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Review

# Going beyond the 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting

Karin Jordan [a,b,*], Evandro de Azambuja [c], María Ángeles García del Barrio [d,e], Franziska Jahn [f], Mario Di Palma [g], Florian Scotté [h], Alex Molassiotis [i], Matti Aapro [i]

[a] Department of Hematology, Oncology and Palliative Care, Ernst von Bergmann Hospital Potsdam, Germany
[b] Department of Hematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany
[c] Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B) and l'Université Libre de Bruxelles (ULB), Brussels, Belgium
[d] Pharmacy Department, Clínica Universidad de Navarra, Universidad de Navarra, Madrid, Spain
[e] School of Pharmacy and Nutrition, Universidad de Navarra, Pamplona, Spain
[f] Department of Hematology and Oncology, University Hospital Martin-Luther University Halle-Wittenberg, Halle, Germany
[g] Interdisciplinary Patient Pathway Division, Gustave Roussy, Villejuif, France
[h] College of Arts, Humanities and Education, University of Derby, Derby, UK
[i] Medical Oncology, Genolier Cancer Center, Genolier, Switzerland

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ABSTRACT

The MASCC/ESMO guidelines for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting were updated in 2023 by a Consensus Committee of 34 multidisciplinary international healthcare professionals and three patient advocates. Guideline-recommended prophylactic anti-emetic strategies can control chemotherapy-induced nausea and vomiting (CINV) in many patients, but unaddressed issues remain. Across a series of meetings, we evaluated these guidelines to identify possible evidence gaps which warrant further exploration. Key topics identified and discussed included the use of dexamethasone-sparing regimens with cisplatin (and other non-anthracycline and cyclophosphamide)-based highly emetogenic chemotherapy regimens, the importance of individual patient risk factors for CINV, the use of a second agent in patients receiving low emetogenic chemotherapy, how to manage CINV with certain new antibody-drug conjugates, the most appropriate approach for managing breakthrough CINV, the options for patients with CINV even after following best guidance, the use of lower than standard doses of olanzapine (<10 mg/day), and the management of long-delayed CINV and CINV in patients receiving oral therapies. Through identifying the current gaps in the updated MASCC/ESMO guidelines and discussing the available evidence, we aim to address these issues and support oncologists who may encounter them in clinical practice. These and other questions need to be considered to help ensure choice of anti-emetic treatments provide optimal effectiveness in clinical practice.

## 1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) are two of the most common and troublesome side effects experienced by patients with cancer undergoing systemic treatments, which can negatively impact quality of life and therapeutic compliance [1,2]. The MASCC/ESMO guidelines for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting were updated in 2023 by a Consensus Committee consisting of 34 multidisciplinary international healthcare professionals and three patient advocates [2].

Based on chemotherapy emetic risk, the MASCC/ESMO guidelines recommend prophylaxis with a four-drug regimen of a 5-hydroxytryptamine-3 receptor antagonist (5-$HT_3$-RA), a neurokinin 1 receptor antagonist ($NK_1$-RA), dexamethasone, and olanzapine for highly emetogenic chemotherapy (HEC). For moderately emetogenic chemotherapy (MEC), 5-$HT_3$-RA and dexamethasone should be used, with the addition of a $NK_1$-RA as part of a triple combination in patients with high-risk MEC, i.e. carboplatin (AUC ≥5), women receiving oxaliplatin-based MEC aged

* Corresponding author at: Department of Hematology, Oncology and Palliative Care, Ernst von Bergmann Hospital Potsdam, Germany.
*E-mail address:* Karin.Jordan@med.uni-heidelberg.de (K. Jordan).

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≤ 50 years, and certain antibody-drug conjugates (ADCs), i.e. sacituzumab govitecan and trastuzumab deruxtecan. Single-agent therapy with 5-$HT_3$-RA, dexamethasone or dopamine-RA should be considered for low emetogenic (LEC) treatments (Table 1).

However, it remains a challenge to accurately define the emetic risk associated with different anticancer agents [3]. The evidence is highly heterogeneous regarding disease (tumour types, disease stage), treatments (use of previous therapies and/or in combination) and whether antiemetic prophylaxis is given or not fully reported. Different reporting systems make it difficult to compare the incidence and severity of CINV. Oral agents provide an additional challenge given that most involve daily administration over an extended period rather than the single administration typical of intravenous agents. As the concept of acute and delayed nausea and vomiting has its limitations here, the classification system for oral agents was revised in the 2023 update.

