Prevention of chemotherapy-induced nausea and vomiting: Updated guidance from the BSMO supportive care task force

C. Fontaine, MD[1], J. Collignon, MD, PhD[2], P. Debruyne, MD, PhD[3], L. Duck, MD[4], E. Everaert, MD[5], T. Feys, MD[6], C. Langenaeken, MD[7], F. Lebrun, MD[8], J. Mebis, MD, PhD[9], E. Naert, MD[1], P. Van Landuyt, MPharm[11], S. Wuyts, MPharm[11], C. van Marcke de Lummen, MD, PhD[12], F. Vanryckeghem, MD[12], V. Verschaeve, MD[14], J. Klaskersky, MD, PhD[8]

SUMMARY

Nausea and vomiting continue to be some of the more dreaded side effects of anticancer therapy. While advances in the prophylaxis of chemotherapy induced nausea vomiting (CINV), and guidance from international cancer societies have yielded important benefits for cancer patients, there remains an important need to further improve patient care. To address the need for a better CINV prophylaxis, and to respond to the introduction of new potentially emetogenic anticancer agents and the publication of new clinical trial data with anti-emetic agents, several international oncological societies have recently updated their guidelines for the prevention of CINV. The objective of this paper was to translate these new international recommendations to a Belgian context.

(BELG J MED ONCOL 2025;19(1):15-26)

INTRODUCTION

Despite the development of effective preventive medication for chemotherapy-induced nausea and vomiting (CINV), recent studies underscore that nausea and vomiting continue to be some of the more dreaded side effects of anticancer therapy.[1,2] In fact, the debilitating effects of CINV have an important impact on the quality of life (QoL) of cancer patients, irrespective of whether the treatment is given in a curative or palliative setting.[2,3] In addition to this, CINV may also be a reason for patients not to adhere to their anticancer therapy. In international guidelines, CINV is classified based on the time of onset of symptoms after treatment. In this respect, acute CINV occurs within 24 hours after administration, whereas delayed symptoms only occur two days after the treatment initiation. Finally, breakthrough CINV is defined as persistent nausea and vomiting despite receiving anti-emetic prophylaxis.[4]

[1]Department of Medical Oncology, University Hospital Brussels, Brussels, Belgium, [2]Department of Medical Oncology, CHU de Liège, Liège, Belgium, [3]Department of Medical Oncology, AZ Groeninge, Kortrijk, Belgium, [4]Department of Medical Oncology, Cliniques Saint-Pierre Ottignies, Ottignies, Belgium, [5]Department of Medical Oncology, VITAZ Sint-Niklaas, Sint-Niklaas, Belgium, [6]Tom Feys Medical Writing, Izegem, Belgium, [7]Department of Medical Oncology, AZ Klina, Brasschaat, Belgium, [8]Department of Medical Oncology, Institut Jules Bordet, Brussels, Belgium, [9]Department of Medical Oncology, Jessa Ziekenhuis, Hasselt, Belgium, [10]Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium, [11]Pharmacy Department, University Hospital Brussels, Brussels, Belgium, [12]Department of Medical Oncology, Cliniques Universitaires St.-Luc, Brussels, Belgium, [13]Department of Medical Oncology AZ Glorieux, Ronse, Belgium, [14]Grand hôpital de Charleroi, Charleroi, Belgium.

Corresponding author: Christel Fontaine, MD, Department of Medical Oncology, University Hospital Brussels, Laarbeeklaan 101, B-1090 Jette, tel: + 32 2 477 60 40, email: Christel.Fontaine@uzbrussel.be.

Conflict of interest: Editorial support for this project was provided by Immedica Pharma, but the company did not have any influence on the content of the article. **Funding:** None.

Keywords: BSMO guidelines, CINV, new emetogenic drugs, quality of life, treatment adherence.

While advances in CINV prophylaxis and guidance from international cancer societies have yielded important benefits for cancer patients, there remains an important need to further improve patient care. The latter is amply illustrated by data from *Gao et al.* indicating suboptimal CINV control in patients treated with high-dose cisplatin chemotherapy. Despite the use of quadruplet anti-emetic prophylaxis with olanzapine, aprepitant, tropisetron, and dexamethasone, a quarter of patients in this study (24%) failed to achieve a complete CINV response, defined as the absence of emetic episodes and no use of rescue medication. Furthermore, more than half of the patients (52.3%) who received this quadruplet treatment indicated that CINV still interfered with their daily activities.[5] Adequate CINV prevention is also hampered by a low adherence to international treatment guidelines. For example, a large retrospective review including 45,324 patients from five European countries that was published in 2021 showed that only 15% of patients treated with a carboplatin-based regimen were receiving the recommended prophylactic treatment for CINV according to the MASCC/ESMO guidelines. Furthermore, about 40% of patients treated with cisplatin- or an anthracycline-cyclophosphamide- (AC) based chemotherapy regimen were prescribed a neurokinin one receptor antagonist (NK1-RA), despite the fact that this drug class was already incorporated in the MASCC guidelines for over a decade prior to this study. Even more alarming is the fact that a striking 12% of patients in this study did not receive any CINV prophylaxis at all.[6] A similarly poor guideline adherence was reported by *Navari et al.* indicating a very low uptake of NK1-RA in the prophylactic CINV strategy for patients treated with carboplatin.[7] The low adherence to CINV prophylaxis may in part be explained by physicians' underestimation of the emetic risk of chemotherapy. The latter is supported by the previously mentioned European retrospective review, indicating that only 55% of cisplatin-, 51% of anthracycline-, and 24% of carboplatin-based treatments were recognised as being highly emetogenic by physicians.[6] Other explanations could be a continued suboptimal awareness of antiemetic guidelines among physicians or country-specific reimbursement constraints. In addition, the lack of a functional managed care network with an integrated functional clinical pharmacy and a specialised onco-nurse might be part of the explanation for a subprime antiemetic treatment of cancer patients.

