Emetogenicity of Chemotherapy Regimens and Recommended Prophylaxis: A Review of MASCC/ESMO Guidelines

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect in patients with cancer, affecting both quality of life and treatment compliance. Despite the advances in pharmacological research of antiemetic drugs, CINV still remains one of the most feared chemotherapy side effects by patients. Currently, the numbers of patients at highest risk of CINV receiving guideline-based prophylaxis remains sub-optimal; this is due, in part, to poor adherence to evidence-based guidelines.

Adequate prevention of CINV, from the first cycle of chemotherapy, requires an understanding of the intrinsic emetogenic risk of the chosen chemotherapy regimen; an awareness of the risk of delayed CINV; and the consideration of patients' individual risk factors, as well as the dose, administration route, and schedule of each drug in the treatment regimen.

The pathophysiology of nausea and vomiting can differ, and a combination of antiemetic drugs may be required to prevent their onset. In addition, CINV that occurs in the acute phase (≤24 hours after starting chemotherapy) and the delayed phase (>25 hours after starting chemotherapy) can also require different combinations of antiemetic drugs to achieve optimal control.

Together, consideration of all these factors can allow clinicians to tailor an antiemetic prophylactic regimen for each individual patient. Optimal prevention of CINV will improve patients' quality of life and treatment adherence, which will ultimately improving outcomes.

This article reviews the impact of CINV, the emetogenic risk associated with different chemotherapy regimens in solid tumours and haematologic malignancies, and guideline-based recommendations for antiemetic prophylaxis according to emetogenic risk.

INTRODUCTION

CINV is experienced by about 70–80% of adult patients with cancer who are receiving chemotherapy, decreasing both quality of life and treatment compliance.[1-3] CINV remains one of the most feared side effects of chemotherapy, despite the availability of new and effective antiemetic medications.[4,5]

With appropriate prophylaxis, vomiting can now be prevented in most patients; however, nausea remains a significant problem.[6] In contrast to clinicians, patients typically consider the prevention of nausea to be more important than the prevention of vomiting.[7] Although nausea often leads to vomiting, these two symptoms can occur independently, with nausea occurring more frequently.[7] Indeed, it has been suggested that these symptoms may involve a different pathophysiology, and that different drugs may, therefore, be needed to control each symptom.[7]

Without prophylactic treatment (other than corticosteroids), acute post-treatment vomiting affects approximately 57% of patients receiving chemotherapy, while acute nausea affects approximately 80%.[7]

Delayed CINV, which occurs 24 hours or more after the start of chemotherapy, is more common than acute CINV.[8] It is also often less responsive to treatment.[9] Uncontrolled CINV in a previous cycle of chemotherapy is a risk factor for CINV in subsequent cycles.[10] It is also a risk factor for anticipatory CINV, a conditioned response to CINV occurring in a previous chemotherapy cycle.[1] For example, one study found that anticipatory CINV was responsible for 7% of vomiting episodes and 30% of nausea episodes in patients with cancer.[7] Effective prevention of CINV in the first cycle of chemotherapy is the best approach to reducing anticipatory CINV in subsequent cycles.

Without effective prevention of CINV, patients may experience reduced quality of life, distress, and work absence.[7] The inadequate caloric and fluid intake associated with CINV can also aggravate cancer-associated symptoms such as muscle wasting, lethargy, and weakness.[7] CINV has also been linked to reductions in cognitive function, and increased anxiety and depression.[7]

This article deals with CINV prophylaxis, with a special emphasis on understanding the estimated emetogenicity of single and combination chemotherapy regimens used in the management of both solid tumours and haematologic malignancies, and highlights current recommendations based on the current Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) guidelines for the prevention of CINV according to emetic risk.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING MANAGEMENT IN CLINICAL PRACTICE

CINV continues to be largely undermanaged in clinical practice. This is due, in part, to low adherence to guideline prescription of antiemetics.[11-14] A large multicentre observational study conducted in Europe (N=1,089) found that only 23% of patients treated with moderately or highly emetogenic chemotherapy received guideline-based antiemetic prophylaxis for both the acute and delayed nausea and vomiting.[12] Similarly, a retrospective real-world study of patients with cancer who received highly emetogenic chemotherapy (N=4,033) found that clinician adherence to guideline-based prevention was highly variable. In the study, guideline adherence rates of >90% were achieved by clinicians in just 35% of patients receiving cisplatin-based chemotherapy, and 58% of those receiving anthracycline plus cyclophosphamide. The omission of a neurokinin-1 receptor antagonist (NK_1 RA) was the principal cause of guideline nonadherence in the vast majority (>90%) of cases.[14]

