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SPECIAL ARTICLE

Guidelines versus individualized care for the management of CINV

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Abstract

Numerous groups have published guidelines for the prevention and management of chemotherapy-induced nausea and vomiting (CINV). The current management of CINV, however, remains suboptimal, due in part to poor adherence to existing antiemetic guidelines. Challenges in clinical trial design have also slowed progress and complicated the selection of optimal antiemetic therapy. In addition, patient-specific characteristics and factors are not included in current CINV guidelines and are an important contributor to an individual's risk for nausea and vomiting. CINV risk prediction algorithms have now emerged and provide the opportunity to individualize antiemetic prophylaxis. Further studies are underway to examine the precise role for risk model-guided antiemetic prophylaxis in patients with cancer.

Keywords Chemotherapy-induced nausea and vomiting · CINV · Antiemetic guidelines · Adherence · CINV risk prediction models · Clinical trial design

Introduction

Despite the existence of numerous antiemetic therapies with demonstrated efficacy in preventing chemotherapy-induced nausea and vomiting (CINV), the management of CINV remains suboptimal. This disconnection is in part related to failure to follow guideline-directed therapy from groups such as the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) [1–3]. Unfortunately however, even when following these guidelines, CINV and the control of nausea, in particular, for many patients remain poor. If we are to further reduce the incidence of CINV, we will need to develop strategies that not only lead to the availability of more effective antiemetic regimens, but we will also need to individualize patient care based on their personal risk of CINV.

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Summary of current antiemetic guidelines

Chemotherapy-induced nausea and vomiting guidelines are primarily based on the emetogenic potential of chemotherapeutic agents when administered without any antiemetic prophylaxis. There are four broad categories: highly emetogenic chemotherapy (HEC; > 90% risk of emesis), moderately emetogenic chemotherapy (MEC; < 30 to 90% risk), low emetogenic chemotherapy (10 to 30% risk), and minimal emetogenic chemotherapy (< 10% risk) [1–4]. Table 1 shows the emetogenic classification of common anticancer therapies according to current consensus guidelines [1–3].

Currently available consensus guidelines demonstrate broad agreement on the key principles of CINV prophylaxis [1–3]. Prophylaxis should be initiated prior to chemotherapy for any patient with a 10% or greater risk of emesis and should continue for long enough to cover the duration of emetic risk. Antiemetic therapy should be based on the chemotherapeutic agents administered; for combination chemotherapy regimens, the agent with the highest emetogenic potential should guide selection of antiemetic therapy. Current CINV guidelines are summarized in Table 2 [1–3].

All three consensus guidelines agree that patients receiving HEC, including anthracycline/cyclophosphamide (AC)-based chemotherapy, should be treated with at least a three-drug antiemetic regimen consisting of a neurokinin-1 (NK-1) receptor antagonist, a 5-hydroxytryptamine (5-HT3) receptor

Table 1 Emetogenic potential of common cancer therapies (when administered without any antiemetics) [1–3]

Highly emetogenic (> 90% frequency of emesis)		
Intravenous agents		Oral agents[d]
• Anthracycline/cyclophosphamide combination	• Cyclophosphamide > 1500 mg/m^2	• Hexamethylmelamine[b, c]
• Carboplatin AUC ≥ 4[a]	• Dacarbazine	• Procarbazine
• Carmustine > 250 mg/m^2[a]	• Doxorubicin ≥ 60 mg/m^2[a]	
• Carmustine[b, c]	• Epirubicin > 90 mg/m^2[a]	
• Cisplatin	• Ifosfamide ≥ 2 g/m^2 per dose[a]	
	• Mechlorethamine	
	• Streptozocin	
Moderately emetogenic (> 30 to 90% frequency of emesis)		
Intravenous agents		Oral agents[d]
• Aldesleukin > 12–15 million IU/m^2[a]	• Doxorubicin < 60 mg/m^2[a]	• Bosutinib[b, c]
• Alemtuzumab[b, c]	• Doxorubicin[b, c]	• Cabozantinib[c]
• Amifostine > 300 mg/m^2[a]	• Epirubicin ≤ 90 mg/m^2[a]	• Ceritinib
• Arsenic trioxide[a]	• Epirubicin[b, c]	• Crizotinib
• Azacitidine	• Idarubicin	• Cyclophosphamide
• Bendamustine	• Ifosfamide < 2 g/m^2 per dose[a]	• Imatinib[b, c]
• Busulfan[a]	• Ifosfamide[b, c]	• Lenvatinib[a, c]
• Carboplatin AUC < 4[a]	• Interferon alfa ≥ 10 million IU/m^2[a]	• TAS-102 (trifluridine-tipiracil)[c]
• Carboplatin[b, c]	• Irinotecan	• Temozolomide
• Carmustine ≤ 250 mg/m^2[a]	• Irinotecan liposomal injection[c]	• Vinorelbine[b, c]
• Clofarabine	• Melphalan[a]	
• Cyclophosphamide < 1500 mg/m^2	• Methotrexate ≥ 250 mg/m^2[a]	
• Cytarabine > 200 mg/m^2[a]	• Oxaliplatin	
• Cytarabine > 1000 mg/m^2[b, c]	• Romidepsin[b, c]	
• Dactinomycin[a]	• Temozolomide	
• Daunorubicin	• Thiotepa[b, c]	
• Dinutuximab[a]	• Trabectedin	