In addition, while the emetogenic risk potential of anticancer therapies is often assessed based on occurrences within the first 24 h, the potential for delayed (i.e. 2 −5 days after administration) or even long delayed (>5 days after administration) nausea and vomiting can be overlooked. In the longer-term, there may be severe nausea that might determine different choices for prevention. For example, evidence from trials on recently developed antibody-drug conjugates (ADCs) suggests that most present an increased nausea and vomiting risk, including delayed or very late onset after several days and with a prolonged duration, i.e., 10 or more days [4–6].

**Table 1**
Anti-emetic treatments.

| | Dose | Half-life | Clinical characteristics |
|---|---|---|---|
| **5-$HT_3$-RA** | | | |
| 1st generation (ondansetron) | IV: 8 mg or 0.15 mg/kg<br>Oral: 8 mg BID or TID | 3 h | Dosing Interval: ~8h<br>Metabolised through CYP2D6: limited use in ultra-rapid metabolisers |
| Granisetron | IV: 0.01 mg/kg<br>Oral: 1–2 mg | 5–9 h IV<br>6 h Oral<br>24 h SC | Dosing Interval: ~12h<br>Metabolised through CYP3A4 |
| Palonosetron | IV: 0.25 mg<br>Oral: 0.50 mg | 40 h | Dosing Interval (covered time): ~48–72 h |
| Tropisetron | IV: 5 mg/day | 8 h | Dosing interval ~24 h<br>Metabolised through CYP2D6: limited use in ultra-rapid metabolisers |
| **$NK_1$-RA** | | | |
| Aprepitant | Oral: 125 mg, 80 mg, 80 mg | 9–13 h | Dosing Interval: ~24h<br>Interactions through CYP3A4 |
| Netupitant[a] | Oral: 300 mg | 88 h | Single dose. Covered time: ~120h<br>Interactions through CYP3A4 |
| Rolapitant | Oral: 180 mg | 169–183 h | Single dose.<br>No interactions through CYP3A4 |
| **Steroids** | | | |
| Dexamethasone | IV/Oral: 8–20 mg | 36–72 h | Interactions through CYP3A4 with some $NK_1$-RA<br>With aprepitant, fosaprepitant, netupitant, fosnetupitant: 12 mg<br>With rolapitant (no interactions): 20 mg |
| **Others** | | | |
| Olanzapine | Oral: 5–10 mg | 42 h[b] | 2.5 mg oral could be enough |
| Dopamine RA (e.g. metoclopramide) | Oral: 10 mg TID | 5-6h | Dosing Interval: ~ 8 h<br>Maximum dose in 24 h is 0.5 mg/kg body weight. Major doses have been related with extrapyramidal symptoms |

BID, two times per day; h, hour; IV intravenous; SC, subcutaneous; TID, three times per day

[a] Netupitant is only available together with palonosetron 0.5 mg in a hard capsule.

[b] Dependent on age and sex (longer in young patients and women).

In clinical practice, choice of antiemetic prophylaxis may also be influenced by individual patient risk factors that can elevate the risk of CINV, meaning an otherwise MEC treatment regimen can pose a high risk to the individual patient. These factors may include younger age, female gender, anxiety, CINV in a previous episode, and a history of motion sickness or nausea and vomiting during pregnancy [7,8]. Multidisciplinary teams may not always take these patient factors into account when making treatment decisions and they continue to not be fully addressed in the MASCC/ESMO guidelines. This may be largely due to difficulties in defining individual risk factors and the lack of adequate evidence.

Adherence to treatment guidelines, including the MASCC/ESMO guidelines, remains sub-optimal, both through inadequate uptake by physicians and poor treatment adherence by patients [9,10]. Reasons for this include underestimation of the incidence of CINV by physicians and a lack of routine screening for nausea, physician preferences for non-guideline recommended regimens, under-reporting by patients, the complexity of some antiemetic regimens, and access restrictions to some antiemetics due to costs. Inadequate adherence with antiemetic prophylaxis can reduce CINV control in both the HEC and MEC settings, and can lead to reduced treatment compliance, reduced relative dose intensity and even discontinuation of anticancer therapy, putting the therapeutic goal at risk.