These results align with a study that analysed a data set of real-world prescribing information in Europe, which included data representing 489,049 anti-cancer treatments requiring NK_1 RA-based antiemetic prophylaxis per MASCC/ESMO guidelines.[15] NK_1 RAs were prescribed in fewer than half of patients receiving cisplatin- or anthracycline plus cyclophosphamide-based chemotherapy (45% and 42%, respectively), and in as few as 19% of those receiving carboplatin-based regimens. Guideline-consistent prophylaxis with NK_1 RA plus 5-hydroxytryptamine-3 ($5\text{-}HT_3$) RA plus dexamethasone on Day 1 was prescribed only

in 18%, 24%, and 7% of these chemotherapy regimens, respectively.

It is important to note that where antiemetic guidelines are followed, a higher rate of complete protection from CINV is achieved.[12,13]

Patient adherence to antiemetic therapy is another potential cause for sub-optimal CINV prevention. For example, a quantitative survey of European oncologists found that patient non-adherence to prescribed antiemetics, due to administration mistakes or missed doses, was considered a major cause of antiemetic treatment failure, suggesting that simpler, more convenient therapies could help to improve patient compliance.[16]

It is also possible that many clinicians underestimate the emetogenicity of chemotherapy. Across three randomised clinical trials of anti-cancer treatment (N=1,090), patient-reported and clinician-reported toxicities were compared. Results showed that agreement between patients and clinicians was low for all toxicities. Nausea was under-reported by physicians in 41% of cases and vomiting in 47%.[17] Under-reporting results in the underestimation of the absolute rate of toxicity, which could lead to undermanagement of CINV.

In clinical practice, decisions regarding optimal prophylaxis should be guided by two considerations: the intrinsic emetogenicity of the chemotherapeutic agents in a treatment regimen, and whether there is a substantial risk of delayed nausea and vomiting. Additional consideration of patient-related risk factors may help healthcare providers to optimise antiemetic coverage in patients at high personal risk of CINV. This approach may make it possible to tailor the appropriate antiemetic regimen to an individual patient, who might benefit from extended or brief antiemetic coverage (Supplementary Figure 1).

EMETOGENICITY OF CHEMOTHERAPY AGENTS

Chemotherapeutic agents vary greatly with respect to their relative ability to cause emesis (i.e., their intrinsic emetogenicity).[21] They are classified into four groups: highly emetogenic chemotherapy (HEC; affecting >90% of patients), moderately emetogenic chemotherapy (MEC; 30–90% of patients), low emetogenic chemotherapy (LEC; 10–30% of patients), and minimally emetogenic chemotherapy (<10% of patients). While both HEC and MEC agents cause CINV during the acute and delayed phases and multi-target antiemetic regimens are recommended in both emetogenicity categories (Supplementary Table 1), LEC agents induce only acute CINV and a single-agent prophylaxis before chemotherapy administration is recommended (Supplementary Table 2).[21,22]

Joint guidelines published by the MASCC and ESMO have recognised carboplatin as being on the borderline between the HEC and MEC categories and have placed it in its own emetogenicity group,[22] which could be described as moderately-to-highly emetogenic (affecting approximately 90% of patients).

The overall emetogenicity of a treatment regimen is influenced not only by the individual chemotherapeutic agents used but by the dose, administration route, and schedule of these agents, as well as patient-related factors.[23]

PATIENT-RELATED RISK FACTORS

Although antiemetic guidelines are based on the intrinsic emetogenicity of individual chemotherapeutic agents, the importance of considering patient-related risk factors and prior experience with antiemetics has also been recognised.[24,25]

A recent systematic literature review identified seven key patient-related risk factors for CINV: a patient history of CINV and/or pregnancy-related nausea or vomiting; female sex, anticipation of CINV; younger age (<50 years); anxiety; and a history of no or low alcohol intake (Supplementary Table 3).[26]