AUC area under the curve, *IU* international units

[a] From the National Comprehensive Cancer Network (NCCN) guidelines

[b] From the Multinational Association for Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO) guidelines

[c] From the American Society of Clinical Oncology (ASCO) Antiemetic Clinical Practice Guideline 2017 update

[d] In the NCCN guidelines, oral antineoplastic agents are grouped together as moderate to high emetic risk (≥ 30% frequency of emesis)

antagonist, and dexamethasone [1–3]. The 2017 updated ASCO guidelines recommend the inclusion of olanzapine for all patients receiving HEC or AC combinations [3]. The MASCC/ESMO and NCCN guidelines also include the addition of olanzapine as an option for patients receiving HEC [1, 2]. If an NK-1 receptor antagonist is not available for prophylaxis in a patient receiving AC, the MASCC/ESMO guidelines recommend palonosetron as the preferred 5-HT3 receptor antagonist [1, 5], while the other two guidelines do not specify a preferred agent [2, 3].

For patients receiving MEC, NCCN guidelines recommend a 5-HT3 receptor antagonist and dexamethasone with or without either an NK-1 receptor antagonist or olanzapine [2]. The MASCC/ESMO guidelines and updated ASCO guidelines do not recommend incorporation of an NK-1 receptor antagonist for MEC unless carboplatin is used (discussed below) [1, 3]. In all three guidelines, the use of dexamethasone after day 1 is optional and should be considered if the MEC has a known potential for delayed CINV [1–3].

General principles for breakthrough and refractory CINV include the addition of another antiemetic agent with a different mechanism of action [2, 3]. For example, adding in an NK-1 receptor antagonist, olanzapine, benzodiazepine,

Table 2 Summary of current CINV guidelines [1–3]

	Recommended antiemetic therapy	
	Acute phase	Delayed phase
MASCC/ESMO guidelines [1]		
Non-AC HEC	5-HT3 RA + DEX + NK-1 RA	DEX
AC	5-HT3 RA[a] + DEX + NK-1 RA	Aprepitant or DEX if aprepitant is used on day 1
Carboplatin	5-HT3 RA + DEX + NK-1 RA	None (continue aprepitant if used on day 1)
Non-carboplatin MEC	5-HT3 RA + DEX	± DEX
LEC	DEX or 5-HT3 RA or dopamine RA	None
NCCN guidelines [2]		
HEC (including AC and carboplatin AUC ≥ 4)	5-HT3 RA + DEX + NK-1 RA Palonosetron + DEX + olanzapine 5-HT3 RA + DEX + NK-1 RA + olanzapine	DEX (+ aprepitant if used on day 1) Olanzapine Olanzapine + DEX (+ aprepitant if used on day 1)
MEC	5-HT3 RA + DEX 5-HT3 RA + DEX + NK-1 RA Palonosetron + DEX + olanzapine	5-HT3 RA + DEX DEX (+ aprepitant if used on day 1) Olanzapine
LEC	DEX or 5-HT3 RA or dopamine RA	None
ASCO guidelines [3]		
Non-AC HEC	5-HT3 RA + DEX + NK-1 RA + olanzapine	Aprepitant (if used on day 1) + DEX + olanzapine
AC	5-HT3 RA + DEX + NK-1 RA + olanzapine	Aprepitant (if used on day 1) + olanzapine
Carboplatin AUC ≥ 4	5-HT3 RA + DEX + NK-1 RA	
MEC (excluding carboplatin AUC ≥ 4)	5-HT3 RA + DEX	DEX if patients are at risk for delayed CINV
LEC	5-HT3 RA or DEX	None