Across a series of meetings attended by members of the author group, all of whom are experienced within the field, held from March to June 2024, we evaluated the recently updated MASCC/ESMO guidelines to identify possible evidence gaps which are not sufficiently covered and that warrant further exploration. This was done through informal discussion rather than any specific process and was based on the clinical experience of authors as well as the knowledge obtained by involvement of several members of the group in the development of the guidelines themselves. Topics identified are also those typically queried by clinicians in clinical forums on managing nausea and vomiting. Based on these discussions, we subsequently developed several key questions, selected and refined through an iterative review process, based on these gaps and provide a review of available evidence together with suggestions of how to address these issues in order to support oncologists in daily clinical practice (Table 2).

### *1.1. Can a dexamethasone-sparing regimen be used with cisplatin (and other non-anthracycline and cyclophosphamide) based HEC chemotherapy?*

Although effective, dexamethasone can be associated with several side effects and may pose a risk to patients with comorbidities, such as diabetes [11,12]. As a result, dexamethasone-sparing regimens have been explored. The 5-$HT_3$-RA, palonosetron, in combination with single-dose dexamethasone, with or without an $NK_1$-RA, was shown to be as effective as a regimen including additional dexamethasone doses in patients with breast cancer receiving anthracycline and cyclophosphamide (AC) [13]. In a randomised, double-blind study, dexamethasone administered on day 1 before chemotherapy initiation was non-inferior to dexamethasone given for three days in the prevention of CINV caused by AC or cisplatin, when combined with palonosetron and an $NK_1$-RA (aprepitant or fosaprepitant) [14]. However, post-hoc analyses failed to show non-inferiority of the dexamethasone-sparing regimen in the subgroup of patients receiving cisplatin [14,15]. In a subsequent open-label proof-of-concept study, an oral fixed-dose combination of netupitant and palonosetron (NEPA) plus single-dose dexamethasone on day 1 was comparable to regimens with additional

**Table 2**
Summary of questions and recommendations.

| | Question | Recommendations/comments |
|---|---|---|
| 1 | Can a dexamethasone-sparing regimen be used with cisplatin (and other non-anthracycline and cyclophosphamide) based HEC chemotherapy? | • Single-dose dexamethasone may provide similar antiemetic control as multiple-day dexamethasone when combined with palonosetron and an $NK_1$-RA for cisplatin-based chenotherapy. |
| 2 | Are lower doses (<10 mg) of olanzapine effective? | • There is evidence that olanzapine 5 mg/day, and possibly 2.5 mg/day or is as effective as standard-dose 10 mg/day in combination with triple antiemetic therapy. |
| 3 | What individual risk factors mean MEC becomes HEC? | • A range of factors have been identified, including age, female sex, anxiety, a history of motion sickness or nausea during pregnancy, prior treatments, inadequate sleep before chemotherapy, and duration of CINV<br>• Increased use of emesis risk calculators to estimate individual risk may be helpful |
| 4 | How should CINV in patients treated with new ADCs be managed? | • ADCs may be associated with a novel pattern of CINV, with onset of nausea at around 2–3 days and vomiting at around 10 days and the risk remaining high throughout each cycle.<br>• A two-drug regimen may possibly be sufficient for some patients, although triple therapy of 5-$HT_3$-RA, a $NK_1$-RA, and dexamethasone will be needed in others and may be considered the gold-standard approach.<br>• Anti-emetics with longer half-life and/or longer protection may be an appropriate option |
| 5 | What is the emetogenic risk of FOLFOX/FOLFIRI/FOLFIRINOX regimens? | • Incidence of CINV for irinotecan-containing regimens is poorly recognised; triple therapy of dexamethasone, 5-$HT_3$-RA and $NK_1$-RA may be advisable as prophylaxis although evidence is limited.<br>• FOLFIRINOX regimen may have be more emetic than FOLFOX/FOLFIRI |
| 6 | When should a second agent be added to patients receiving LEC? | • If CINV control is inadequate with initial monotherapy, switching to an alternative agent should be considered.<br>• In patients with poor control of CINV in the previous cycle, the prophylaxis regimen recommended for the MEC could be considered.<br>• However, overtreatment may be a concern, and the addition of a second agent might only be considered if it addresses a particular issue. |
| 7 | How should CINV be managed in patients receiving oral therapies? | • Data on the emetic risk potential of oral anticancer agents are very limited and guidance is based on the use of on-demand antiemetics, typically, a combination of 5-$HT_3$-RA (days 1–7) and dexamethasone (days 1–3) should be considered.<br>• An $NK_1$-RA may need to be added if this is inadequate and multiple dosing should also be considered. |
| 8 | What is the best drug for breakthrough CINV? | • Deliver the optimal adapted prophylaxis from the first cycle and to assess the correct adherence to the treatment.<br>• Olanzapine if not used for primary prophylaxis.<br>• Cannabinoids may also be considered although evidence for their use and access is limited. |
| 9 | What are the options for patients with CINV after following best guidance (i.e., already receiving four-drug regimen including olanzapine)? | • If CINV occurred in previous cycles, ensure guideline-recommended treatment was prescribed and received, with the correct dosing and duration.<br>• Check that nausea and vomiting is chemotherapy-induced, or whether other factors may be involved.<br>• Consider choice of 5-$HT_3$-RA basded on PK/PD characteristics (e.g. half-life, CYP2D6 metabolism).<br>• Consider increasing dexamethasone dose and/or duration. Also, if the patient received olanzapine 5 mg, increasing the dose to 10 mg may be needed. |
| 10 | How should long delayed CINV be managed? | • The entire CINV risk period and not just the initial 24 h or even 120 h should be considered when choosing anti-emetic prophylaxis.<br>• Properties of anti-emetics, such as half-life and duration of effect, may be relevant<br>• Addition of an $NK_1$-RA to 5-$HT_3$-RA and dexamethasone may reduce CINV over a 7-day period versus 5-$HT_3$-RA plus dexamethasone |

