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SPECIAL ARTICLE

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

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INTRODUCTION

Nausea and vomiting are still considered to be two of the most troublesome adverse events (AEs) for patients treated with antineoplastic therapy. To optimise the utility of available antiemetic prophylaxis, updated reviews of the relevant literature and evidence-based guideline recommendations are crucial.

The European Society for Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) completed the fourth Consensus Conference on Antiemetics for the prevention of nausea and vomiting in patients with cancer in Copenhagen in June 2015.[1] This article is an update of the 2015 guidelines.

METHODOLOGY

The methodology for the guideline process is described in detail in the 2010 publication.[2] The reporting of the literature search followed the PRISMA criteria for systematic reviews.[3] The current update of the recommendations includes studies published from 1 June 2015 to 31 January 2023 (for details of the literature search and reporting, refer to the paragraphs reviewing the specific topic).

The Consensus Committee consisted of 34 multidisciplinary, health care professionals with expertise in antiemetic research (physicians, nurses, pharmacists and pharmacologists) and three patient advocates representing a total of 18 countries and five continents.

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Table 1. Topics defined for the MASCC–ESMO Antiemetic Guideline Update 2023

Working group	Topic
I	Emetic risk classification and evaluation of the emetogenicity of antineoplastic agents.
II	Prevention of acute and delayed nausea and vomiting induced by highly emetogenic chemotherapy.
III	Prevention of acute and delayed nausea and vomiting induced by moderately emetogenic chemotherapy.
IV	Prevention of acute and delayed nausea and vomiting induced by chemotherapy of low or minimal emetic risk.
V	Prevention of nausea and vomiting in patients treated with high-dose chemotherapy, multiple-day chemotherapy or those with breakthrough nausea and vomiting.
VI	Integrative and non-pharmacological therapies for the management of treatment-related nausea and vomiting.
VII	Prevention of radiotherapy- and chemoradiotherapy-induced nausea and vomiting.

ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer.

To change a 2015 recommendation or for a new guideline recommendation to be accepted, a consensus of at least 67% of the expert panellists was needed. The panel considered changes of $\geq$10% to be sufficient to warrant the changing of a 2015 recommendation. Levels of evidence (I-V) and grades of recommendation (A-E) are given according to the adapted version of the grading of the Infectious Diseases Society of America.[4]

In order to update the recommendations, seven working groups (WGs) were established, each including five to eight members of the Consensus Committee. The topics are defined in Table 1.

All WGs presented preliminary guideline updates within their specific area of antiemetic research at a consensus conference in June 2022. More mature guideline updates were presented, discussed and if necessary modified at five subsequent virtual meetings with the participation of all Consensus Committee members.

EMETIC RISK CLASSIFICATION AND EVALUATION OF THE EMETOGENICITY OF ANTINEOPLASTIC AGENTS

It remains a challenge to accurately define the emetic risk associated with antineoplastic agents. The data on emesis in various trials of anticancer agents are usually highly heterogeneous [different tumour types, advanced versus non-advanced disease, systemic treatment naive or previously treated, used alone or in combination with other agents, different antiemetic prophylaxis if given or not reported, different reporting systems such as Common Terminology Criteria of AEs (CTCAE) all grades versus only grade 3-4].[5,6] Oral anticancer agents provide additional challenges. Most oral agents tend to be used in extended regimens of daily use rather than the single bolus administration schedule commonly employed with intravenous (i.v.) agents. As these agents are typically administered continuously over protracted periods, traditional concepts of acute and delayed nausea and vomiting lose their relevance in these settings.[5,7]

The MASCC–ESMO Consensus Committee classified the emetogenicity of the identified new antineoplastic agents based on non-systematic reviews of randomised controlled trials (RCTs), analysis of product labelling, evaluation of emetic classification in other international guidelines and informal consensus. The emetogenic classification system for oral anticancer agents was revised into two emetic risk categories (minimal-low, moderate-high) to be consistent with the system reported by the American Society of Clinical Oncology (ASCO) in their 2020 guideline update.[5] The previously employed four emetic risk classification categories for intravenously administered antineoplastic agents were retained for this update (Table 2).

From 1 June 2015 to 31 January 2023, 107 new antineoplastic agents (44 intravenously administered and 63 orally administered agents) were identified. The reported incidence of vomiting varied significantly across studies for many agents, especially oral anticancer agents.

The i.v. anticancer agents were classified as being at minimal, low, moderate or high emetic risk in accordance with the summarised vomiting rates (Table 3).

Oral anticancer agents were placed into one of two emetic categories: minimal-low risk and moderate-high risk (Table 4). Of note, the emetic risk classification only refers to adult patients.

The reported incidence of vomiting with three newly added antineoplastic agents (sacituzumab–govitecan, trastuzumab–deruxtecan and selinexor) deserves special mention. Based on the literature search, the two intravenously administered agents (sacituzumab–govitecan and trastuzumab–deruxtecan) warrant classification on the higher end of the moderate emetic risk category analogous to carboplatin (Table 3). The oral agent selinexor warrants classification on the higher end of the moderate-high risk category (Table 4).

Table 2. MASCC–ESMO emetic risk groups 2023

Intravenous agents[a]	Emetic risk	Oral agents[b]	Emetic risk
High	Risk in nearly all patients (>90%)	High/moderate	Risk in 30% or more of patients
Moderate	Risk in 30%-90% of patients		
Low	Risk in 10%-30% of patients	Low/minimal	Risk in fewer than 30% of patients
Minimal	Fewer than 10% at risk		

ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer.
[a]Proportion of patients experiencing emesis in the first 24 h after start of intravenous antineoplastic agents in the absence of effective antiemetic prophylaxis. Nausea is not part of the risk classification.
[b]The emetic potential of the oral anticancer agents is based on a full course of therapy and not a single dose within the first cycle.

Table 3. Emetogenic potential of single intravenous antineoplastic agents

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

[a]The combination of an anthracycline and cyclophosphamide in patients with breast cancer is highly emetogenic.
[b]Emetic potential appears to be at the high end of the moderate category.
[c]Emetic potential appears to be at the high end of the moderate category, most closely resembling that of carboplatin.
[d]No direct evidence found for temozolomide intravenous; as all sources indicate a similar safety profile of oral temozolomide, the classification was based on oral temozolomide.
[e]Classification refers to individual evidence from paediatric trials.

Table 4. Emetogenic potential of single oral antineoplastic agents[a]

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

[a]Classified emetic potential of oral agents based on a full course of therapy and not a single dose within the first cycle.
[b]Emetic potential appears to be at the high end of the moderate category.