5-HT3 5-hydroxytryptamine, *AC* anthracycline/cyclophosphamide, *ASCO* American Society of Clinical Oncology, *AUC* area under the curve, *CINV* chemotherapy-induced nausea and vomiting, *DEX* dexamethasone, *ESMO* European Society for Medical Oncology, *HEC* highly emetogenic chemotherapy, *LEC* low emetogenic chemotherapy, *MASCC* Multinational Association of Supportive Care in Cancer, *MEC* moderately emetogenic chemotherapy, *NCCN* National Comprehensive Cancer Network, *NEPA* netupitant/palonosetron, *NK-1* neurokinin-1, *RA* receptor antagonist

[a] If an NK-1 receptor antagonist is not available, palonosetron is the preferred 5-HT3 receptor antagonist for patients receiving AC-based chemotherapy in the MASCC/ESMO guidelines

cannabinoid, or dopamine receptor antagonist, or changing the 5-HT3 receptor antagonist.

Important changes in current CINV guidelines

There have been several significant updates to the consensus guidelines for CINV prophylaxis [1–3]. In addition to the many novel agents now added to the emetogenic classification categories (over 40 new drugs added in the recently updated MASCC/ESMO CINV guidelines), AC has been reclassified as HEC instead of MEC [1–3]. Chemotherapy-induced nausea and vomiting prophylaxis for carboplatin has also been revised in the MASCC/ESMO, NCCN, and ASCO guidelines. Although carboplatin is classified as MEC [1–3], the emetogenic potential is at the higher end of the MEC range (82 to 84% according to clinical trials) [5]. Recent phase II and phase III studies have shown that adding an NK-1 receptor antagonist to a 5-HT3 receptor antagonist and dexamethasone therapy can increase the complete response (CR; no vomiting and no use of rescue medication) by approximately 10 to 15% in patients receiving carboplatin chemotherapy [1, 6, 7]. As a result, current MASCC/ESMO guidelines recommend incorporation of an NK-1 receptor antagonist such as aprepitant, fosaprepitant, netupitant, or rolapitant [1]. NCCN and ASCO guidelines also recommend inclusion of an NK-1 receptor antagonist for patients receiving carboplatin at does resulting in an area under the curve (AUC) ≥ 4 mg/mL per minute [2, 3].

Olanzapine is now included in the NCCN guidelines for treatment of breakthrough CINV and as an alternative to an NK-1 receptor antagonist in combination with palonosetron and dexamethasone for prevention of CINV in patients receiving HEC or MEC [2]. In addition, olanzapine can be added as a fourth agent with aprepitant or fosaprepitant, a 5-HT3 receptor antagonist, and dexamethasone for patients receiving HEC. Prophylactic olanzapine is administered at a dose of 10 mg orally on days 1 through 4 for patients receiving HEC and on days 1 through 3 for those receiving MEC. However, the guidelines include a recommendation to consider a lower dose of 5 mg in elderly patients or those who experience sedation with 10 mg of olanzapine. Recent

ASCO guidelines also suggest olanzapine should be administered as a four-drug regimen in combination with a 5-HT3 receptor antagonist, an NK-1 receptor antagonist, and dexamethasone in all patients receiving HEC, including those receiving an AC-based combination [3]. Olanzapine is also recommended for patients experiencing breakthrough nausea and vomiting in the ASCO guidelines. In the most recent MASCC/ESMO guidelines, olanzapine is listed as an option with a 5-HT3 receptor antagonist and dexamethasone for prophylaxis of CINV, particularly when nausea is an issue [1]. An extended-release formulation of granisetron for subcutaneous injection was also added to the NCCN guidelines as a reasonable 5-HT3 receptor antagonist option for combination antiemetic therapy [2].

Dexamethasone-sparing strategies have also been included in the NCCN guidelines for patients without significant CINV risk factors who are receiving MEC or non-cisplatin HEC based on data from several studies showing no significant increase in CINV when dexamethasone was only administered on day 1 [2, 8–10].

Optimizing antiemetic therapy: the challenges in clinical trial design

Despite the availability of multiple guidelines, many patients still have poorly controlled CINV [11–14]. The nature of clinical trials in this field presents considerable challenges and contributes to the difficulty in selecting optimal therapy. For instance, there is considerable diversity in the clinical trial endpoints reported for each study, making cross-trial comparisons difficult, especially as most trials simply ignore measures of nausea in their primary endpoints [15]. In a meta-analysis of 30 randomized clinical trials in CINV, comprehensive outcome measures such as total control (no vomiting, no nausea, and no use of rescue medications) and complete protection (no vomiting, no significant nausea, and no use of rescue medications) were reported in less than 25% of the trials. Clinical trials commonly focus on vomiting and underreport outcomes related to nausea control. Nausea is a particularly important outcome measure given that it occurs more frequently than vomiting and significantly decreases patient quality of life [16]. Unfortunately, many clinical trials use CR (no vomiting and no use of rescue medications) as their primary endpoint, which may not accurately reflect the patients' actual experience with CINV.