To address the need for a better CINV prophylaxis, and to respond to the publication of new clinical trial data with anti-emetic agents, several international oncological societies have recently updated their guidelines for the prevention of CINV.[8-10] Importantly, these updated guidelines now also include recommendations for anti-emetic prophylaxis in patients who are being treated with novel anticancer agents. Arguably the most important addition in this respect consists of antibody-drug conjugates (ADCs), a novel class of anticancer drugs that is rapidly gaining momentum in different oncological indications. In addition to this, given the wide range of side effects that can be caused by corticosteroids, there is a growing interest in the oncological community to opt for steroid sparing treatment regimens in the context of CINV prevention. The objective of this paper was to translate these new international recommendations to a Belgian context. The main source of inspiration has been the recently updated CINV guidelines from the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC).[8]

EMETIC RISK CLASSIFICATION OF ANTI-EMETIC DRUGS

The most important factor determining the likelihood of acute or delayed CINV during anticancer therapy consists of the intrinsic emetogenicity of the agent that is being administered. In this respect, the management of CINV has been greatly facilitated by the development of classification schemes that reflect the likelihood of emesis following treatment with a particular agent.[10] In these schemes, intravenous chemotherapy agents are divided into four categories based upon the risk for CINV in the absence of anti-emetic prophylaxis:

Highly emetogenic agents: >90% risk of CINV
Moderately emetogenic agents: >30% to 90% risk of CINV
Low emetogenic agents: 10% to 30% risk of CINV
Minimally emetogenic agents: <10% risk of CINV

Compared to intravenous agents, the classification of oral (targeted) anticancer agents is complicated by the fact that these agents are usually given continuously over an extended period. In this context, concepts like acute and delayed CINV are no longer relevant. For the emetogenic risk classification of these oral agents, both the MASCC/ESMO and ASCO guidelines use just two risk categories:[8,10]

High/moderate risk: ≥30% risk of CINV
Low/minimal risk: <30% risk of CINV.

In the updated MASCC/ESMO guidelines, special attention is given to two new ADCs that have entered the anticancer armamentarium: trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG). According to these recommendations and as discussed at ESMO 2024, these agents should

TABLE 1. Emetogenic risk classification of intravenous and oral anticancer agents (Table based on the most recent ESMO/MASCC guidelines)[8]
 # Emetogenic potential of these agents is at the high end of the moderate category

Single intravenous anticancer agents			
High	Anthracycline/cyclophosphamide combination Carmustine Chlormethine (mechlorethamine) Cisplatin Cyclophosphamide (≥1500 mg/m^2) Dacarbazine Streptozocin		
Moderate	Alemtuzumab Arsenic trioxide Azacitidine Bendamustine Busulfan Carboplatin# Clofarabine Cyclophosphamide <1500 mg/m^2 Cytarabine >1000 mg/m^2	Cytarabine/daunorubicin liposomal Daunorubicin Dinutuximab beta Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Irinotecan peg-liposomal	Lurbinectedin Naxitamab Oxaliplatin Romidepsin Sacituzumab–govitecan# Temozolomide Thiotepae Trabectedin Trastuzumab-deruxtecan#
Low	Aflibercept Amivantamab Axicabtagene–ciloleucel Belinostat Blinatumomab Bortezomib Brentuximab–vedotin Cabazitaxel Carfilzomib Catumaxomab Cetuximab Copanlisib Cytarabine ≤1000 mg/m^2 Decitabine Docetaxel Doxorubicin peg-liposomal Elotuzumab	Enfortumab–vedotin Eribulin Etoposide 5-Fluorouracil Gemcitabine Gemtuzumab–ozogamicin Inotuzumab–ozogamicin Isatuximab Ixabepilone Loncastuximab–tesirine Margetuximab Melphalan–flufenamide Methotrexate Mirvetuximab–soravtansine Mitomycin Mitoxantrone Moxetumomab–pasudotox	Necitumumab Nelarabine Paclitaxel Paclitaxel nab-albumin Panitumumab Pemetrexed Pertuzumab Tafasitamab Tagraxofusp Teclistamab Temsirolimus Tisagenlecleucel Tisotumab–vedotin Topotecan Trastuzumab–emtansine Vinflunine
Minimal	Asparaginase Atezolizumab Avelumab Belantamab–mafodotin Bevacizumab Bleomycin Cemiplimab Cladribine (2-chlorodeoxyadenosine) Daratumumab Dostarlimab	Durvalumab Emapalumab Fludarabine Ipilimumab Mosunetuzumab Nivolumab Obinutuzumab Ofatumumab Pembrolizumab Pixantrone	Polatuzumab–vedotin Pralatrexate Ramucirumab Rituximab Trastuzumab Tremelimumab Vinblastine Vincristine Vinorelbine

be classified on the higher end of the moderate emetogenic risk category.[8] As such, these agents are considered to be as emetogenic as high-dose carboplatin. Of note, while both MASCC/ESMO and ASCO see T-DXd and SG as moderately emetogenic, the most recent update of the NCCN antiemesis guidelines classifies these ADCs as highly emetogenic agents.[8,10]

As RIZIV/INAMI refers to the emetogenic classification of the MASCC/ESMO guidelines in their reimbursement criteria for the different anti-emetic drugs, this will be the classification that will be used for these guidelines. A complete overview of the emetogenic classification of anticancer drugs is depicted in *Table 1*.[8] Importantly, this classification only refers to adult patients.