PREVENTION OF ACUTE AND DELAYED NAUSEA AND VOMITING INDUCED BY HIGHLY EMETOGENIC CHEMOTHERAPY

High emetic risk (>90% risk of vomiting in the first 24 h after administration) antineoplastic agents administered intravenously include cisplatin, carmustine, dacarbazine, mechlorethamine, streptozocin and cyclophosphamide in doses of $\geq$1500 mg/m^2 and the combination of

cyclophosphamide and an anthracycline in women with breast cancer (Table 3). This is unchanged from the 2015 guidelines.[6]

Very few data on the emetic risk potential of orally administered antineoplastic agents exist, and the emetic risk potential refers to the risk during the entire treatment period rather than the first 24 h. As mentioned above, oral agents are classified into two categories only. Data are very limited concerning prophylaxis of nausea and vomiting in patients treated with one of these agents, and consequently, no precise recommendations can be given. In general, only on-demand antiemetics are recommended.

The literature search of high emetic risk i.v. antineoplastic agents was completed from 1 June 2015 through 31 January 2023 and disclosed 1058 references of which 46 new references were identified as relevant for the update. Only RCTs, systematic reviews and meta-analyses were considered. The main topics identified were as follows: (i) steroid-sparing regimens, (ii) olanzapine-containing regimens and (iii) other issues such as comparative studies of antiemetics from the same drug class effect, and safety of i.v. neurokinin $(NK)_1$-receptor antagonists (RAs) and studies of potentially new antiemetics.

Steroid-sparing regimens in anthracycline—cyclophosphamide chemotherapy

One RCT[8] and two meta-analyses[9,10] published since 2015 were identified.

A randomised, double-blinded, placebo-controlled, non-inferiority trial included 396 patients receiving cisplatin-based ($\geq$50 mg/m^2) or anthracycline—cyclophosphamide (AC) chemotherapy (ChT). All patients received palonosetron 0.75 mg i.v. and dexamethasone (DEX) 12 mg i.v. day 1 plus aprepitant 125 mg by mouth (p.o.) day 1 followed by 80 mg p.o. days 2-3 or fosaprepitant 150 mg i.v. day 1. Patients were randomised to placebo on days 2-3 or to DEX 8 mg on days 2-3. Stratification for age and ChT (cisplatin versus AC) was done. The primary endpoint was complete response (CR) in the overall period, defined as no emetic episodes and no use of rescue medication on days 1-5 after ChT, and the non-inferiority margin was 15%. CR was 46.9% (3 days of DEX) versus 44% (1 day of DEX) [95% confidence interval (CI) −12.6% to 6.8%, $P = 0.007$]. A subgroup analysis of patients receiving AC confirmed non-inferiority of the 1-day DEX regimen, whereas non-inferiority was not confirmed in patients receiving cisplatin-based ChT.

A meta-analysis from 2019 included eight studies and concluded that a single day of DEX is as good as a 3-day regimen in patients receiving AC ChT [or moderately emetogenic chemotherapy (MEC)].[9] Another systematic review and meta-analysis from 2019 included five studies that used a non-inferiority margin of −8% and also confirmed non-inferiority of a 1-day DEX regimen compared with a 3-day DEX regimen in AC (and MEC) patients.[10]

It is concluded that in combination with a 5-hydroxytryptamine$_3$ (5-HT$_3$)-RA and an NK_1-RA, a 1-day regimen of DEX is as good as a 3-day regimen in patients treated with AC ChT.

Steroid-sparing regimens in non-AC highly emetogenic ChT

Celio et al. investigated ChT-naive patients who received their first course of cisplatin-based ($\geq$70 mg/m^2) ChT.[11] They used a randomised, open, non-inferiority design. All patients received oral netupitant—palonosetron (NEPA; netupitant 300 mg plus palonosetron 0.5 mg) and DEX 12 mg i.v. before ChT and were randomised to no DEX on days 2-4 (DEX1), DEX 4 mg p.o. once daily on days 2-3 (DEX3) or DEX 4 mg p.o. twice daily on days 2-4 (DEX4). The primary endpoint was CR (defined as above) from 0 to 120 h after the start of cisplatin. Non-inferiority was confirmed for the DEX1 arm compared with the DEX4 arm (95% CI −12.3% to 15%). It should be noted that only 33% of the patients were women and that the overall CR in the control arm was lower (75%) than estimated in the patient sample size calculation (90%).

None of the above studies included olanzapine as an antiemetic. The SPARED study[12] investigated a DEX-sparing regimen including olanzapine, but has only been presented in abstract form to date (September 2023).

In conclusion, the data of steroid-sparing regimens in non-AC highly emetogenic ChT (HEC) are not as clear as those for AC ChT, and the recommendation of a 3- to 4-day regimen of dexamethasone stands.

Olanzapine-containing regimens in AC and non-AC HEC

Six randomised, double-blind, controlled trials[13-18]; one randomised, open, controlled trial[19]; and two systematic reviews[5,20] were identified.

Two large phase III studies investigated the outcomes of adding olanzapine to a three-drug antiemetic regimen of a 5-HT$_3$-RA, DEX and an NK_1-RA.[14,16] Both trials were randomised, double-blind, placebo-controlled and included a high number of patients receiving either AC ChT or cisplatin-based ChT[16] or cisplatin-based ChT only.[14]

Navari et al.[16] compared an oral dose of olanzapine 10 mg once daily for 4 days with placebo in patients receiving cisplatin-based ($\geq$70 mg/m^2) or AC ChT. All patients also received a 5-HT$_3$-RA plus DEX plus aprepitant or fosaprepitant. The study included 380 patients and stratification for sex, ChT (cisplatin-based versus AC) and the specific 5-HT$_3$-RA was done.[16] No nausea [defined as 0 mm on a visual analogue scale (VAS) during the overall assessment period from 0 to 120 h after ChT] was the primary endpoint. The no-nausea rates were significantly higher in the olanzapine group than in the placebo group, with no-nausea rates of 74% versus 45% (0-24 h, $P = 0.002$), 42% versus 25% (24-120 h, $P = 0.002$) and 37% versus 22% (0-120 h, $P = 0.002$). Furthermore, CR rates (defined as no emetic episodes and no need of rescue medication) were significantly higher in the olanzapine group (86% versus 65%, 67% versus 52% and 64% versus

41% in the acute, delayed and overall phase, respectively). Sedation was more frequent in the olanzapine group, but both antiemetic regimens were well tolerated.

Hashimoto et al. compared a single oral dose of olanzapine 5 mg for 4 days with placebo in 705 patients receiving cisplatin-based ($\geq$50 mg/m^2) ChT. All patients also received palonosetron (0.75 mg $\times$ 1 i.v.), DEX and aprepitant/fosaprepitant[14] and were stratified for sex, dose of cisplatin and age. The primary endpoint was CR in the delayed phase (24-120 h after cisplatin), obtained by a significantly higher number of patients treated with olanzapine than with placebo (79%, 95% CI 75% to 83% versus 66%, 95% CI 61% to 71%, $P < 0.0001$). Furthermore, the number of patients obtaining complete control (defined as CR, no more than mild nausea) and total control (defined as CR, no nausea) was also significantly higher in the olanzapine group. Sedation was not significantly more frequent in the olanzapine group.