Another issue is the small patient numbers in many of the CINV trials and a lack of head-to-head randomized clinical trial data to definitively establish which antiemetic agents are most effective against CINV. Lastly, several clinical trials investigating antiemetic therapies have been criticized for utilizing a suboptimal control arm not consistent with standard practice patterns. In order to improve our understanding of the CINV landscape and effectively evaluate the available data, there is a need for future clinical trials to use consistent reporting of outcomes based on a uniform definition. Nausea should be included as a part of the primary study outcome to better gauge the effectiveness of CINV control and patients' experience. Guideline-based antiemetic therapy should also be used as the control arm for CINV clinical trials to improve the integrity of the results. In addition, all emesis data should be publicly and freely available so that investigators can compare the effects of different antiemetic regimens.

Beyond the guidelines: individualizing CINV prophylaxis

The field of oncology is moving toward a more precise, individualized approach that incorporates biomarkers and patient-related characteristics into treatment decision-making. Unfortunately, the recommendations of national and international consensus guidelines are based largely on the emetogenic potential of chemotherapeutic agents when given in the absence of any antiemetic therapy and show less consideration for other therapy-related and patient-related risk factors.

Beyond the emetogenic potential of the chemotherapeutic agents, therapy-related factors that contribute to CINV include drug dosage, treatment schedule, route of administration, and combinations with other emetogenic agents or radiation therapy [17, 18]. Established patient-related risk factors include young age (< 55 years), female gender, history of low alcohol intake, motion sickness, and prior emesis during pregnancy [19–21]. In addition, patient anxiety, expectation of emesis, metabolic abnormalities, gastrointestinal irritation, and intracranial pressure can also contribute to CINV [17, 19, 22–24]. Risk factors for anticipatory CINV have also been assessed and include CINV in a previous cycle of therapy, metastatic disease, and higher levels of anxiety prior to chemotherapy administration [25]. Ongoing studies continue to explore additional potential risk factors.

A personalized approach to CINV that incorporates these patient-related risk factors into antiemetic recommendations could significantly improve the management of CINV. For example, the range of emetogenic risk for MEC is extremely wide (30 to 90% risk of emesis), making it challenging for current CINV consensus guidelines to provide appropriate recommendations for every clinical scenario [2]. Patients receiving MEC with additional personal risk factors may benefit from the addition of other antiemetics. On the other hand, the majority of patients who are at lower risk of CINV can be safely treated without additional agents, reducing the risks of drug side effects and the financial toxicity of these agents.

Several CINV risk prediction models have been developed, including two repeated measures cycle-based models that

Predictive Factor	Before a Cycle of Chemotherapy
Baseline score	10
Impact of patient risk factors	
Patient < age	+1
Patient expects to have CINV	+1
Patient slept <7 h the night before chemotherapy	+1
Patient has a history of morning sickness	+1
Patient is about to receive platinum or anthracycline chemotherapy	+2
Patient on-prescription antiemetics are used at home in the prior cycle	+3
Patient had nausea or vomiting in the prior cycle	+5
About to receive the 2nd cycle	-5
About to receive the ≥3rd cycle	-6
Total composite risk score[a]	?

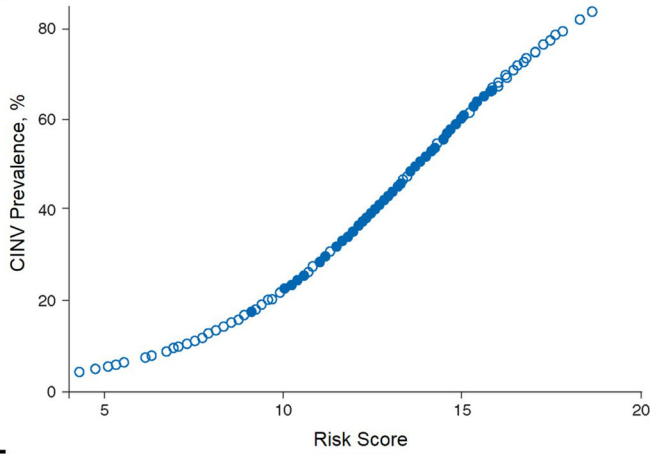

Fig. 1 Risk scoring algorithm for grade ≥ 2 CINV [29]. [a]The probability of developing ≥ grade 2 CINV during that cycle of therapy can then be estimated from the accompanying graph