For optimal CINV management, it is crucial that clinicians follow evidence-based clinical antiemetic guidelines and that they also consider key patient-related risk factors.[24] These factors can be captured during clinical assessment prior to chemotherapy, helping clinicians to predict patient's risk of developing CINV and make decisions regarding antiemetic prophylaxis.[26]

PHARMACOLOGIC THERAPIES FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING PREVENTION

Guidelines recommend that patients scheduled to receive chemotherapy containing HEC or MEC agents should receive combination prophylaxis with antiemetic drugs targeting the peripheral and central pathways to vomiting centre in the brain (Supplementary Table 4).[22,24]

The major classes of antiemetic drugs recommended for CINV prophylaxis are 5-HT_3 RAs, NK_1 RAs, corticosteroids, and olanzapine.[11,27] Current MASCC/ESMO guidelines include the following recommendations for CINV prophylaxis:

- 5-HT_3 RAs should be used in the acute phase of HEC/MEC agents and are one of the recommended options in the acute phase of LEC agents;
- Corticosteroids such as dexamethasone should be used in the acute phase of HEC/MEC regimens and the delayed phase of HEC (unless the regimen is based on the combination of an anthracycline and cyclophosphamide). They are optional in the delayed phase of MEC agents, with a known potential of delayed CINV such as oxaliplatin, anthracycline, or cyclophosphamide;
- NK_1 RAs should be used in the acute and delayed phases of HEC agents/combinations or carboplatin (which falls between the usual HEC/MEC categories in terms emetogenicity); and
- Olanzapine is optional in the acute and delayed phases of HEC regimens. Also, clinicians may opt to add olanzapine to antiemetic regimen in selected patients when nausea control may be an issue.

In general, when devising a prophylactic strategy for CINV due to combination chemotherapy, the antiemetic regimen should be tailored to the anti-cancer agent with the highest intrinsic emetogenicity. It is also important to be aware that antiemetic efficacy can be affected by the route of chemotherapy administration (Supplementary Figure 1).[23]

5-Hydroxytryptamine-3 Receptor Antagonists

The 5-HT_3 RAs block the binding of serotonin at 5-HT_3 receptors in the gastrointestinal tract.[27] This pathway is primarily associated with acute emesis induced by chemotherapeutic agents. While $5HT_3$ RAs are considered the most efficacious antiemetics for the prevention of acute CINV, their effect against delayed CINV is more modest.[6] Generally well tolerated, 5-HT_3 RAs may nevertheless be associated with constipation, headache, QTc prolongation, and slight reversible increase in liver transaminases.[6]

The efficacy of first-generation 5-HT_3 RAs (ondansetron, granisetron, dolasetron, and tropisetron) is similar; however, with a higher binding affinity for the 5-HT_3 receptor and a significantly longer half-life, the second-generation 5-HT_3 RA palonosetron is more effective in preventing delayed CINV associated with HEC/MEC regimens.[24]

Guidelines currently recommend palonosetron as the preferred 5-HT_3 RA where an NK_1 RA is not part of the antiemetic regimen.[22,24]

Corticosteroids

Single-agent corticosteroids are effective against CINV in patients receiving LEC, and they improve the effects of other antiemetics in patients receiving HEC or MEC. They are effective for the prevention of both acute and delayed CINV.[6,24]

Dexamethasone is the most investigated corticosteroid for CINV prophylaxis and it has been used in combination with other antiemetics for many years.[6,24] While other corticosteroids are also known to be effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability has established it as the guideline agent of choice in CINV.[18]

Common adverse effects of corticosteroids include weight gain, insomnia, agitation, epigastric discomfort, and hyperglycaemia.[28,29] In addition, corticosteroid-related side effects may be evident only after prolonged use of these agents during consecutive cycles of chemotherapy treatment.[30-32] Corticosteroids also have a broad immunosuppressive effect, which could potentially promote immunological tolerance to tumours, reducing the effectiveness

of immune checkpoint inhibitor therapy. Indeed, baseline administration of supraphysiological doses of corticosteroids has been associated with adverse clinical outcomes in melanoma, non-small-cell lung cancer, and glioblastoma.[33] However, it should be noted that at least one study suggests that corticosteroids may impact the immune checkpoint inhibitor therapy differentially, depending on the tumour site.[34] Another found that corticosteroids only had a negative impact on overall survival when used for supportive care and not when used to mitigate adverse events.[19]