The 5-mg dose of olanzapine was also investigated in a randomised, double-blind, placebo-controlled study ($n = 208$) in ChT-naive patients with breast cancer receiving four cycles of neoadjuvant or adjuvant AC (90%) or cyclophosphamide (non-anthracycline)-based ChT.[13] All patients, in addition to olanzapine or placebo, received ondansetron—DEX—aprepitant. Olanzapine significantly reduced the number of patients reporting nausea during all four cycles (27.7% versus 41.3%, $P < 0.001$), whereas the number of vomiting episodes was not statistically significantly different. Mild sedation was more frequent in the olanzapine group (54.1% versus 40.8%, $P < 0.001$).

Another randomised but open-label study ($n = 120$) in ChT-naive breast cancer patients receiving neoadjuvant or adjuvant AC ChT compared aprepitant—ondansetron—DEX with or without the addition of olanzapine 10 mg p.o. once daily for 5 days.[19] The authors concluded that the addition of olanzapine increased the number of patients with CR (no vomiting and no use of rescue medication), the rates of no nausea (VAS <5 mm) and no significant nausea (nausea VAS <25 mm).

Mild sedation is a frequent AE of olanzapine but can be troublesome in older patients. Therefore, some studies have used a 5-mg daily dose[14,21] instead of the more frequently investigated dose of 10 mg daily,[16,19] and some studies have even dosed the 5 mg at bedtime to reduce the risk of sedation.[14] A few studies have compared 5 mg and 10 mg of olanzapine,[15,17,18] but unfortunately, none of these studies used guideline-recommended methodology or included a sufficient number of patients in order to conclude the benefits and harms of 5 mg versus 10 mg. Based on the above studies it is now recommended that olanzapine is included as a fixed component of the antiemetic regimen in both AC- and non-AC HEC, although issues of dosage and duration of olanzapine treatment remain.

Other issues in HEC

Comparison of different 5-HT3-RAs. In a single-blind, non-inferiority study, 279 patients were treated with cisplatin-based or AC-based ChT. All patients received aprepitant (on days 1-3) and DEX (on days 1-4) and were randomised to ramosetron or palonosetron on day 1. The antiemetic efficacy of ramosetron was non-inferior to palonosetron, and no differences in AEs were observed.[22] In another single-blind, non-inferiority study, 299 patients received cisplatin-based or AC-based ChT, and all received aprepitant—DEX and were randomised to ramosetron or ondansetron on day 1. Ramosetron was non-inferior to ondansetron[23]; however, more women were allocated to the ondansetron arm, which may have led to a misinterpretation of results.

Two randomised, double-blind studies compared the antiemetic effect of granisetron and palonosetron in patients treated with cisplatin-based[24] and AC ChT,[25] respectively. In the first study,[24] 842 patients treated with cisplatin-based ($\geq$50 mg/m^2) ChT received aprepitant (on days 1-3) and DEX (on days 1-4) for antiemetic prophylaxis and were randomised to palonosetron or granisetron (on day 1). The primary endpoint (CR in the first 120 h after the start of cisplatin) was not statistically significantly different between palonosetron and granisetron [65.7% versus 59.1%, 95% CI 1.35 (0.99-1.82), $P = 0.0539$]. A number of secondary endpoints favoured palonosetron in the delayed phase, but differences were all <10%. In the second study,[25] 326 patients were treated with AC ChT and all received DEX (on days 1-3) and fosaprepitant (on day 1) and were randomised to granisetron versus palonosetron (on day 1). The primary endpoint (CR 24-120 h after ChT) did not differ significantly between the two antiemetic therapies. Furthermore, no differences in acute CR (0-24 h) or overall CR (0-120 h) were seen.

In an open-label trial, transdermal granisetron was non-inferior to i.v. ondansetron, when both were combined with DEX—aprepitant in patients treated with HEC.[26]

A recently published systematic review and meta-analysis[27] included 12 studies. The authors concluded that palonosetron was superior to granisetron, but in a subanalysis of only three studies including an NK_1-RA, this advantage disappeared except for a minor advantage of palonosetron in the delayed phase. It should be noted that olanzapine was not included in the above studies or the systematic review.

New studies of i.v. NK_1-RAs and comparison of different NK_1-RAs. An injectable emulsion of rolapitant was approved by the Food and Drug Administration in 2017, but due to serious hypersensitivity reactions,[28] the rolapitant emulsion approval was withdrawn in January 2021.

Fosaprepitant induces injection-site reactions (ISRs) in a small number of patients, particularly those receiving AC-based ChT. Another i.v. formulation of aprepitant (HTX-019, an injectable emulsion of aprepitant free of polysorbate 80) has a lower incidence of ISRs.[29,30]

Fosaprepitant was already proven non-inferior to aprepitant and described in the 2016 guidelines. Non-inferiority was recently confirmed in a large study in

Chinese patients receiving HEC, primarily cisplatin-based ChT.[31]

Two different doses of fosnetupitant were compared with placebo in a randomised, double-blind, phase II study, including 584 patients treated with cisplatin-based (>70 mg/m^2) ChT.[32] All patients received palonosetron–DEX. The high dose of fosnetupitant (235 mg) significantly improved the antiemetic effect of palonosetron–DEX compared with placebo and this dose was chosen for phase III studies.

Schwartzberg and colleagues compared i.v. NEPA (fosnetupitant and i.v. palonosetron) with oral NEPA both combined with DEX in two randomised, double-blind studies in patients receiving cisplatin-based (n = 404) and AC-based (n = 402) ChT, respectively.[33,34] No significant differences between i.v. and oral NEPA were detected regarding the antiemetic efficacy or safety.

Three studies compared a (fos)netupitant-based regimen against a (fos)aprepitant-based antiemetic regimen.[35-37]

In a large randomised, double-blind, non-inferiority, phase III study (n = 828) oral NEPA–DEX was compared with aprepitant–granisetron–DEX in patients receiving cisplatin-based (≥50 mg/m^2) ChT.[35] Non-inferiority was demonstrated for acute CR (0-24 h), delayed CR (24-120 h), overall CR (0-120 h) and for no emesis, no nausea (<5 mm on a 0- to 100-mm VAS) and no significant nausea (<25 mm) both in the acute, delayed and overall phases.