TABLE 1. Emetogenic risk classification of intravenous and oral anticancer agents (Table based on the most recent ESMO/MASCC guidelines)[8]
 # Emetogenic potential of these agents is at the high end of the moderate category

Single oral anticancer agents (full course of therapy)			
High/moderate	Abemaciclib Adagrasib Avapritinib Bosutinib Cabozantinib Ceritinib Crizotinib Cyclophosphamide Enasidenib	Fedratinib Hexamethylmelamine (altretamine) Imatinib Lenvatinib Lomustine Midostaurin Mobocertinib Niraparib	Olaparib Procarbazine Ribociclib Rucaparib Selinexor# Temozolomide Vinorelbine
Low/minimal	Acalabrutinib Afatinib Alectinib Alpelisib Apalutamide Asciminib Axitinib Bexarotene Brigatinib Capecitabine Capmatinib Chlorambucil Cobimetinib Dabrafenib Dacomitinib Darolutamide Dasatinib Duvelisib Encorafenib Entrectinib Erdafitinib Erlotinib Estramustine Etoposide Everolimus Fludarabine Futibatinib Gefitinib	Gilteritinib Glasdegib Hydroxyurea Ibrutinib Idelalisib Infigratinib Ivosidenib Ixazomib Lapatinib Larotrectinib Lenalidomide Lorlatinib Melphalan Methotrexate Neratinib Nilotinib Nintedanib Olutasidenib Osimertinib Palbociclib Panobinostat Pazopanib Pemigatinib Pexidartinib Pomalidomide Ponatinib Pralsetinib Regorafenib	Relugolix Ripretinib Ruxolitinib Selpercatinib Sonidegib Sorafenib Sotorasib Sunitinib Talazoparib Tazemetostat Tegafur–uracil Tepotinib Thalidomide Tioguanin (6-thioguanine) Tivozanib Topotecan Trametinib Trifluridine–tipiracil Tucatinib Umbralisib Vandetanib Vemurafenib Venetoclax Vismodegib Vorinostat Zanubrutinib

THE PREVENTION OF ACUTE AND DELAYED CINV IN PATIENTS TREATED WITH HIGHLY EMETOGENIC REGIMENS

According to the updated MASCC/ESMO guidelines, the preferred treatment for CINV prophylaxis in patients treated with highly emetogenic chemotherapy (HEC) consists of a four-drug combination of an NK1-RA (aprepitant, fosaprepitant, netupitant, fosnetupitant, or rolapitant), a 5-hydroxytryptamine receptor antagonist (5-HT3-RA) (palonosetron, ondansetron, or granisetron), dexamethasone and olanzapine.[8] As such, these updated guidelines are now in line with the recommendations formulated by ASCO and NCCN in the sense that they now also incorporate olanzapine in the recommended CINV prophylaxis regimen for patients treated with HEC (this was not the case in the 2016 edition).[8-10,12]

The recommendation to add olanzapine to the acute CINV prophylaxis regimen for patients treated with HEC is based on the results of a pivotal clinical trial published by *Navari et al.*[13] In this randomised, phase III trial (N=380), the addition of olanzapine (10 mg once daily for four days) to a 5-HT3-RA plus dexamethasone and aprepitant significantly increased the 'no-nausea' rate in patients treated with cisplatin-(≥70mg/m^2) or AC-based chemotherapy (74% *vs.* 45% during the first 24 hours [p= 0.001]; 37% *vs.* 22% over the entire 120-hour study period [p= 0.002]).[13] In a second randomised controlled trial (N=705), a lower dose of olanzapine was evaluated in this setting, with a particular interest in the effect on delayed CINV. In this trial, cancer patients who were treated with cisplatin-based chemotherapy (≥50 mg/m^2) were randomly assigned (1:1) to receive either oral olanzapine

(5 mg once daily on days 1-4) or placebo, both in combination with aprepitant, palonosetron, and dexamethasone. Patients who received olanzapine had a significantly higher chance of obtaining a complete response (CR), defined as the absence of vomiting and no use of rescue medications in the delayed phase (24-120 hours) (79% *vs.* 66%, p< 0.0001).[14] As mild sedation can be an issue with the use of olanzapine (especially in older patients), the randomised phase III OLAnzaPINE trial showed non-inferiority of low-dose olanzapine (2.5 mg for four days) compared to a standard dose of 10 mg olanzapine in controlling CINV. In this trial, the CR rate (*i.e.*, the proportion of patients without emetic episodes) during hours 0 to 120 after the administration of HEC was similar with 2.5 mg and 10 mg of olanzapine, respectively (44.7% *vs.* 43.7%, p= 0.856). Furthermore, the incidence of significant daytime somnolence was significantly lower with the 2.5 mg dose (65.2% *vs.* 89.6% with the 10 mg dose, p< 0.001).[15] Based on these results, a 2.5 mg dose of olanzapine has become a viable option for CINV prevention in patients receiving HEC. Of note, the data that were obtained with this lower olanzapine have mainly been generated in women with breast cancer who received anthracycline-based chemotherapy. As such, it remains unclear to what extent these data can be extrapolated to all patients treated with HEC (*e.g.*, no data with the 2.5 mg dose in patients receiving high-dose cisplatin).

When discussing the place of olanzapine, it is important to note that long-term use of this agent increases the risk for QT prolongation.[16] In this respect, it is recommended to assess whether the patient has other risk factors for QT prolongation before considering the (long-term) use of this agent (*e.g.*, look for electrolyte disorders, cardiac comorbidities, thyroid dysfunction, congenital LQTS, renal impairment, co-medication with other QT prolonging drugs, etc.). After this evaluation, the need for olanzapine and the expected duration of its use should be balanced against the potential cardiac risk. In patients presenting with several other risk factors, it is recommended to perform an ECG before and during the treatment. In patients with a baseline QTc ≥ 500 ms, QT-prolonging medication is contra-indicated.

Of note, *Kinomura et al.* also published promising results with the addition of mirtazapine to standard CINV prophylaxis in lung cancer patients treated with cisplatin-based chemotherapy.[17] For the moment, however, this agent is not part of the treatment guidelines.