ADC, antibody-drug conjugate; CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; 5-$HT_3$-RA, 5-hydroxytryptamine3-receptor antagonist; LEC, low emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; $NK_1$-RA, neurokinin-1 receptor antagonist; PD, pharmacodynamics; PK, pharmacokinetics

dexamethasone doses on days 2–4 in patients receiving high-dose cisplatin-based chemotherapy [15]. In a pooled analysis of these studies, single-dose dexamethasone offered similar antiemetic control as multiple-day dexamethasone when combined with palonosetron and an $NK_1$-RA in the setting of single-day cisplatin administration [16]. Even though stronger evidence is needed, the use of dexamethasone on the first day only could be considered for cisplatin-based chemotherapy in specific patients who are at high risk of side effects with repeated administration of corticosteroids.

### *1.2. Are lower doses (<10 mg) of olanzapine effective?*

In patients where olanzapine is advised (i.e., HEC regimens), the standard dose of olanzapine is 10 mg/day for four days. However, studies have reported that olanzapine 5 mg/day for 4 days is also effective [17–19]. In the recent phase 2 ERICA trial of patients with HER2-positive or HER2-low breast cancer treated with trastuzumab deruxtecan, olanzapine 5 mg over 6 days was effective [6]. Low-dose olanzapine 2.5 mg/day was non-inferior to standard-dose 10 mg/day in combination with triple antiemetic therapy for prevention of HEC-induced nausea and vomiting in a randomised, open-label trial in patients with solid tumours [20]. However, an olanzapine analysis of Japanese inpatient data indicated higher use of additional antiemetics in patients receiving olanzapine 2.5 mg versus 5 mg [21]. As such,

initiating olanzapine at a dose of 5 mg or even 2.5 mg and up-titrating as necessary may be equally effective as standard dosing with fewer side effects.

### 1.3. What individual risk factors mean MEC becomes HEC?

The risk of nausea and vomiting following antineoplastic therapy depends on patient characteristics, as well as the emetic risk potential of the antineoplastic therapy. Thus, individual risk factors may necessitate a more intensive antiemetic regimen than would typically be recommended. For example, a patient receiving a MEC regimen might experience nausea and vomiting comparable to that seen with HEC, while a patient receiving LEC could have effects similar to MEC. Although a number of factors have been identified that influence the risk of CINV (age, female gender, anxiety, travel sickness or nausea during pregnancy, previous treatments, insufficient sleep before chemotherapy, duration of CINV [7,8,22]), it is not yet possible to define the extent of the increased risk or to determine which factors are likely to be most important in an individual.