To improve the tolerability profile of the corticosteroids in CINV prophylaxis and to reduce immunosuppression, there has been growing interest in minimising the dose and frequency of dexamethasone without a loss of antiemetic efficacy.[35] Because of the COVID-19 pandemic, the ESMO highlighted that the use of antiemetic corticosteroids should be critically reviewed and a reduced dose of dexamethasone on Day 1 without additional use on the following days should be considered even in HEC treatment. In addition, clinicians may consider the long-acting 5-HT_3 RA, palonosetron, due to its potential better efficacy in the delayed phase of CINV specifically when sparing the dexamethasone dose.[36,37]

A recent randomised study demonstrated that dexamethasone sparing on Days 2–4 is an effective antiemetic option in patients receiving cisplatin-based HEC when associated with netupitant plus palonosetron (NEPA) plus single-dose dexamethasone on Day 1.[38] The dexamethasone-sparing regimen based on NEPA permits the administration of a simplified but guideline-consistent three-drug regimen before chemotherapy initiation in the challenging setting of CINV caused by cisplatin.

Neurokinin-1 Receptor Antagonists

The introduction of NK_1 RAs to the field of antiemetic prophylaxis has been considered the most significant advance in CINV control since 5-HT_3 RAs.[35]

The two oral NK_1 RAs marketed in Europe are aprepitant and netupitant.[6] Both are primarily metabolised through the cytochrome P450 3A4 pathway and block the binding of substance P at NK_1 receptors, which are expressed in the central and peripheral nervous system.[6,27] The available evidence supports a principal role for central NK_1 activation in delayed CINV.[27] The most common adverse effects of this drug class include headache, constipation, and hiccups.[6,27]

The standard 3-day treatment with oral aprepitant, though inferior to 5-HT_3 RAs in preventing acute CINV, is more effective against delayed CINV.[39] Aprepitant also increases the antiemetic effect of combined 5-HT_3 RA plus dexamethasone treatment.[40]

Netupitant was developed and investigated in combination with palonosetron as a single oral dose antiemetic.[6] Clinical studies have shown that the efficacy of oral NEPA was superior to palonosetron alone in terms of preventing both acute and delayed CINV associated with HEC/MEC therapy.[30,31] Intravenous NEPA was equally effective to oral NEPA and was not associated with injection-site or hypersensitivity reactions that can occur with other NK_1 RAs.[41-43]

The MASCC/ESMO guidelines recommend that patients receiving HEC are given a dose of 20 mg dexamethasone on Day 1 to prevent acute emesis; however, if the NK_1 RAs aprepitant or netupitant are also used, a reduced dose of 12 mg dexamethasone is recommended.[17] This dose reduction is due to the ability of both aprepitant and netupitant to inhibit the metabolism of dexamethasone leading to higher dexamethasone concentrations.[24]

By delivering both a 5-HT_3 RA and an NK_1 RA in a single dose before chemotherapy administration, NEPA can help simplify the antiemetic prophylaxis that patients must take at home. Therefore, it improves convenience and has the potential to improve the adherence to antiemetic therapy.[43,44]

Olanzapine

Olanzapine is an atypical antipsychotic drug approved for use for the treatment of schizophrenia and moderate-to-severe manic episodes.[45] However, it has also been investigated as an antiemetic drug in several clinical trials[6] and it has been used off-label for both acute and delayed CINV in combination with a 5-HT_3 RA and dexamethasone.[18,27]

Unlike other antiemetic drug classes, olanzapine acts on multiple receptors in the emetic pathway, blocking both dopaminergic and serotonergic neurotransmission.[27] It has been associated with several side effects, including sedation, dry mouth, hyperglycaemia, and diarrhoea, as well as an increased risk of extrapyramidal effects.[27]

A recent double-blind, randomised study demonstrated that a four-drug prophylaxis containing low-dose olanzapine (5 mg) is superior to a three-drug antiemetic regimen for CINV control in patients receiving cisplatin.[46] Despite the lack of a randomised study comparing the two doses of antiemetic olanzapine (10 mg or 5 mg per day on Days 1–4 post-chemotherapy), low-dose olanzapine has a high profile of tolerability in terms of drug-induced sedation.