In addition to the evaluation of lower doses of olanzapine, several studies investigated the possibility of using steroid sparing CINV prophylaxis regimens. Patients are exposed to higher levels of dexamethasone due to the inhibition of CYP3A4 caused by aprepitant and netupitant. In a randomised controlled, phase III, non-inferiority trial (N= 396) patients receiving cisplatin- (≥50mg/m^2) or AC-based chemotherapy were randomly assigned to receive either dexamethasone on days one to three or dexamethasone on day one and placebo on days two and three, both combined with an NK1-RA and palonosetron. With a CR rate of 46.9% with the three-day regimen as compared to 44.0% with one day of dexamethasone, non-inferiority of the one-day regimen was demonstrated (p= 0.007). Interestingly, a further subgroup analysis of this trial confirmed this non-inferiority in patients receiving AC-based chemotherapy, while this was not the case for patients receiving cisplatin.[18] The finding that one day of dexamethasone is as effective as a three-day regimen in patients treated with AC-based chemotherapy was further confirmed in two large meta-analyses.[19,20] Based on these findings, both ASCO and MASCC/ESMO do not recommend the use of dexamethasone in the delayed phase for patients receiving AC-based chemotherapy. Data concerning corticosteroid-sparing CINV prophylaxis in patients treated with non-AC HEC are less clear than what has been reported in patients treated with AC-based chemotherapy. Very recently, results of the randomised phase III SPARED trial have demonstrated non-inferiority in terms of complete response rate during the delayed phase for one day of dexamethasone as compared to four days of dexamethasone in patients treated with cisplatin-based chemotherapy. However, the study did show a lower total control rate during the delayed and overall phase with one day of dexamethasone and this regimen also came with a higher incidence of nausea and appetite loss.[21] The feasibility of this regimen in clinical practice, especially in combination with a low dose of olanzapine, remains subject to debate. For the moment, a lower dose of dexamethasone (8 mg PO or IV per day) on days 2-4 is therefore still recommended for patients treated with non-AC HEC.[8,10]

Based on the available evidence, the BSMO supportive care task force embraces the recommendations for CINV prophylaxis stipulated in the most recent guidelines of MASCC/ESMO and ASCO. A schematic representation of these recommendations is depicted in *Table 2*.

THE PREVENTION OF ACUTE AND DELAYED CINV IN PATIENTS TREATED WITH MODERATELY EMETOGENIC REGIMENS

When discussing anti-emetic prophylaxis in patients treated with moderately emetogenic chemotherapy (MEC), special attention needs to be given to patients treated with carboplatin

TABLE 2. BSMO recommendations for the prevention of acute and delayed CINV in patients treated with highly emetogenic regimens

Acute phase (day of chemotherapy)	
Four-drug regimen consisting of: • 5-HT3-RA (granisetron, ondansetron, or palonosetron#) • NK-1-RA (aprepitant or netupitant#) • Dexamethasone (12 mg PO or 10 or 20mg IV) • Olanzapine (2.5 mg for AC-based chemotherapy in breast cancer patients, individualized choice between 2.5, 5 or 10 mg in other cases) # netupitant and palonosetron are given as a single, fixed-dose combination (Akynzeo®)	
Delayed phase (days 2-4)	
AC-based chemotherapy	*Non-AC-based chemotherapy*
Olanzapine (2.5 mg, days 2-4)	Dexamethasone (8 mg PO or 10mgIV, days 2-4) Olanzapine (2.5 mg, days 2-4)
If aprepitant in acute phase: Aprepitant (80 mg PO on days 2-3)	If aprepitant in acute phase: Aprepitant (80 mg PO on days 2-3)

and oxaliplatin. More recently, also ADCs such as T-DXd and SG have been added to the list of moderately emetogenic agents warranting a more specific anti-emetic strategy.[22]

With respect to carboplatin, the recommendations for CINV prophylaxis are dose dependent, with the MASCC/ESMO guidelines making a distinction between patients receiving carboplatin at a dose with an area under the curve (AUC) ≥ and < 5 (≥ and < 4 in ASCO and NCCN guidelines). In this, a more intensive CINV prophylaxis is recommended for patients receiving the higher carboplatin dose.[8-10] In a post-hoc analysis of a large randomised controlled trial including 401 carboplatin-treated patients, the addition of the NK1-RA rolapitant to dexamethasone and granisetron (5-HT3-RA) significantly increased the rate of patients with a CR (*i.e.*, no emesis and no need for rescue medication), both in the period 24-120 hours after the treatment (82.3% *vs.* 65.6%, p< 0.001) and during the entire 120 hours after the carboplatin administration (80.2% *vs.* 64.6%, p< 0.001).[23] Similarly, also in a randomised controlled trial including 324 gynaecological cancer patients treated with carboplatin (AUC 5-6) and paclitaxel, adding aprepitant to a 5-HT3-RA and dexamethasone led to a significantly lower incidence of CINV (CR rate 61.6% *vs.* 47.3% with placebo, p= 0.0073).[24] In addition to this, two large meta-analyses confirmed the benefit of a three-drug anti-emetic regimen including a 5-HT3-RA, dexamethasone, and a NK1-RA over a combination of 5-HT3-RA and dexamethasone alone in patients treated with (high-dose) carboplatin.[25,26] Based on these findings, a three-drug combination of an NK1-RA, a 5-HT3-RA, and dexamethasone (day one only) is currently the preferred anti-emetic prophylaxis regimen for cancer patients receiving carboplatin with an AUC of ≥5. Of note, there is currently no evidence supporting the use of a NK1-RA in patients receiving carboplatin at a lower dose (AUC <5).[8]

For the prophylaxis of CINV in patients treated with non-carboplatin MEC, both ASCO and MASCC/ESMO recommend a two-drug combination including single doses of a 5-HT3-RA and dexamethasone given on the first day of chemotherapy.[8,10] Of note, in the MASCC/ESMO guidelines an additional recommendation is made for patients who are treated with an oxaliplatin-based chemotherapy regimen.[8] In fact, for women aged ≤50 years the updated guidelines suggest that an NK1-RA can be added to the two-drug combination.[8] This suggestion is based on the results of two clinical trials. In the SENRI study (N=413), the addition of aprepitant to a 5HT3-RA and dexamethasone significantly improved the CINV control in a cohort of colorectal cancer patients treated with oxaliplatin.[27] Interestingly, a subgroup analysis of this trial revealed that this benefit was mainly driven by female patients.[28] In a second randomised controlled trial, 248 women (age ≤50 years) with gastrointestinal cancer who were treated with FOLFOX (*i.e.*, oxaliplatin-based) or FOLFIRI were randomised to anti-emetic prophylaxis with palonosetron plus dexamethasone and either aprepitant or placebo. Also, in this trial the three-drug regimen proved to be associated with a higher CR rate (no emesis, no rescue medication) 0-120 hours after the start of chemotherapy (87%

TABLE 3. BSMO recommendations for the prevention of acute and delayed CINV in patients treated with moderate emetogenic regimens