The MASCC/ESMO guidelines state there is insufficient evidence and, other than those from the National Comprehensive Cancer Network (NCCN), guidelines typically make antiemetic recommendations based on the emetogenicity of the chemotherapy alone. Many clinicians do not take these individual factors into account when making treatment decisions. Emesis risk calculators have been developed to estimate individual risk [8,23–25]. Using data from 1198 patients to identify relevant predictive factors and a receiver-operating characteristic curve analysis to measure the predictive accuracy of the scoring algorithm, 8 risk factors were identified, which were age $< 60$ years, the first two cycles of chemotherapy, anticipatory nausea and vomiting, history of morning sickness, less than 7 h of sleep the night before chemotherapy, CINV in the prior cycle, patient self-medication with non-prescribed treatments, and the use of platinum or anthracycline-based regimens [8]. Increased adoption of this tool could help to standardise data and compare results across studies and allow better comprehension of emetic control in clinical practice.

The use of a risk calculator is being further investigated in the MyRisk trial, a phase IV, open-label multinational study in which patients scheduled to receive three consecutive cycles of an intravenous MEC regimen are randomised to either NEPA plus dexamethasone or 5-$HT_3$-RA plus dexamethasone standard of care [26]. An algorithm incorporating 7 predictive risk factors is used to select patients at increased risk of CINV.

However, clinician workloads limit the utility of available calculators to estimate individual risk for emesis and greater effort and resources are required to increase their use. One possible strategy could be the training of other health professionals, e.g., nurses, to use them and to present the result to physicians before seeing patients. However, patients can also complete risk factor forms online. The use of telemedicine and e-health interventions, e.g. the use of various apps, such as Resilience (https://www.resilience.care), may also be useful in helping capture patient-reported health data and allow remote monitoring and management of CINV [27].

In addition to the assessment of individual factors that may increase the risk of CINV, there is a need to assess other potential confounding risk factors for nausea and vomiting. These include severe constipation, hypercalcemia, hypomagnesemia, infection, brain metastases, ascites, thoracic radiotherapy, and starting or increasing dose of opioids.

### 1.4. How should CINV in patients treated with new ADCs be managed?

ADCs such as sacituzumab govitecan, trastuzumab deruxtecan and datopotamab deruxtecan, appear to have high emetogenic potential comparable to carboplatin AUC $\geq 5$. For example, in a pooled analysis of clinical trials involving patients with metastatic breast cancer treated with ADCs, frequencies (all grades) of nausea and vomiting were 66 % and 44 % with sacituzumab govitecan and 75 % and 45 % with trastuzumab deruxtecan, respectively [28]. These frequencies were significantly higher than observed with trastuzumab emtansine. Guidelines suggest ADCs may warrant their own classification between the current MEC and HEC [3]. Of note, NCCN guidelines classify these agents as highly emetogenic [29].

ADCs may also be associated with a novel pattern of CINV, with onset of nausea at around 2–3 days and vomiting at around 10 days, although the pattern may vary with events occurring one week or more after each infusion [4,5]. ADCs are typically administered continuously, and the risk remains high throughout each cycle, with sacituzumab govitecan administered twice per cycle (days 1 and 8, of every 21-day cycle), meaning repeat prophylaxis is required on these days. Persistent long-term delayed nausea and the high level of need for rescue medication can represent a major burden for patients receiving ADCs [4,30]. In the ERICA trial, the addition of olanzapine 5 mg for 6 days to 5-$HT_3$-RA and dexamethasone reduced persistent and delayed nausea and vomiting in patients with HER2-positive or HER2-low breast cancer treated with trastuzumab deruxtecan [6]. In the persistent phase, which was defined as 120–504 h post-dose (or days 6–21), olanzapine was more effective although nearly half (48.6 %) of patients experienced nausea (versus 68.1 % with 5-$HT_3$-RA/ dexamethasone). Overall, 51.4 % of olanzapine-treated patients experienced emesis and/or use of rescue medication and 62.5 % experienced nausea at some point during the entire 21-day treatment cycle. Use of rescue medication was also still frequent in the group receiving olanzapine (7.9 vs.10 times in the 5-$HT_3$-RA/ dexamethasone group over the 21-day period). There was also considerable variability between patients in the occurrence, timing, duration, and recurrence of nausea throughout the 21-day period, with no consistent pattern. A prophylactic regimen including an $NK_1$-RA, as recommended in the HEC setting by the MASCC/ESMO guidelines, was not used in this study so how much additional benefit might be achieved with the use of an $NK_1$-RA as well as olanzapine is unknown.