Another randomised, double-blind, non-inferiority, phase III study (n = 785) compared fosnetupitant with fosaprepitant both combined with palonosetron and DEX in patients receiving cisplatin-based (≥70 mg/m^2) ChT.[36] Non-inferiority was proven for all efficacy endpoints, and no differences in AEs were observed, with the exception of ISR, which was more frequently observed with fosaprepitant. Finally, a small randomised, double-blind, phase III study (n = 102) compared fosnetupitant–palonosetron–DEX with fosaprepitant–palonosetron–DEX in patients treated with AC or epirubicin–cyclophosphamide (EC) ChT.[37] The incidence of treatment-related AEs (TRAEs) was the primary endpoint. No significant differences in TRAEs were seen, except for TRAEs relevant for ISRs more frequently observed in patients treated with fosaprepitant. It should be noted that neither this nor the above two studies compared fosnetupitant with HTX-019 which seems to have a lower risk of ISRs than fosaprepitant.[29,30]

Potentially new antiemetics. The dopamine$_3$-RA, amisulpride, was investigated in a randomised, double-blind, phase II dose-finding trial (n = 318) and improved the effect of ondansetron on delayed nausea and vomiting in patients receiving their first course of cisplatin-based (≥70 mg/m^2) ChT.[38]

Mirtazapine, an atypical tetracyclic antidepressant with affinity for multiple receptors (serotonin, histamine, adrenergic) was investigated in an open-label study (n = 100). Mirtazapine seemed to improve the effect of palonosetron, DEX and aprepitant in delayed emesis in patients who had suffered from delayed emesis in the preceding course of AC or cisplatin-based ChT.[39] Thalidomide was investigated in a randomised, double-blind trial (n = 638) in ChT-naive patients scheduled to receive cisplatin-based (≥50 mg/m^2) or AC/EC ChT.[40] Patients received palonosetron on day 1 and DEX on days 1-4 and were randomised to oral thalidomide 100 mg twice daily on days 1-5 or placebo. Thalidomide significantly improved the rates of CR in the delayed and overall phases (76.9% versus 61.7%, P < 0.001 and 66.1% versus 53.3%, P = 0.001, respectively). Dizziness, constipation, sedation and dry mouth were AEs more frequently observed with thalidomide, whereas insomnia was more frequent in the placebo-treated patients.

Unfortunately none of these studies used guideline-recommended antiemetic therapy in the control arm and consequently cannot be recommended for inclusion in the current guideline update.

Recommendations for high emetic risk ChT

Prevention of acute nausea and vomiting following non-AC ChT of high emetic risk

- A four-drug regimen including single doses of a 5-HT$_3$-RA, dexamethasone, an NK$_1$-RA (aprepitant, fosaprepitant, netupitant, fosnetupitant or rolapitant) and olanzapine given before ChT is recommended [I, A].
  - o Netupitant/fosnetupitant is administered with palonosetron as part of the fixed-dose combination agent NEPA.

Prevention of delayed nausea and vomiting following non-AC ChT of high emetic risk

- In patients receiving non-AC high emetic risk ChT treated with a combination of a 5-HT$_3$-RA, DEX, an NK$_1$-RA and olanzapine to prevent acute nausea and vomiting, dexamethasone–olanzapine on days 2-4 is suggested to prevent delayed nausea and vomiting [II, B].
  - o A few studies have investigated a 1-day dexamethasone regimen as an option in cisplatin with one study demonstrating comparable efficacy between a 1-day and multi-day dexamethasone schedules.
  - o If aprepitant 125 mg is used on day 1, then aprepitant 80 mg × 1 should be administered on days 2 and 3.

Prevention of acute nausea and vomiting following AC-based ChT of high emetic risk

- In women treated with AC-based ChT, a four-drug regimen including single doses of a 5-HT$_3$-RA, dexamethasone, an NK$_1$-RA (aprepitant, fosaprepitant, netupitant, fosnetupitant or rolapitant) and olanzapine given before ChT is recommended [I, A].
  - o This recommendation is based on extensive data in women treated with adjuvant AC for breast cancer.
  - o Netupitant/fosnetupitant is administered with palonosetron as part of the fixed-dose combination agent NEPA.

Prevention of delayed nausea and vomiting following AC-based ChT of high emetic risk

- In women treated with a combination of a 5-HT_3-RA, dexamethasone, an NK_1-RA and olanzapine to prevent acute nausea and vomiting, olanzapine on days 2-4 is suggested to prevent delayed nausea and vomiting [II, B].
  - o This recommendation is based on extensive data in women treated with adjuvant AC for breast cancer.
  - o If aprepitant 125 mg is used on day 1, then aprepitant 80 mg × 1 should be administered on days 2 and 3.

Dose and schedule of olanzapine in the prevention of acute and delayed nausea and vomiting following ChT of high emetic risk

- The best investigated dose is 10 mg. 5 mg is superior to placebo, but it is unknown if it is as effective as 10 mg, because no robust studies have compared the 5 mg and 10 mg doses. The only schedule investigated is once daily for 4 days (see sub-bullet about sedation) [II, B].
  - o If sedation is a concern, a starting daily dose of 5 mg and/or administration at bedtime is an option.

PREVENTION OF ACUTE AND DELAYED NAUSEA AND VOMITING INDUCED BY MODERATELY EMETOGENIC CHEMOTHERAPY

The literature search covered the period from 1 June 2015 through 31 January 2023 and disclosed 342 references of which 41 new references were identified as relevant for the update and 19 finally selected after consensus global review. The antineoplastic agents considered to be moderately emetogenic (30%-90% risk of vomiting in the first 24 h after administration) are listed in Tables 3 and 4.

The main topics identified for a potential update of the recommendations for MEC were as follows:

1) Carboplatin—dose-dependent recommendations;
2) Oxaliplatin—patient demographic risk factors;
3) Other moderately emetogenic antineoplastic agents;
4) Steroid-sparing regimens in MEC; and
5) Olanzapine in MEC.

Carboplatin—dose-dependent recommendations

Antiemetic regimens were specifically assessed in two randomised, double-blinded trials and two meta-analyses.

A large RCT included AC HEC and MEC patients and compared the efficacy of the NK_1-RA, rolapitant (180 mg p.o. day 1) versus placebo, both combined with DEX 20 mg p.o. day 1 and granisetron 2 mg p.o. daily on days 1-3 after ChT. A *post hoc* analysis included a subgroup of 401 patients who received carboplatin-based ChT[41] of which 192 were randomised to the rolapitant cohort and 209 to the placebo cohort. The vast majority of patients received carboplatin in a dose of AUC 5 [area under the concentration curve (mg) × 5]. Significantly more patients receiving rolapitant (versus placebo) achieved a CR (no emesis and no rescue antiemetics) in the period 24-120 h after ChT (primary endpoint) and 0-120 h after ChT, with CR rates of 82.3% versus 65.6% ($P < 0.001$) and 80.2% versus 64.6% ($P < 0.001$), respectively.