Acute phase (day of chemotherapy)	
Carboplatin AUC ≥5 & T-DXd or SG	*Non-carboplatin or Carboplatin AUC <5*
Three-drug regimen consisting of: • 5-HT3-RA (granisetron, ondansetron, or palonosetron#) • NK-1-RA (aprepitant or netupitant#) • Dexamethasone (12 mg PO or 10mgIV) # netupitant and palonosetron are given as a single, fixed-dose combination (Akynzeo®)	Two-drug regimen consisting of: • 5-HT3-RA (granisetron, ondansetron, or palonosetron#) • Dexamethasone (12 mg PO or 10mgIV) A NK-1-RA can be added in women ≤50 years receiving oxaliplatin
Delayed phase (days 2-4)	
Carboplatin AUC ≥5, T-DXd or SG *FOLFOX in women ≤50 years*	*Non-carboplatin or Carboplatin AUC <5*
No prophylaxis Rescue with a dopamine receptor antagonist (alizapride, metoclopramide) can be considered if needed	No prophylaxis Rescue with a dopamine receptor antagonist (alizapride, metoclopramide) can be considered if needed
If aprepitant in acute phase: Aprepitant (80 mg PO on days 2-3)	If aprepitant in acute phase: Aprepitant (80 mg PO on days 2-3)

vs. 66.7%, p< 0.001). A further subgroup analysis of this trial showed that this significant benefit was limited to patients treated with the oxaliplatin-based FOLFOX regimen, while this was not the case in patients treated with FOLFIRI.[29]

A final important novelty in the recommendations for CINV prophylaxis in patients treated with MEC relates to patients treated with T-DXd and SG. As already indicated, the MASCC/ESMO and ASCO guidelines consider these agents to be moderately emetogenic. More specifically, the MASCC/ESMO guidelines, place these agents at the higher end of the MEC spectrum, similar to (high dose) carboplatin. In the absence of dedicated clinical trial data on CINV prophylaxis with these agents it seems wise to also employ the three-drug strategy that is recommended for carboplatin (AUC ≥5) in these patients.[8]

Irrespective of the type of MEC, the use of dexamethasone in the delayed phase is not recommended. The latter is based on the fact that several clinical trials and meta-analyses have demonstrated non-inferiority of one day of dexamethasone compared to a three-day regimen in cancer patients treated with MEC.[20, 26, 30-32] Similarly, there is limited evidence supporting the use of olanzapine in patients treated with MEC.[19] The only published data in this respect come from a Chinese study suggesting better CINV control when olanzapine (5 mg) was added to palonosetron and dexamethasone in female patients with gastrointestinal cancer treated with an oxaliplatin- and irinotecan-containing regimen.[33] Given the limited amount of data, the use of olanzapine is currently not recommended as part of the CINV prophylaxis for patients treated with MEC. For delayed phase nausea and vomiting, a dopamine receptor antagonist, such as metoclopramide or alizapride, can be considered.

A schematic representation of the BSMO recommendations for CINV prevention in patients receiving moderately emetogenic regimens is depicted in *Table 3*.

THE PREVENTION OF ACUTE AND DELAYED CINV IN PATIENTS TREATED WITH LOW OR MINIMAL EMETOGENIC REGIMENS

The international guidelines for acute CINV prophylaxis in patients treated with low emetogenic antineoplastic agents are fairly similar and all recommend the use of a single antiemetic agent (*Table 4*).[8-10] According to the MASCC/ESMO guidelines, these single agent options consist of dexamethasone, a 5-HT3-RA or a dopamine receptor antagonist, such as metoclopramide and alizapride.[8] Also, the dopamine receptor domperidone is sometimes used in this context. However, we must underscore that this agent is associated with a potential QT prolongation and is therefore not the preferred choice.

TABLE 4. BSMO recommendations for the prevention of acute and delayed CINV in patients treated with low emetogenic regimens

Acute phase (day of chemotherapy)	
Standard	Dopamine receptor antagonist (alizapride, metoclopramide) OR 5-HT3-RA (granisetron, ondansetron, or palonosetron)
Optional	Dexamethasone (4-8 mg once)

Acute CINV prophylaxis is not warranted for patients treated with agents with a minimal emetogenic risk. Similarly, no prophylaxis is foreseen for delayed CINV in patients treated with either low- or minimally emetogenic agents (*Table 4*).[8] Importantly, the MASCC/ESMO guidelines recognise that nausea and/or vomiting during a previous course of treatment is a major risk factor for new CINV. Therefore, the guidelines recommend employing an anti-emetic regimen for MEC in patients who experience nausea or vomiting during a previous treatment course with treatment with a low or minimal emetogenic potential.[8]

THE PREVENTION OF (CHEMO) RADIOTHERAPY-INDUCED NAUSEA AND VOMITING

Several observational studies have demonstrated that radiotherapy-induced nausea and vomiting (RINV) often remains undertreated, with only a small proportion of patients receiving anti-emetic prophylaxis.[34,35] The emetic risk of radiotherapy is divided into four risk levels (high, moderate, low, and minimal) and is solely based on the site of radiation.[8] In this respect, total body irradiation comes with a high risk for RINV, while irradiation to the upper abdomen and the craniospinal area is associated with a moderate emetogenic risk. Radiotherapy to the brain, the head and neck area, the thorax, and the pelvis comes with a low emetogenic risk, whereas the risk for RINV is deemed minimal for patients receiving radiotherapy to the breast, or the extremities.