A two-drug regimen may possibly be sufficient for some patients, although triple therapy of 5-$HT_3$-RA, a $NK_1$-RA, and dexamethasone will be needed in others and may be considered the gold-standard approach, even mandatory, especially given the continuous therapy and the late and very late onset of nausea and vomiting. Also, an anti-emetic with longer half-life and/or longer protection may be an appropriate option. In addition, the presence of risk factors (e.g., female gender, younger patient, nauseas during pregnancy) could impact the overall risk associated with trastuzumab-deruxtecan and sacituzumab-govitecan. In patients for whom a two-drug regimen did not lead to a sufficient response, a triple combination with an $NK_1$-RA or even a quadruple combination with the addition of olanzapine should be considered as a secondary prophylaxis in each subsequent cycle [31].

### 1.5. What is the emetogenic risk of FOLFOX/FOLFIRI/FOLFIRINOX regimens?

Regimens based on 5-fluorouracil-leucovorin-oxaliplatin (FOLFOX), or 5-fluorouracil-leucovorin-irinotecan (FOLFIRI) are classified as MEC by the MASCC/ESMO guidelines. A two-drug regimen, including single doses of a 5-$HT_3$-RA (palonosetron preferred) and dexamethasone, is recommended for patients receiving oxaliplatin, with the addition of an $NK_1$-RA suggested for women aged $\leq 50$ years old.

The incidence of CINV for irinotecan-containing regimens is less well recognised due to a lack of studies. A prospective and retrospective review of the emetogenic potential of chemotherapy regimens indicated that irinotecan-containing regimens may have high rather than moderate emetogenic potential and so may require more intensive antiemetic prophylaxis [32]. Further evidence is needed for this to be confirmed, but triple therapy of dexamethasone, 5-$HT_3$-RA and $NK_1$-RA may be advisable as prophylaxis.

A recent randomised trial in patients with solid malignant tumours who were receiving MEC regimens involving oxaliplatin, irinotecan, or

carboplatin, found that olanzapine significantly reduced CINV [33]. However, this trial had several limitations, and a four-drug regimen cannot be recommended based on these findings.

The triple combination of 5-$HT_3$-RA, $NK_1$-RA and dexamethasone was shown to poorly control FOLFIRINOX-induced CINV in patients with advanced pancreatic cancer, with emesis persisting beyond 5 days [34]. FOLFIRINOX may have greater emetic potential than FOLFOX or FOLFIRI and so require additional anti-emetic considerations.

### 1.6. When should a second agent be added to patients receiving LEC?

In patients receiving LEC, the guidelines recommend monotherapy with dexamethasone, 5-$HT_3$-RA or a dopamine receptor antagonist. Individual risk factors can move patients from low to moderate emetogenic risk. Nausea and/or vomiting in the previous course is a risk factor that should generally lead to consideration of the antiemetic regimen recommended for the next higher risk level. However, overtreatment may be a concern (e.g., when leading to unjustified exposure to risk of side-effects or financial toxicity), and a second agent might only be considered if it addresses a particular issue (e.g., prolonged nausea).

### 1.7. How should CINV be managed in patients receiving oral therapies?

Oral agents are generally administered daily over an extended period and so the concept of acute and delayed nausea and vomiting may not apply. However, for a continuous therapy, CINV may put the therapeutic goal at risk through lowering the relative dose intensity or lack of adherence. The classification system for oral agents was revised in the 2023 update into just two emetic risk categories (minimal-low or moderate-high) with the emetic risk potential referring to the risk during the entire treatment period rather than the first 24 h. However, data on the emetic risk potential of oral anticancer agents are very limited and, in the absence of good evidence on the prophylaxis of CINV, guidance is based on the use of on-demand antiemetics. In the medium- to high-risk category, a procedure based on the recommendations for radiation-induced nausea and vomiting may be an option. Similar to multi-week radiotherapy concepts with a medium to high risk of emetogenicity, a combination of 5-$HT_3$-RA (days 1–7) and dexamethasone (days 1–3) would initially be possible, followed by discontinuation and, if necessary, a resumption of therapy if symptoms occur [35]. An $NK_1$-RA may need to be added if this is inadequate, and multiple dosing should also be considered. Clinical trials are expected in order to provide stronger recommendations in this setting. If an oral drug is interrupted because of CINV, its reintroduction should be made with secondary prophylaxis. The choice of the best drug will depend on the pattern of emesis.