A total of 324 patients were included in a multicentre, randomised, double-blind, placebo-controlled study in women with a gynaecological cancer treated with carboplatin (AUC 5-6) and paclitaxel.[42] All patients received DEX 20 mg i.v. on day 1 and granisetron 1 mg or ondansetron 4 mg p.o. on day 1 and were randomised to aprepitant on days 1-3 or placebo. The primary endpoint assessed hypersensitivity reaction (HSR) to paclitaxel, but secondary endpoints analysed antiemetic efficacy (CR, no vomiting and no nausea). The antiemetic efficacy of aprepitant was significantly superior to placebo (CR 61.6% versus 47.3 %, $P = 0.0073$).

Sixteen trials (3848 patients) were identified in a systematic review with the intent to assess the utility of an NK_1-RA in MEC, in which nine studies (1790 patients) received a carboplatin-based regimen.[43] The odds ratio for achieving an overall CR was 1.96 (95% CI 1.57-2.45, $P < 0.00001$) in favour of the NK_1-RA regimens. Of note, the dose of carboplatin in the nine studies was always ≥AUC 5, and the authors questioned the use of an NK_1-RA in patients receiving carboplatin in a lower dose.

A meta-analysis analysed 10 trials for the efficacy of a triplet regimen containing an NK_1-RA versus a two-drug regimen of a 5-HT_3-RA and DEX in patients treated with MEC.[44] In six of these trials, 1668 patients received carboplatin-based ChT (AUC ≥5). Patients treated with carboplatin and receiving a three-drug antiemetic regimen including an NK_1-RA showed significantly better CR (response rate 1.22, 95% CI 1.14-1.32, $P = 0.001$) in the overall phase compared with patients receiving a two-drug regimen of a 5-HT_3-RA and DEX.

As it appears from the above, all studies used a standard dose of 3-weekly carboplatin (AUC ≥5). No data were available for patients receiving a lower dose of carboplatin.

Oxaliplatin—patient demographic risk factors

In the SENRI trial, 413 patients received an oxaliplatin-based regimen for colorectal cancer. Patients were randomised to a two-drug regimen of a 5-HT_3-RA and DEX or to a three-drug antiemetic regimen including aprepitant on days 1-3 or fosaprepitant on day 1, a 5-HT_3-RA and DEX.[45] There was no difference in the characteristics of patients as concerns age or sex. The aprepitant/fosaprepitant group had significantly higher rates of complete overall response (85.0% versus 74.3%, $P = 0.01$). A subgroup analysis of the above study investigated risk factors for nausea and vomiting.[46] In women, the rate of no nausea, no vomiting and total control was higher in the aprepitant group than in the control group. The benefit of triple antiemetic association was higher in the female cohort compared with males. The no-vomiting rate on days 1-5 increased from 76.4% to 93.2% (Δ16.8%) in women compared with 89.1% to 97.4% (Δ8.3%) in men. A highly significant difference in

the no-nausea rate (days 1-5) was also seen in women (37.5% versus 61.6%, $P = 0.005$) but not in men.

A total of 248 women (aged ≤50 years) were enrolled in a randomised, double-blind, placebo-controlled trial for women with gastrointestinal cancer treated with 5-fluorouracil–leucovorin–oxaliplatin (FOLFOX) or 5-fluorouracil–leucovorin–irinotecan (FOLFIRI).[47] The women were randomised to antiemetic prophylaxis with palonosetron on day 1, DEX on day 1 and placebo on days 1-3 versus aprepitant on days 1-3. The primary efficacy endpoint CR (no emesis and no rescue antiemetics) from 0 to 120 h after the start of ChT was obtained in 87.0% in the aprepitant group compared with 66.7% in the placebo group ($P < 0.001$). Results were also significantly superior in the acute and delayed phase. More specifically, for the 193 patients receiving the oxaliplatin-based regimen (FOLFOX), the CR rate (0-120 h) was also significantly higher in the aprepitant versus the placebo group (89.8% versus 66.3%, $P < 0.001$), whereas this was not the case in patients receiving irinotecan-based ChT (FOLFIRI).

Other moderately emetogenic antineoplastic agents

Among 21 RCTs, meta-analyses and systematic reviews identified, none revealed significant new data to change the previous recommendations for MEC antineoplastic agents other than carboplatin- and oxaliplatin-based regimens.

Exceptions may be the new antibody–drug conjugates (ADCs), sacituzumab–govitecan and trastuzumab–deruxtecan which appear to have an emetogenic potential comparable to carboplatin AUC ≥ 5. However, in the absence of clinical trials evaluating antiemetic approaches for these agents, definitive antiemetic treatment recommendations cannot be made at this time.

Steroid-sparing regimens in MEC

As it appears from the recommendations for preventing delayed nausea and vomiting in MEC (carboplatin-based, oxaliplatin-based or other MEC), no steroid is routinely recommended after day 1 MEC administration. Below is a short update of the steroid-sparing literature identified for MEC.[48-53]

In a randomised, controlled, open-label study, 320 ChT-naive patients treated with mFOLFOX6 (modified FOLFOX regimen) received palonosetron 0.25 mg i.v. on day 1 and were randomised to aprepitant (125 mg p.o. on day 1, followed by 80 mg on days 2-3) or DEX (10 mg i.v. on day 1, followed by 5 mg on days 2 and 3).[48] CR (defined as no emesis and no rescue antiemetic 0-120 h after ChT) was the primary endpoint and was obtained by 88.8% in the aprepitant group versus 74.2% in the DEX group ($P = 0.0010$). Delayed CR (24-120 h) also favoured the aprepitant group, whereas no significant differences were seen in acute CR or any nausea endpoint. A randomised, controlled, phase III, open-label, non-inferiority study in 305 patients treated with non-AC MEC evaluated the antiemetic effect of a 1-day DEX regimen and a 3-day DEX regimen both compared with palonosetron administered on day 1.[49] The primary endpoint was CR (0-120 h after ChT) and the non-inferiority margin was set at −15%. CR (0-120 h) was obtained in 66.2% in the 1-day DEX group and 63.6% in the 3-day DEX group (95% CI −7.8% to 12.8%, *P*-value for non-inferiority test = 0.0004).

Two phase II, randomised, controlled, open-label, non-inferiority trials[50,51] investigated a DEX-sparing regimen in patients receiving carboplatin (AUC 5 or AUC 6) and paclitaxel. Delayed CR (24-120 h after ChT)[50] and overall CR (0-120 h after ChT)[51] were the primary endpoints.