Results of a large meta-analysis published in 2017 show superior efficacy of a 5-HT3-RA compared to other anti-emetic agents in patients receiving total body irradiation and in patients receiving abdominal radiotherapy. A further addition of dexamethasone to a 5-HT3-RA was associated with a (modest) improvement in RINV protection.[36] Due to a lack of clinical trials, the potential for NK1-RA in RINV prophylaxis remains unclear. The resulting recommendations for RINV prophylaxis formulated by MASCC/ESMO are depicted in *Table 5*.[8]

In patients receiving concomitant chemoradiotherapy (CRT), the prophylactic CINV strategy should be steered by the antineoplastic agent with the highest emetic risk (only if the risk of emesis is higher with the systemic therapy than with radiotherapy).[8] Based on the results of the randomised, phase III GAND trial, the updated MASCC/ESMO guidelines formulate a specific recommendation for patients receiving concomitant radiotherapy and weekly cisplatin (40 mg/m^2).[8] In this trial, the addition of the NK1-RA fosaprepitant (day one) to a once weekly anti-emetic regimen of palonosetron (day one) and dexamethasone (days 1-4) significantly increased the rate of patients who were completely emesis free during five weeks of CRT (66% *vs.* 49% with placebo; p< 0.008).[37] Inspired by this trial, the updated MASCC/ESMO guidelines have embraced the 'GAND-regimen' as the preferred regimen to prevent nausea and vomiting in patients receiving concomitant radiotherapy and weekly cisplatin (40 mg/m^2).[8] Of note, this regimen was only evaluated in patients with cervical cancer, and it is unclear to what extent the conclusions of this study can be extrapolated to other cancer types.

REMAINING CHALLENGES

Despite the existing guidance for the management of CINV, clinicians may still encounter some challenging situations in their clinical practice.

CINV PROPHYLAXIS IN PAEDIATRIC AND ADOLESCENT PATIENTS

Due to a paucity of clinical trial data on CINV prophylaxis in paediatric and adolescents patients, it is difficult to formulate strong guidelines for these patients. For paediatric/adolescent patients treated with HEC, the ASCO and MASCC/ESMO guidelines for acute CINV prophylaxis recommend a three-drug regimen consisting of an NK1-RA, an 5HT3-RA and dexamethasone. If a NK1-RA is unavailable, a combination of a 5HT3-RA and dexamethasone is an alternative option. In patients for whom dexamethasone is not an option,

TABLE 5. MASCC/ESMO guidelines for the prevention of RINV[8]

Radiotherapy		
Risk category	*Irradiated area*	*Anti-emetic guideline*
High	Total body irradiation	Prophylaxis with 5HT3-RA + dexamethasone
Moderate	Upper abdomen, craniospinal	Prophylaxis with 5HT3-RA (+ dexamethasone)
Low	Brain	Rescue with dexamethasone
	Head & Neck, thorax, pelvis	Rescue with dexamethasone, dopamine-RA, or 5HT3-RA
Minimal	Breast, Extremities	
Chemoradiotherapy		
Concurrent CRT		antiemetic prophylaxis according to chemotherapy-related antiemetic guidelines of the corresponding risk category (unless emesis risk of RT is higher than that of chemotherapy)
Concomitant radiotherapy + weekly cisplatin (40 mg/m^2)		Acute phase: 5-HT3-RA+NK1-RA+dexamethasone 12mg PO or 10mgIV(day 1) Delayed phase: dexamethasone 8mg PO (days 2-4)

the guidelines recommend palonosetron + an NK1-RA (only aprepitant is endorsed by MASCC/ESMO).[10,38] For children and adolescents receiving MEC, both guidelines recommend a combination of a 5HT3-RA and dexamethasone. If dexamethasone is not an option, a combination of a 5HT3-RA and an NK1-RA can be considered (again only aprepitant in MASCC/ESMO guidelines). In the case of LEC, ASCO and MASCC/ESMO recommend single agent CINV prophylaxis with a 5HT3-RA. Neither set of guidelines provides recommendations for delayed CINV prevention in children and adolescents treated with HEC, MEC, or LEC.[10,38]

CINV PREVENTION IN PATIENTS RECEIVING MULTIDAY CHEMOTHERAPY

Another challenge in clinical practice consists of CINV management in patients receiving multiday chemotherapy. Recently, a Chinese, randomised-controlled, phase III trial specifically addressed CINV prophylaxis in patients receiving chemotherapy over multiple days. This trial included a total of 349 patients with solid tumours who were scheduled to receive three days of cisplatin-based chemotherapy.[39] In this study, adding olanzapine (5 mg daily for five days) to a three-drug anti-emetic regimen consisting of fosaprepitant and ondansetron on day one and dexamethasone on days 1-5, resulted in significantly higher CR rate (no vomiting or rescue medication on days 1-8) (69% *vs.* 58% with placebo, $p< 0.031$).[39] These findings formed the basis for MASCC/ESMO to recommend a four-drug regimen for CINV prophylaxis in patients receiving multiday, cisplatin-based chemotherapy.[8] The recommended regimen consists of a 5HT3-RA (once daily on the days of chemotherapy), dexamethasone (once daily from day one, until two days post chemotherapy), aprepitant (125 mg on day one and 80 mg once daily from day two until two days post chemotherapy) and olanzapine (5 mg daily from day one and until two days post chemotherapy). In Belgium, however, the use of this regimen is hampered by the reimbursement criteria for aprepitant which only allow reimbursement of one package per chemotherapy cycle.

Alternative (reimbursed) CINV prophylaxis regimens for patients receiving multiday chemotherapy are depicted in *table 6*. In these alternatives, a 5HT3-RA (*e.g.*, ondansetron) is only used on day one. For selected cases, however, one may also consider its use on every day of the chemotherapy. When opting for the latter it is important to acknowledge the potential QT-prolonging and constipating effect of this drug class (ondansetron has a higher risk for QTc prolongation than palonosetron).

TABLE 6. BSMO recommendations for CINV prophylaxis in patients receiving multiday chemotherapy

2-3 days of chemotherapy	
Day 1	*Day 2 (+3)*
Once daily, 30 min before chemotherapy	
5-HT3-RA + NK-1-RA + Dexamethasone 10mg IV	Dexamethasone 10mgIV
Optional: Olanzapine (dose t.b.d.)	

5 days of chemotherapy			
Day 1	*Day 2-3*	*Day 4*	*Day 5*
Once daily, 30 min before chemotherapy			
5-HT3-RA + NK-1-RA + Dexamethasone 10mgIV	Dexamethasone 10mgIV	Dexamethasone 10mgIV + palonosetron (optional)	Dexamethasone 10mgIV
Optional: Olanzapine (dose t.b.d.)			