In the minimal-low risk category, antiemetics should be used on demand, with consideration that individual risk factors may make primary prophylaxis necessary. The choice of the best drug will depend on the pattern of emesis

Some oral therapies are not administered daily. For example, oral vinorelbine administration is on day 8. To ensure absorption and subsequent effectiveness, it is essential to avoid vomiting. Antiemetic prophylaxis must be appropriate, especially since it is not recommended to repeat the dose after vomiting to avoid toxicity. MASCC/ESMO guidelines consider this drug as HEC-MEC, and the use of prophylaxis is indicated. However, risk factors for vomiting beyond the emetogenic potential of treatment also need to be considered. Similar principles of avoiding vomiting and ensuring absorption apply to 5-day cycles of temozolomide, 14-day cycles of cyclophosphamide and 3–5-day cycles of etoposide.

### 1.8. What is the best drug for breakthrough CINV?

Breakthrough CINV is defined as vomiting and/or nausea occurring on the day of chemotherapy in patients receiving guideline-recommended prophylaxis [2]. The best way to reduce breakthrough CINV risk is to deliver the optimal adapted prophylaxis from the first cycle and to assess the correct adherence to the treatment. For patients experiencing breakthrough CINV, the available evidence suggests using olanzapine if not used for primary prophylaxis, with some evidence suggesting a single daily dose of 10 mg for 3 days. However, olanzapine may be associated with somnolence [33], with the 10 mg dose having a greater sedative effect than the 5 mg dose [36], so evening administration may be preferable.

Cannabinoids, such as the FDA-approved dronabinol and nabilone, may also be considered for the treatment of breakthrough CINV but are not recommended by the MASCC/ESMO guidelines. In a phase 2 trial, the addition of oral tetrahydrocannabinol:cannabidiol (THC:CBD) cannabis extract to standard antiemetics was associated with less nausea and vomiting but with additional side-effects including sedation, dizziness, or disorientation [37,38]. Still, evidence for their use is limited and access and stigma may be barriers to use of cannabinoids, as may the use of a more complex antiemetic combination [39].

Methotrimeprazine or metoclopramide may also be considered.

### 1.9. What are the options for patients with CINV after following best guidance (i.e., already receiving four-drug regimen including olanzapine)?

If CINV occurred in previous cycles, there is a need to ensure guideline-recommended treatment was prescribed and received, with the correct dosing, correct number of days, and taken as indicated. It is also important to check that nausea and vomiting is chemotherapy-induced, or whether other factors may be involved (as per patient assessment above).

Choice of 5-$HT_3$-RA may also need to be considered. If ondansetron or tropisetron were previously unsuccessfully used, palonosetron or granisetron may be an alternative option, i.e. switching the 5-$HT_3$-RA. Ondansetron and tropisetron are metabolised through CYP2D6 and therefore of limited use in patients with the ultrarapid metaboliser genotype but, there is no clinically meaningful interaction between palonosetron or granisetron and CYP2D [40]. Palonosetron may also offer better efficacy in delayed CINV due to its longer half-life. If the patient is vomiting, one can consider sublingual or subcutaneous administration [41,42]. The use of granisetron transdermal patch is generally not recommended since the time to peak concentration from this formulation is ~48 h. However, as noted in the NCCN guidelines, it can have a role in oral chemotherapy as it provides protection for up to 5 days per patch.

Regarding the choice of $NK_1$-RA, there is a lack of head-to-head studies demonstrating superiority between aprepitant and netupitant. However, a fixed combination of netupitant and palonosetron (NEPA) administered on day 1 only was non-inferior to a 3-day aprepitant /granisetron regimen in preventing CINV associated with cisplatin-based HEC [43]. A pooled analysis of this with two other trials also showed that NEPA administered on day 1 was more effective than a 3-day aprepitant regimen in preventing delayed nausea and vomiting associated with cisplatin [44]. Similarly, a single dose of NEPA was at least as effective as a 3-day aprepitant regimen in patients with cancer receiving anthracycline cyclophosphamide and non- anthracycline cyclophosphamide MEC [45]. NEPA was also more effective than a 3-day aprepitant regimen in preventing CINV for an extended duration in patients receiving MEC and in those with emetic risk factors [46].