In the AUC 5 carboplatin study,[50] all patients received DEX 20 mg i.v. and palonosetron 0.75 mg i.v. on day 1. In addition, patients in the non-sparing group received DEX 8 mg p.o. on days 2-3. Delayed CR was not statistically significantly different [76.9 % (3-day DEX) versus 69.8 %, $P = 0.4652$]. Patients in the AUC 6 carboplatin study[51] received palonosetron 0.75 mg i.v. and DEX 9.9 mg i.v. (a few DEX 20 mg i.v.) on day 1 and were randomised to no DEX on days 2-3 or DEX 8 mg p.o. on days 2-3. No significant difference was seen in the overall CR, observed in 67.9% (95% CI 53.7% to 80.1%) of patients in the 3-day DEX arm and 60.7% (95%CI 46.8% to 73.5%) of patients in the 1-day DEX arm.

A systematic review and meta-analysis including 17 RCTs and 4534 patients compared the antiemetic efficacy of a 5-HT_3-RA in combination with an NK_1-RA and either a 1-day DEX regimen or a 3-day DEX regimen in patients treated with carboplatin or non-carboplatin MEC.[52] There was an absolute risk difference in the primary endpoint (CR 24-120 h after ChT) of 9% (95% CI −2.3% to 21.1%) and of 24.7% as concerns the no-nausea rate (24-120 h after ChT).

Finally, a systematic review (previously mentioned) confirmed the non-inferiority of a 1-day DEX regimen compared with a 3-day DEX regimen in patients treated with AC or MEC.[10] The non-inferiority of the DEX-sparing regimen was demonstrated with a risk difference between the two cohorts at −1.5% (95% CI −7.1% to 4.0%).

In summary, the studies reviewed led to the recommendations mentioned above that no steroid (or other antiemetic) should be routinely administered after day 1 MEC administration.

Olanzapine in MEC

The literature is very sparse as concerns the utility of olanzapine in MEC. In a randomised open-label study, 81 ChT-naive patients were treated with carboplatin-based ChT and received oral olanzapine 10 mg, palonosetron 0.25 mg i.v. and 16 mg DEX i.v. on day 1 as antiemetic prophylaxis. Patients were randomised to olanzapine 10 mg p.o. once daily on days 2 and 3 or olanzapine (same dose) and DEX 4 mg p.o. once daily on days 2-3 or DEX 4 mg p.o. twice daily on days 2-3. The primary endpoint was total control (no vomiting, no rescue treatment and no nausea). No significant difference was found between the three cohorts.[53]

Recommendations

Prevention of acute nausea and vomiting following carboplatin-based MEC

- A three-drug regimen including single doses of a 5-HT_3-RA, dexamethasone and an NK_1-RA (aprepitant, fosaprepitant, fosnetupitant, netupitant or rolapitant), given before ChT is recommended for patients receiving carboplatin AUC $\geq$5.
  - o Netupitant/fosnetupitant is administered with palonosetron as part of the fixed-dose combination agent NEPA.
- There are no data justifying the use of an NK_1-RA for carboplatin AUC $<$5 [I, A].

Prevention of delayed nausea and vomiting following carboplatin-based MEC

- No steroid (or other antiemetic) should be routinely administered after day 1 carboplatin administration [II, B].
  - o If aprepitant 125 mg is used on day 1, then aprepitant 80 mg $\times$ 1 should be administered on days 2 and 3.
  - o One day of steroids has demonstrated non-inferiority compared with 3 days of steroids.

Prevention of acute nausea and vomiting following oxaliplatin-based MEC

- A two-drug regimen, including single doses of a 5-HT_3-RA and DEX, given before ChT, is recommended for patients receiving oxaliplatin.
  - o Palonosetron is the preferred 5-HT_3-RA in this population.
- The addition of an NK_1-RA (aprepitant, fosaprepitant, netupitant, fosnetupitant or rolapitant) is suggested for oxaliplatin ChT-induced nausea and vomiting (CINV) prophylaxis in women aged $\leq$50 years old [III, B].
  - o Netupitant/fosnetupitant is administered with palonosetron as part of the fixed-dose combination agent NEPA.
- There is no evidence that an NK_1-RA should be routinely used first line in women $>$50 years old [III, B].

Prevention of delayed nausea and vomiting following oxaliplatin-based MEC

- No steroid (or other antiemetic) should be routinely administered after day 1 oxaliplatin administration [II, B].
  - o If aprepitant 125 mg is used on day 1, then aprepitant 80 mg $\times$ 1 should be administered on days 2 and 3.
  - o One day of steroids has demonstrated non-inferiority compared with 3 days of steroids.

Prevention of acute nausea and vomiting following other MEC (non-carboplatin, non-oxaliplatin)

- A two-drug regimen including single doses of a 5-HT_3-RA and DEX, given before ChT, is recommended for patients receiving other MEC [II, C].
  - o The emetic potential of sacituzumab—govitecan and trastuzumab—deruxtecan appears to be at the high end of the moderate category, most closely resembling that of carboplatin AUC $\geq$5. While prospective studies are needed, it is suggested to prevent emesis as for carboplatin AUC $\geq$5.

Prevention of delayed nausea and vomiting following other MEC (non-carboplatin, non-oxaliplatin)

- No steroid (or other antiemetic) should be routinely administered after day 1 MEC administration [II, B].
  - o One day of steroids has demonstrated non-inferiority compared with 3 days of steroids.

Olanzapine in ChT of moderate emetic risk prevention

- No evidence exists for the use of olanzapine as first-line prophylaxis [II, C].

PREVENTION OF ACUTE AND DELAYED NAUSEA AND VOMITING INDUCED BY CHEMOTHERAPY OF LOW OR MINIMAL EMETIC RISK

The antineoplastic agents considered to be of low (10%-30% risk of vomiting in the first 24 h after administration) or minimal emetic risk ($<$10% risk) are listed in Tables 3 and 4. For many of these agents, there is a lack of data to be able to classify their emetogenicity, and more research is needed that specifically documents the risk of nausea and vomiting over time. The literature search of low emetogenic ChT (LEC) and minimal-risk antineoplastic agents (from 1 June 2015 through 31 January 2023) identified 293 papers, of which 15 were judged relevant for the guideline update.

The main topics identified for potential update of the recommendations for low and minimal emetic risk ChT were as follows: (i) overuse and underuse of antiemetics in patients treated with LEC or minimal emetic risk ChT, and (ii) should risk factors other than the emetic risk of ChT be considered?

Overuse and underuse of antiemetics in patients treated with low or minimal emetic risk ChT

Significant causes of overuse of antiemetics occurred with LEC where two antiemetic agents, often a 5-HT_3-RA and a steroid, were used when the recommendation was just for a single agent, and in the minimal emetic potential where single agents or a 5-HT_3-RA were used where no prophylactic antiemetics were recommended.[54-57] Under-usage usually occurred where steroids were omitted in patients receiving low emetic potential ChT.[58]

Should risk factors other than the emetic risk of ChT be considered?