MANAGING BREAKTHROUGH NAUSEA AND VOMITING

Notwithstanding an excellent efficacy of the available anti-emetic regimens in most patients, some may still experience nausea and/or vomiting despite prophylaxis (breakthrough CINV). Given the challenging nature of breakthrough CINV, it is preferable to use maximally effective anti-emetics prophylactically rather than withholding more effective anti-emetics for later use at the time of anti-emetic failure.[8] The general principle in dealing with breakthrough emesis is to use an agent from a different drug-class than the one(s) used in the prophylactic phase. In this respect, the strongest evidence is available for the use of olanzapine in patients who did not receive it during prophylaxis. This approach is supported by a meta-analysis from 2021 that identified olanzapine (10 mg for three days) as a tolerable and effective rescue anti-emetic for patients who did not receive it during prophylaxis.[40] Importantly, if the chosen CINV prophylaxis strategy failed to protect the patient during a first chemotherapy cycle, the anti-emetic strategy needs to be reassessed prior to the next chemotherapy cycle.

REFERENCES

1. Kuchuk I, Bouganim N, Beusterien K, et al. Patient perceptions about potential side effects and benefits from chemotherapy agents. Journal of Clinical Oncology. 2013;31:6595.
2. Matzka M, Köck-Hódi S, Jahn P, et al. Relationship among symptom clusters, quality of life, and treatment-specific optimism in patients with cancer. Support Care Cancer. 2018;26(8):2685-93.
3. Ballatori E, Roila F. Impact of nausea and vomiting on quality of life in cancer patients during chemotherapy. Health Qual Life Outcomes. 2003;1:46.
4. Navari RM. Treatment of Breakthrough and Refractory Chemotherapy-Induced Nausea and Vomiting. Biomed Res Int. 2015;2015:595894.
5. Gao J, Zhao J, Jiang C, et al. Olanzapine (5 mg) plus standard triple anti-emetic therapy for the prevention of multiple-day cisplatin hemotherapy-induced nausea and vomiting: a prospective randomised controlled study. Support Care Cancer. 2022;30(7):6225-32.
6. Aapro M, Scotté F, Escobar Y, et al. Practice Patterns for Prevention of Chemotherapy-Induced Nausea and Vomiting and Antiemetic Guideline Adherence Based on Real-World Prescribing Data. Oncologist. 2021;26(6):e1073-e82.
7. Navari RM, Ruddy KJ, LeBlanc TW, et al. Impact of Addition of Carboplatin AUC ≥ 4 to Antiemetic Guidelines for Triple Antiemetic Prophylaxis: A Gap in Quality of Care, Guideline Adoption, and Avoiding Acute Care. JCO Oncol Pract. 2020;16(2):e132-e8.
8. Herrstedt J, Clark-Snow R, Ruhlmann CH, et al. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO Open. 2024;9(2):102195.
9. Berger M, Ettinger D, Agarwal R, et al. Antiemesis Version 1.2024. 2024.
10. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. Journal of Clinical Oncology. 2020;38(24):2782-97.
11. Roila F, Hesketh PJ, Herrstedt J. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol. 2006;17(1):20-8.
12. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27(suppl 5):v119-v33.

KEY MESSAGES FOR CLINICAL PRACTICE

1. Nausea and vomiting continue to be some of the more dreaded side effects of anticancer therapy.
2. The most important factor determining the likelihood of acute or delayed CINV during anticancer therapy consists of the intrinsic emetogenicity of the agent that is being administered.
3. The preferred treatment for CINV prophylaxis in patients treated HEC consists of a four-drug combination of a NK1-RA, a 5-HT3-RA, dexamethasone, and olanzapine.
4. For the prophylaxis of CINV in patients treated with non-carboplatin MEC, a two-drug combination including single doses of a 5-HT3-RA and dexamethasone given on the first day of chemotherapy is recommended.
5. A more intensive CINV prophylaxis is recommended for patients receiving high-dose carboplatin, T-DXd, SG or oxaliplatin-based chemotherapy (in women ≤50 years old).
6. Research efforts are underway to reduce the use of corticosteroids and high doses of olanzapine in the CINV prophylaxis for patients treated with HEC, or MEC.
7. CINV prophylaxis in patients receiving low emetogenic antineoplastic agents consists of single anti-emetic therapy with dexamethasone, a 5-HT3-RA, or a dopamine receptor antagonist.
8. CINV prophylaxis is not warranted for patients treated with agents with a minimal emetogenic risk.
9. Be aware that netupitant/palonosetron administration leads to higher exposure of etoposide with 21% and docetaxel with 37%.
10. The emetic risk of radiotherapy depends on the site of radiation.
11. In patients receiving concomitant (CRT), the prophylactic CINV strategy should be steered by the anti-neoplastic agent with the highest emetic risk.
12. CINV prevention in adolescent patients and in patients treated with multiday chemotherapy remains challenging.
13. Given the challenging nature of breakthrough CINV, it is preferable to use maximally effective anti-emetics prophylactically rather than withholding more effective anti-emetics for later use at the time of anti-emetic failure.

13. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting. N Engl J Med. 2016;375(2):134-42.
14. Hashimoto H, Abe M, Tokuyama O, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(2):242-9.
15. Bajpai J, Kapu V, Rath S, et al. Low-dose versus standard-dose olanzapine with triple antiemetic therapy for prevention of highly emetogenic chemotherapy-induced nausea and vomiting in patients with solid tumours: a single-centre, open-label, non-inferiority, randomised, controlled, phase 3 trial. Lancet Oncol. 2024;25(2):246-54.
16. Rivas JC, Galindo AJ, Zambrano LF, et al. Risk of corrected QT interval prolongation in patients receiving antipsychotics. Int Clin Psychopharmacol. 2024.
17. Kinomura M, Iihara H, Fujii H, et al. Effect of Mirtazapine for the Prevention of Nausea and Vomiting in Patients With Thoracic Cancer Receiving Platinum-based Chemotherapy. Anticancer Res. 2023;43(3):1301-7.
18. Ito Y, Tsuda T, Minatogawa H, et al. Placebo-Controlled, Double-Blinded Phase III Study Comparing Dexamethasone on Day 1 With Dexamethasone on Days 1 to 3 With Combined Neurokinin-1 Receptor Antagonist and Palonosetron in High-Emetogenic Chemotherapy. J Clin Oncol. 2018;36(10):1000-6.