predict the risk for acute and delayed CINV [26, 27]. A repeated measure approach allows CINV risk to be continually reassessed prior to each cycle of chemotherapy, rather than relying only on a single evaluation of baseline data to inform CINV prophylaxis for the entire course of cancer treatment. Predictors of CINV in these models included younger age, platinum or anthracycline-based chemotherapy, history of motion sickness or morning sickness, low daily alcohol consumption, patients' expectation of nausea, and emesis in previous cycles of chemotherapy. Both CINV risk models demonstrated good predictive accuracy, with high-risk patients three times more likely to develop acute or delayed CINV than low-risk patients [28].

These models were subsequently evaluated in a clinical trial in which patients with breast cancer receiving anthracycline- and cyclophosphamide-containing chemotherapy regimens were randomized to either risk model-guided antiemetic prophylaxis or physician's choice prophylaxis [26]. In the risk model-guided arm, low-risk patients received a 5-HT3 antagonist and dexamethasone, while high-risk patients also received aprepitant with or without olanzapine based on their risk of CINV. Risk model-guided prophylaxis was more effective than prophylaxis according to the treating physician's discretion in preventing acute nausea and vomiting (53.7% with no nausea vs 41.6%; $P < .001$ and 91.8% with no vomiting vs 82.2%; $P < .001$) and delayed nausea and vomiting (39.6% with no nausea vs 30.7%; $P = .01$ and 87.1% with no vomiting vs 78.0%; $P < .001$).

These models are somewhat limited by the small sample size and geographic region used for their development, leading to a multinational collaborative effort to develop a new repeated measures prediction model based on a larger data set of almost 1200 patients from 5 prospective CINV studies [29]. This model was designed to assess individualized risk of grade ≥ 2 CINV (≥ 2 vomiting episodes or a decrease in oral intake due to nausea) over the first 5 days from chemotherapy administration. Eight risk factors were significantly associated with CINV risk: age < 60 years, anticipatory nausea and vomiting, sleep < 7 h the night before chemotherapy, history of morning sickness, use of non-prescribed antiemetics (e.g., dimenhydrinate, antacids, herbal supplements), receiving platinum or anthracycline-based chemotherapy, first-line of chemotherapy, and the occurrence of CINV in the previous chemotherapy cycle. These factors were combined into a risk prediction model that showed good predictive accuracy with an area under the curve of 0.69 (95% confidence interval 0.67–0.70) (Fig. 1) [29]. On a 32-point scale, the threshold for high risk was defined as a score of ≥ 16, which correlates with a CINV risk of at least 60%. However, the authors add that this threshold is not fixed and may be adjusted to reflect the risk tolerance of patients and clinicians. This risk model has now been made freely available online at http://www.cinvrisk.org for patients and oncologists to use.

The development of risk prediction algorithms with high sensitivity and specificity will likely aid decision-making and improve CINV prophylaxis in the future. Risk model-guided antiemetic prophylaxis may also be more economical than physician choice prophylaxis. A recent cost-utility analysis of these two approaches showed that risk model-guided therapy was cost effective and was associated with gains in quality-adjusted life years [30]. However, this area of CINV management is a work in progress and further randomized studies are needed to fully elucidate the role of these prediction models in individualization of patient care. For example, my group is currently leading a large randomized phase III trial in which patients with newly diagnosed breast cancer receiving anthracycline/cyclophosphamide-containing regimens or platinum-based chemotherapy regimens are

randomized to either doublet (5-HT3 receptor antagonist and dexamethasone) or triplet (NK-1 and 5-HT3 receptor antagonists plus dexamethasone) antiemetic therapy based on their individual risk [31]. This study is also evaluating the role of olanzapine at a dose of 5 mg in these patients, as we know many patients will still have significant nausea even when receiving "optimal" guideline-recommended antiemetic therapy. The need for more personalized antiemetic approaches is reflected in the current NCCN guidelines, which state that decisions regarding CINV prophylaxis should be "individualized for each chemotherapy regimen and each patient" [2]. It is our hope that the introduction of "individualized" antiemetic therapy will lead to a move away from the current cookie cutter recommendations of guideline groups, as ultimately personalized therapy will improve CINV control and enhance the quality of life of our patients.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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