapine to the antiemetic regimen is also recommended by the American Society of Clinical Oncology (ASCO) [8]. In the subsequent days, this regimen is partially continued for the prevention of delayed nausea and vomiting. For doxorubicin–cyclophosphamide (AC)-based regimens, evidence suggests that glucocorticosteroids may be discontinued after day 1, while the NK_1 receptor antagonist (e.g., aprepitant 80 mg on days 2 and 3) and olanzapine (on days 2–4) are continued.

In other (non-AC) highly emetogenic regimens, deviation from maintenance glucocorticosteroid therapy is currently not recommended; for example, dexamethasone 4 mg twice daily on days 2–4 should be continued. With the long-acting NEPA combination, sustained 5-HT_3 and NK_1 receptor blockade has been reported, which may improve control of delayed nausea and vomiting without the need for additional doses from these drug classes. In this setting, intravenous administration has no advantage over oral administration [6]. For highly emetogenic multidrug regimens, extended use of antiemetic agents should be considered to maintain efficacy throughout the treatment cycle, even up to 2 days after completion of cytotoxic infusions – particularly for glucocorticosteroids and olanzapine [8].

For moderately emetogenic chemotherapy, the standard approach for most regimens is a two-drug antiemetic premedication consisting of a 5-HT_3 receptor antagonist and a glucocorticosteroid, usually dexamethasone 4–8 mg, administered on the day of anticancer drug administration. There is no clear evidence supporting routine continuation of these agents on subsequent days. Specific recommendations apply to certain agents. For carboplatin at a dose ≥AUC 5, the addition of an NK_1 receptor antagonist is recommended (with aprepitant continued on days 2 and 3). For oxaliplatin-based regimens, palonosetron is the preferred 5-HT_3 receptor antagonist, and in women <50 years of age, the addition of an NK_1 receptor antagonist – such as in the NEPA regimen – is considered optimal [6]. In moderately emetogenic regimens, the role of olanzapine remains inconclusive [8].

For systemic therapies with low emetogenic potential, administration of a single antiemetic agent (either a 5-HT_3 receptor antagonist or a glucocorticosteroid) is recommended, and only on day 1. For regimens with minimal emetogenic potential, routine premedication is not recommended [6]. It should be noted that tolerance to treatment-related nausea and vomiting varies among individuals, and if necessary, a more intensive antiemetic regimen should be considered, incorporating agents with different mechanisms of action to enhance efficacy [8]. Anticipatory vomiting, due to its distinct underlying mechanism, requires a different therapeutic approach, typically involving psychotherapy and treatment with benzodiazepines or other psychoactive agents [11].

5-HT_3 RECEPTOR ANTAGONISTS

Numerous clinical studies have evaluated several agents in this class, including ondansetron, palonosetron, granisetron, dolasetron, and tropisetron. In clinical practice, due to availability and reimbursement considerations, ondansetron and palonosetron are the most relevant. These agents remain the cornerstone of antiemetic therapy, particularly for acute vomiting, because of their high efficacy and generally favorable tolerability profile. In two-drug regimens or as monotherapy, palonosetron has also demonstrated efficacy in the prevention of delayed vomiting (the only agent in this class with such evidence) [12, 13]. Therefore, either alone or as part of the NEPA regimen, it is currently considered the preferred option in many of the previously mentioned settings [6]. The most common adverse effects of this drug class are headache (3–20%) and constipation (5–18%). Less commonly, these agents may increase the risk of gastrointestinal obstruction or serotonin syndrome.

These adverse effects are similar among agents in this class and represent a class effect. In selected populations – such as patients at increased risk of gastrointestinal obstruction (e.g., oncology patients with gastrointestinal involvement), those with underlying cardiovascular disease (due to the risk of QT interval prolongation), or those receiving other serotonergic medications (e.g., antidepressants) – a shorter-acting agent may initially be considered to minimize the risk of obstruction and/or serotonin syndrome. Given the difference in half-life between ondansetron (approximately 3–4 h) and palonosetron (40 h), this distinction may be clinically relevant in managing potential adverse effects. However, if the drug is well tolerated, therapy with a long-acting agent should generally be continued [6].

NK_1 RECEPTOR ANTAGONISTS

The first agent in this class, now well characterized and extensively studied, was aprepitant, which has been in clinical use for nearly 20 years. Its introduction established the role of NK_1 receptor antagonists in antiemetic treatment guidelines. Overall tolerability is very good, with only a small proportion of patients

experiencing adverse effects such as hiccups or elevated aminotransferase levels. The use of agents in this class generally does not require dose adjustment, even in older or cachectic patients. These drugs are typically administered orally and may be taken regardless of meals. Potential drug interactions related to CYP3A4 inhibition should be considered; however, clinically significant interactions are relatively uncommon. Subsequent studies have confirmed their favorable safety profile.

The intravenous formulation, fosaprepitant, as well as newer agents in this class (netupitant and rolapitant), have also been studied and are currently approved for clinical use. At the time of writing, only aprepitant and netupitant are reimbursed in our country. Netupitant is available in oral form in a fixed combination with palonosetron (NEPA). Netupitant has a half-life several times longer than that of aprepitant, which simplifies dosing, improves convenience for both patients and healthcare staff, and may enhance treatment adherence. The NEPA combination provides a comprehensive, modern, long-acting option for the prevention of both acute and delayed vomiting in a single tablet. However, similar to 5-HT_3 receptor antagonists, in selected populations – such as older patients with cardiovascular comorbidities or cachectic patients – use of a shorter-acting agent may allow better control of potential adverse effects and may therefore influence drug selection. NK_1 receptor antagonists used in multidrug regimens demonstrate comparable and very high efficacy in preventing vomiting, reaching rates of up to 90% [6].

OTHER ANTIEMETICS

In addition to the two groups described above, glucocorticosteroids (GCSs) play an important role in antiemetic therapy. The most commonly used agent is dexamethasone at a dose of 8–20 mg/24 h; methylprednisolone 40–125 mg/24 h is used less frequently. Other agents used in the management of nausea and vomiting include D_2 receptor antagonists (metoclopramide), antihistamines (cetirizine, hydroxyzine), and neuroleptics (chlorpromazine, prochlorperazine, droperidol, olanzapine, tiethylperazine). With the exception of olanzapine, which has an established role in current guidelines, these agents are generally considered adjunctive to the primary drug classes. They are currently used mainly when standard treatment is ineffective, as rescue or complementary therapy. Neuroleptics may also have a role in managing the psychogenic component of nausea and vomiting. However, their efficacy is lower than that of 5-HT_3 receptor antagonists, glucocorticosteroids, or NK_1 receptor antagonists, and they are associated with a less favorable adverse effect profile [7].

CONCLUSIONS

When used in accordance with established standards, modern antiemetic therapy can prevent nausea and vomiting associated with systemic treatment in the vast majority of patients, with overall effectiveness reaching up to 90%. The efficacy of individual agents is generally attributable to a class effect, although they differ in pharmacokinetic properties and potential drug interactions. These agents are typically well tolerated, and adverse effects are relatively uncommon, generally moderate in severity, and predictable. Moreover, due to the prolonged duration of action of newer drugs, the number of required doses is reduced. This contributes to improved comfort and convenience in the delivery of oncologic care for both patients and healthcare professionals.

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