19. Celio L, Bonizzoni E, Zattarin E, et al. Impact of dexamethasone-sparing regimens on delayed nausea caused by moderately or highly emetogenic chemotherapy: a meta-analysis of randomised evidence. BMC Cancer. 2019;19(1):1268.
20. Okada Y, Oba K, Furukawa N, et al. One-Day Versus Three-Day Dexamethasone in Combination with Palonosetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Systematic Review and Individual Patient Data-Based Meta-Analysis. Oncologist. 2019;24(12):1593-600.
21. Minatogawa H, Izawa N, Shimomura K, et al. Dexamethasone-sparing on days 2-4 with combined palonosetron, neurokinin-1 receptor antagonist, and olanzapine in cisplatin: a randomised phase III trial (SPARED Trial). Br J Cancer. 2024;130(2):224-32.
22. Kennedy SKF, Goodall S, Lee SF, et al. 2020 ASCO, 2023 NCCN, 2023 MASCC/ESMO, and 2019 CCO: a comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Support Care Cancer. 2024;32(5):280.
23. Hesketh PJ, Schnadig ID, Schwartzberg LS, et al. Efficacy of the neurokinin-1 receptor antagonist rolapitant in preventing nausea and vomiting in patients receiving carboplatin-based chemotherapy. Cancer. 2016; 122(15):2418-25.
24. Yahata H, Kobayashi H, Sonoda K, et al. Efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting with a moderately emetogenic chemotherapy regimen: a multicenter, placebo-controlled, double-blind, randomised study in patients with gynecologic cancer receiving paclitaxel and carboplatin. Int J Clin Oncol. 2016;21(3):491-7.
25. Zhang Y, Hou X, Zhang R, et al. Optimal prophylaxis of chemotherapy-induced nausea and vomiting for moderately emetogenic chemotherapy: a meta-analysis. Future Oncol. 2018;14(19):1933-41.
26. Jordan K, Warr DG, Hinke A, et al. Defining the efficacy of neurokinin-1 receptor antagonists in controlling chemotherapy-induced nausea and vomiting in different emetogenic settings-a meta-analysis. Support Care Cancer. 2016;24(5):1941-54.
27. Nishimura J, Satoh T, Fukunaga M, et al. Combination antiemetic therapy with aprepitant/fosaprepitant in patients with colorectal cancer receiving oxaliplatin-based chemotherapy (SENRI trial): a multicentre, randomised, controlled phase 3 trial. Eur J Cancer. 2015;51(10):1274-82.
28. Takemoto H, Nishimura J, Komori T, et al. Combination antiemetic therapy with aprepitant/fosaprepitant in patients with colorectal cancer receiving oxaliplatin-based chemotherapy in the SENRI trial: analysis of risk factors for vomiting and nausea. Int J Clin Oncol. 2017;22(1):88-95.
29. Wang DS, Hu MT, Wang ZQ, et al. Effect of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Women: A Randomised Clinical Trial. JAMA Netw Open. 2021;4(4):e215250.
30. Komatsu Y, Okita K, Yuki S, et al. Open-label, randomised, comparative, phase III study on effects of reducing steroid use in combination with Palonosetron. Cancer Sci. 2015;106(7):891-5.
31. Furukawa N, Kanayama S, Tanase Y, et al. Palonosetron in combination with 1-day versus 3-day dexamethasone to prevent nausea and vomiting in patients receiving paclitaxel and carboplatin. Support Care Cancer. 2015;23(11):3317-22.
32. Watanabe D, Iihara H, Fujii H, et al. One-Day Versus Three-Day Dexamethasone with NK1RA for Patients Receiving Carboplatin and Moderate Emetogenic Chemotherapy: A Network Meta-analysis. Oncologist. 2022;27(6):e524-e32.
33. Shen J, Zhao J, Jin G, et al. A prospective randomised controlled clinical trial investigating the efficacy of low-dose olanzapine in preventing nausea and vomiting associated with oxaliplatin-based and irinotecan-based chemotherapy. J Cancer Res Clin Oncol. 2024;150(5):283.
34. Enblom A, Bergius Axelsson B, Steineck G, et al. One third of patients with radiotherapy-induced nausea consider their antiemetic treatment insufficient. Support Care Cancer. 2009;17(1):23-32.
35. Maranzano E, De Angelis V, Pergolizzi S, et al. A prospective observational trial on emesis in radiotherapy: analysis of 1020 patients recruited in 45 Italian radiation oncology centres. Radiother Oncol. 2010;94(1):36-41.
36. Li WS, van der Velden JM, Ganesh V, et al. Prophylaxis of radiation-induced nausea and vomiting: a systematic review and meta-analysis of randomised controlled trials. Ann Palliat Med. 2017;6(2):104-17.
37. Ruhlmann CH, Christensen TB, Dohn LH, et al. Efficacy and safety of fosaprepitant for the prevention of nausea and emesis during 5 weeks of chemoradiotherapy for cervical cancer (the GAND-emesis study): a multinational, randomised, placebo-controlled, double-blind, phase 3 trial. Lancet Oncol. 2016;17(4):509-18.
38. Dupuis LL, Sung L, Molassiotis A, et al. 2016 updated MASCC/ESMO consensus recommendations: Prevention of acute chemotherapy-induced nausea and vomiting in children. Support Care Cancer. 2017;25(1):323-31.
39. Zhao Y, Yang Y, Gao F, et al. A multicenter, randomised, double-blind, placebo-controlled, phase 3 trial of olanzapine plus triple antiemetic regimen for the prevention of multiday highly emetogenic chemotherapy-induced nausea and vomiting (OFFER study). EClinicalMedicine. 2023;55:101771.
40. Chow R, Herrstedt J, Aapro M, et al. Olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting: a systematic review, meta-analysis, cumulative meta-analysis and fragility assessment of the literature. Support Care Cancer. 2021;29(7):3439.