Other risk factors could be of importance for the selection of specific antiemetics. For example, in treating pancreatic cancer, steroid exposure may need to be minimised to avoid the development of diabetes.[59] There are successful salvage regimens for LEC in the acute and delayed phase, which spare steroids by using palonosetron. This suggests that this single agent could be used for LEC when steroid sparing is desirable.[10,60] Likewise, olanzapine has been shown to be effective in patients with refractory LEC.[61] Nausea and/or

vomiting in the previous course is a major risk factor and should generally lead to the antiemetic regimen recommended for the next higher level of emesis.[62]

In summary, no new evidence was reported that would change the current recommendations for the management of systemic cancer treatment of low or minimal emetic potential.

Recommendations for low and minimal emetic risk ChT

Prevention of acute nausea and vomiting following ChT of low emetic risk

- A single antiemetic agent, such as dexamethasone, a 5-HT_3-RA or a dopamine-RA, such as metoclopramide, may be considered for prophylaxis in patients receiving ChT of low emetic risk [II, B].

Prevention of acute nausea and vomiting following ChT of minimal emetic risk

- No antiemetic should be routinely administered before ChT of minimal emetic risk to patients without a history of nausea and vomiting [IV, D].

Prevention of delayed nausea and vomiting following ChT of low or minimal emetic risk

- No antiemetic should be routinely administered for the prevention of delayed nausea and vomiting induced by low or minimal emetogenic ChT [IV, D].

PREVENTION OF NAUSEA AND VOMITING IN PATIENTS TREATED WITH HIGH-DOSE CHT, MULTI-DAY CHT OR THOSE WITH BREAKTHROUGH NAUSEA AND VOMITING

The literature search included 113 hits of which 56 were clinical trials. After removal of duplicates, 40 publications remained of which 17 were considered for this update.

High-dose ChT

Based on two phase III studies, it was recommended to include the use of an NK_1-RA in patients treated with high-dose ChT and stem cell transplantation. This is a very heterogeneous group of patients, and several factors contribute to CINV in addition to the ChT regimens. These factors include the use of prophylactic antibiotics, the presence of gastritis as well as mucositis and the concurrent use of opioids. A high proportion of these patients undergo treatment with total body irradiation, and this constitutes an additional risk factor for nausea and vomiting.[63,64]

The addition of olanzapine to an NK_1-RA-based triplet antiemetic regimen significantly improves clinically relevant outcomes in the haematopoietic cell transplant population.[65] The randomised, double-blinded, placebo-controlled trial, FOND-O, investigated the prophylaxis of CINV in patients undergoing autologous or allogeneic stem cell transplant receiving single-day or multi-day HEC. All patients received triplet antiemetic therapy (ondansetron 8 mg i.v. or 16 mg p.o., DEX 8 mg i.v. or 20 mg p.o. on each day of ChT and fosaprepitant 150 mg i.v. on day 1) and were randomised to olanzapine (10 mg p.o., once daily on ChT days plus 3 additional days after ChT) or to placebo in addition to the triplet antiemetic regimen. Based on 80% power and a type 1 error of 0.05, it was estimated that 98 patients should be included to disclose a difference of at least 25%. CR was significantly higher for FOND-O in the overall (55% versus 26%, $P < 0.003$) and delayed phases (61% versus 30%, $P < 0.001$) but not in the acute phase (76% versus 62%, $P < 0.130$). Complete protection (no emesis, no breakthrough antiemetic use and no significant nausea) was significantly better in favour of olanzapine in the delayed phase (33% versus 16%, $P < 0.05$) and minimal nausea 58% versus 28% ($P < 0.0001$). In the transplantation subgroup analysis, the benefit of olanzapine was restricted to the autologous stem cell transplant group.

Additional evidence for the usage of olanzapine in this population comes from a retrospective study ($n = 100$) comparing multi-day administration of fosaprepitant—tropisetron—olanzapine (FTO) with a standard regimen of aprepitant—tropisetron—DEX (ATD) in patients treated with high-dose ChT followed by autologous stem cell transplantation. The overall rate of CR, defined as no emesis and no rescue therapy, was 70% in the FTO group compared with 36% in the ATD group. Although CR rates are comparable in the acute phase, significantly more patients treated with FTO achieved CR in the delayed phase (74% versus 38%, $P < 0.001$).[66]

Multi-day ChT

Studies investigating the antineoplastic effect of multi-day ChT included agents such as dactinomycin, dacarbazine, ifosfamide, etoposide and cisplatin. Only a few small studies have been carried out with this type of ChT schedule. In the 2015 MASCC/ESMO Antiemetic Guidelines, it was recommended that patients affected by metastatic germ-cell tumours treated with multi-day cisplatin-based ChT should receive a 5-HT_3-RA plus DEX—aprepitant for the prevention of acute nausea and vomiting and DEX for delayed nausea and vomiting.[1,67]

A multicentre, randomised, double-blind, placebo-controlled, phase III trial, adequately powered, evaluated the efficacy of olanzapine combined with triple antiemetic therapy for the prevention of CINV in patients receiving multi-day ChT.[68] The study was conducted in 349 Chinese patients with solid tumours scheduled to receive 3-day cisplatin-based ($\geq$75 mg/m^2) ChT. Patients were randomly assigned to receive either 5 mg olanzapine or placebo p.o. once daily before bedtime for 5 days. All patients also received 150 mg fosaprepitant i.v. and 8 mg ondansetron i.v. on day 1 and DEX 6 mg p.o. on days 1-5. The proportion of patients who achieved a CR (no vomiting and no rescue medication on days 1-8, overall phase) was significantly higher in the olanzapine group than in the placebo group (69% versus 58%, $P < 0.031$). The study demonstrated that olanzapine in combination with triple therapy was superior to triple therapy alone in the prevention of CINV in patients receiving multi-day cisplatin-based ChT. Based on the results obtained from this study, the strategy consisting of a four-agent prophylaxis is recommended for the management of these patients.

A prospective randomised, open trial was conducted in patients treated with a 3-day cisplatin-based (25 mg/m^2/day) ChT regimen. Patients (n = 120) received olanzapine 5 mg, tropisetron and DEX (all on days 1-3) with or without aprepitant (on days 1-3).[21] No statistically significant differences in CR (day 1, days 2-5 or days 1-5) between the two groups were observed, but it cannot be concluded that patients receiving a 3-day cisplatin-based ChT regimen can do without an NK_1-RA because the study was only powered to investigate differences >15%.