If the patient received AC-based chemotherapy and CINV started after day 1, increasing the number of days of dexamethasone may be considered. Also, if the patient received olanzapine 5 mg, increasing the dose to 10 mg may be needed. It is unlikely that metoclopramide will offer any benefit since this also acts at D2-receptors, already covered by olanzapine.

If there is a component of anxiety, which may include anticipatory nausea at hospital admission before chemotherapy is administered, in a setting where olanzapine and similar drugs may be effective, lorazepam or other benzodiazepines could be of use [47–49]. As discussed above, cannabinoids are approved in some countries and act at receptors (CB1

and others) not already covered, although they are not recommended by MASCC/ESMO guidelines due to limited evidence.

The worst-case scenario is in patients who received cisplatin-based chemotherapy and took all four antiemetics in the correct doses and correct number of days (4 days). In such patients, dexamethasone at high doses might be considered as a rescue antiemetic. Anecdotally, this has been used with some success but there is currently no evidence from clinical trials to support this approach and it may not be sufficient. Methylprednisolone, haloperidol, alizapride, midazolam and propofol might also be considered. Complementary medicine such as relaxation measures, e.g., yoga, acupuncture, and dietary modification etc may also be a useful option as adjuncts to anti-emetics, although higher quality evidence is needed [50].

### *1.10. How should long delayed CINV be managed?*

Typically, studies of antiemetic agents have evaluated CINV in the first 24 h post-chemotherapy (i.e., acute CINV) and in the 24–120 h after chemotherapy (i.e., delayed CINV), with delayed CINV generally less well controlled. However, recent studies have shown that CINV, and especially nausea, can persist beyond day 5. Prolonged or late-onset (>5 days after treatment) CINV affects a significant proportion of patients and severity is similar to acute and delayed CINV [51]. Patients with delayed CINV are at increased risk of also experiencing long-delayed CINV with extended duration of CINV beyond 120 h strongly predicting recurrent CINV [22]. However, this is not sufficiently addressed by guidelines, despite it being, as discussed previously, frequent with some anticancer therapies, such as certain ADCs. In a trial of patients with breast cancer receiving trastuzumab deruxtecan, triple therapy of granisetron, dexamethasone and aprepitant reduced CINV over a 168-hour period versus granisetron plus dexamethasone and the authors note the need for an observation period longer than 168 h in future studies [52]. The entire CINV risk period and not just the initial 24 h or even 120 h should be considered when choosing anti-emetic prophylaxis, and properties of anti-emetics, such as half-life and duration of effect, may be relevant. As the long-delayed CINV phase in the outpatient setting is most likely to occur when the patient is at home, the focus here is on the educational discussion and the prescription and dosing instructions for rescue or additive medication.

## 2. Conclusions

CINV is a frequent side effect of many chemotherapy regimens that impacts patients' quality of life and can potentially reduce the effectiveness of treatment. Guideline-recommended prophylactic anti-emetic strategies can control CINV in many patients, but unaddressed issues remain. Through identifying the current gaps in the updated MASCC/ESMO guidelines and discussing the available evidence, we have addressed some of these issues and provide expert support to oncologists who may encounter them in clinical practice. These and other questions need to be considered in formal studies of anti-emetic prophylaxis, where possible, that will provide optimal effectiveness in clinical practice.

## CRediT authorship contribution statement

**María Ángeles García del Barrio:** Writing – review & editing, Writing – original draft, Conceptualization. **Franziska Jahn:** Writing – review & editing, Writing – original draft, Conceptualization. **Mario Di Palma:** Writing – review & editing, Writing – original draft, Conceptualization. **Florian Scotté:** Writing – review & editing, Writing – original draft, Conceptualization. **Karin Jordan:** Writing – review & editing, Writing – original draft, Conceptualization. **Evandro de Azambuja:** Writing – review & editing, Writing – original draft, Conceptualization. **Alex Molassiotis:** Writing – review & editing, Writing – original draft, Conceptualization. **Matti Aapro:** Writing – review & editing, Writing – original draft, Conceptualization.

## Author contributions

All authors were involved in the conceptualisation and writing of this manuscript.

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