Use of Neurokinin-1 Receptor Antagonists with Moderately Emetogenic Chemotherapy Agents in Patients with Increased Chemotherapy-Induced Nausea and Vomiting Risk

The MEC category of chemotherapeutic agents covers drugs associated with a broad risk of CINV (affecting 30–90% of patients). Current MASCC/ESMO guidelines do not recommend the use of NK_1 RAs as prophylaxis with MEC agents, though they do recommend dexamethasone as an optional agent for delayed CINV when oxaliplatin, anthracycline, and cyclophosphamide chemotherapy are used.[22]

However, healthcare providers may consider using an NK_1 RA in patients receiving MEC agents for whom CINV is a particular concern (Supplementary Table 4). This approach is supported by a recent placebo-controlled randomised study that evaluated the efficacy of a three-drug prophylaxis regimen, including an NK_1 RA in patients with gastrointestinal cancer receiving oxaliplatin- or irinotecan-based chemotherapy (both MEC).[47]

The study enrolled patients who were at increased risk of CINV due to patient-related factors, with eligibility criteria including female sex, age <50 years, and a history of little or no alcohol use. Patients were randomly assigned to receive palonosetron and dexamethasone plus either placebo or aprepitant.[47]

Results indicated that a statistically significant improvement in the control of emesis was achieved with the inclusion of an NK_1 RA versus placebo in the acute phase (92.7% versus 75.8%; p=0.001), the delayed phase (88.6% versus 70.0%; p=0.001), and overall (primary endpoint: 87.0% versus 66.7%; p<0.001). The incidence of adverse events was similar between the two prophylactic treatment groups.[47]

Multiple-Day Chemotherapy Regimens Containing Cisplatin

Chemotherapy regimens in which cisplatin is administered for multiple consecutive days (typically 5 days) represent a challenging setting of CINV control because acute and delayed CINV overlap.[24]

Current MASCC/ESMO guidelines recommend that patients receiving multiple-day cisplatin (HEC) should receive a combination of a 5-HT_3 RA plus aprepitant plus dexamethasone in the acute phase, and dexamethasone in the delayed phase.[17] Guidelines also recommend that while first-generation 5-HT_3 RAs should be administered at Days 1–5, palonosetron should be administered on Days 1, 3, and 5 only.[22,24] Similarly, the NK_1 RA inhibitor netupitant, which has a much longer half-life than aprepitant, may be administered on Day 1 only in this setting.[8]

EMETOGENICITY OF CHEMOTHERAPY REGIMENS FOR SOLID TUMOURS AND HAEMATOLOGIC CANCER

The estimated emetogenicity of commonly used combination chemotherapy regimens in the treatment of non-haematologic and haematologic malignancies are listed in Supplementary Table 5 and Supplementary Table 6, respectively.

Patients undergoing chemotherapy for haematologic malignancies are at particular risk of CINV because of their young age, exposure to HEC agents at high doses over multiple days, and the heavy psychological burden of such intensive treatments.[48]

High-dose chemotherapy is widely used as a conditioning regimen prior to autologous stem cell transplant (ASCT) in patients with the haematologic malignancy multiple myeloma.[49] Although any high-dose chemotherapy regimen

is classified as HEC, research into the incidence of CINV and the efficacy of antiemetics in patients treated with high-dose chemotherapy and ASCT can be confounded by the emetogenicity of antibiotics and opioids prescribed for mucositis management in this population, and by the use of irradiation therapy.[25] The most widely used high-dose chemotherapy regimens used prior to ASCT are listed in Supplementary Table 7.

Following a Phase III clinical trial,[50] the American Society of Clinical Oncology (ASCO) published an update to their antiemetic guidelines, recommending olanzapine as an optional addition to a triple-drug regimen in this population.[51] The use of NEPA has also been shown to be effective in preventing CINV in adult patients with multiple myeloma receiving high-dose melphalan and undergoing ASCT, even without the concurrent use of dexamethasone,[49] suggesting again that NEPA may have the potential to support corticosteroid-sparing treatment strategies.

CONCLUSION

Nausea and vomiting are two of the most feared side effects of chemotherapy in patients with cancer, and current management of CINV still remains sub-optimal. Effective prevention of CINV requires an understanding of the emetogenic risk of a chemotherapeutic regimen as well a patients' individual risk factors. Adherence to evidence-based guidelines for antiemetic prophylaxis is needed to reduce the incidence of CINV, improve patients' quality of life and treatment adherence, and ultimately improve outcomes.

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