Breakthrough nausea and vomiting

Breakthrough CINV (defined as vomiting and/or nausea occurring on the day of ChT in patients receiving guideline-recommended prophylaxis) continues to be an unsolved clinical challenge. Although antiemetics are most effective when used prophylactically, a proportion of patients will experience breakthrough CINV, depending on the emetogenicity of the drugs administered. Additionally, it is recommended to prescribe maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure. Previous studies suggest the use of olanzapine 10 mg p.o. daily for 3 days[69] in patients who did not receive olanzapine as part of the prophylactic antiemetic regimen.

In an open-label, randomised study (n = 62), olanzapine was shown to be an effective treatment of breakthrough CINV.[70] Patients received aprepitant—ondansetron for primary prophylaxis. In case of emesis, patients were randomised to:

1) Ondansetron 32 mg (infusion over 24 h); or
2) Olanzapine (10 mg wafer) plus ondansetron 8 mg i.v. three times daily; or
3) A single dose of palonosetron 0.25 mg i.v.

The primary endpoint (a composite endpoint of no emesis, no use of rescue antiemetics and a reduction in the VAS nausea score of >50%) was achieved in 6% (ondansetron), 45% (olanzapine—ondansetron) and 18% (palonosetron), respectively.

A meta-analysis including four studies of the efficacy and safety of olanzapine 10 mg in patients with a haematological malignancy or a solid tumour concluded that olanzapine is effective and tolerable as a rescue antiemetic in patients who did not receive olanzapine as part of the primary antiemetic prophylaxis.[71]

Recommendations

Prevention of nausea and vomiting in patients receiving high-dose ChT for stem cell transplant

- For patients receiving high-dose ChT for stem cell transplant, a combination of a 5-HT_3-RA, DEX and an NK_1-RA is recommended before ChT [I, A].
  - o Olanzapine could be considered as prophylaxis as part of the antiemetic regimen. It should be used once daily at bedtime and continued for 2-3 days after ChT, as the regimen is very likely to cause significantly delayed emesis.

Prevention of nausea and vomiting in patients receiving multi-day cisplatin-based ChT

- Patients receiving multi-day cisplatin should receive a 5-HT_3-RA (once daily on the days of ChT) plus DEX (once daily from day 1 and until 2 days post-ChT) plus aprepitant (125 mg p.o. on day 1 and 80 mg p.o. from day 2 and once daily until 2 days post-ChT) plus olanzapine (5 mg once daily from day 1 until 2 days post-ChT) for acute and delayed nausea and vomiting [I, A; II, B for the number of days].
  - o Palonosetron could be used and should be given days 1, 3 and 5 (if 5 days of ChT). Olanzapine should be given at bedtime.

Prevention of nausea and vomiting in patients with breakthrough nausea and vomiting

- The available evidence for breakthrough nausea and vomiting suggests the use of olanzapine if not used for primary prophylaxis (some evidence supports a single daily dose of 10 mg for 3 days) [II, B].

INTEGRATIVE AND NON-PHARMACOLOGICAL THERAPIES FOR THE MANAGEMENT OF TREATMENT-RELATED NAUSEA AND VOMITING

Integrative and non-pharmacological therapies have gained momentum over the past two decades. However, in the absence of appropriate guidelines and a lack of knowledge in this area, health care professionals may feel helpless when faced with questions about such therapies. A preliminary scoping search identified the following possible interventions to review:

- Acupuncture/acupressure/electrical stimulation of PC6/auricular therapy;
- Hypnosis;
- Inhaled aromatherapy;
- Progressive muscle relaxation therapy (PMRT);
- Distraction;
- Education;
- Guided imagery (GI);
- Abdominal/foot massage;
- Reflexology;
- Music therapy;
- Ginger; and
- Nutrition.

Due to the range and number of interventions and considering that there were many available systematic reviews and/or meta-analyses in the field, this group did not carry out a new systematic review for each topic, but instead used existing reviews where available. A systematic literature search was conducted from 2010 to 31 January 2023 specifically for related reviews. Thirty-nine systematic reviews were identified and assessed using the AMSTAR 2 tool for the critical appraisal of systematic reviews. Each member of the WG undertook reviews for a specific intervention. All findings were discussed with all members (and subsequently the entire Consensus Committee) until agreement was reached and voting confirmed the

recommendations as per standard MASCC—ESMO guideline development processes.

General conclusion

The vast majority of the published literature is associated with methodological flaws. Most of the RCTs were of poor quality. Among the most frequent shortcomings were the failure to use appropriate antiemetic regimens, the lack of a precise description of the non-pharmacological intervention used and conflicting results, sometimes for identical studies reported in two different RCTs, making it impossible to give recommendations for the use of many treatments. Following analysis of all published work, the consensus was that no integrative therapy or non-pharmacological intervention could replace the guideline-recommended antiemetic drug regimens.

Ginger

The evidence for the effect of ginger in combination with standard antiemetics on CINV included six reviews.[72-77] The conflicting results led to a further step, with a second literature search that included both positive and negative studies with ginger. This step identified 15 studies, but it did not lead to any conclusions for ginger, because seven negative studies were of higher quality and outweighed the eight positive studies which mainly used inadequate antiemetics. Studies suggest that adjuvant use of ginger (in tablets or consumed as tea) may improve CINV outcomes, particularly acute nausea and acute vomiting, with additional improvements in quality of life. The effect is significant, but the certainty of the results is low. In addition, there were some mixed results,[72] including one meta-analysis (with only three RCTs and a low AMSTAR 2 score) that showed no effect of ginger on CINV, leading to the conclusion that the overall clinical benefit of ginger is questionable. A recent double-blind, placebo-controlled trial using guideline-consistent antiemetics was published after the deadline for the literature search. It has further complicated any conclusions as it did not show effects on acute nausea and vomiting but instead on delayed symptoms, nausea and vomiting-related quality of life and nutrition status.[78] Furthermore, the heterogeneity of ginger doses across trials makes it difficult to recommend ginger.

Therapies based on meridian treatment, acupressure, acupuncture, auricular therapy and electrical stimulation of acupoint PC6

The literature on meridian treatment included 11 systematic reviews, five for the use of acupressure,[79-83] three for acupuncture,[84-86] two for auricular therapy[79,87] and one for electrical stimulation of acupoint PC6.[88] Once again, there was a lack of methodological quality in many trials, which does not allow for a robust positioning of the practice within the CINV therapeutic spectrum. However, high-quality trials existed, allowing for recommendations to be made.

Food-based interventions

Two reviews were used for food-based interventions.[89,90] Confidence in the findings was low, and the studies included in the reviews were heterogeneous and mostly of low quality, requiring further investigation before stronger recommendations could be made. The strongest evidence with the highest certainty was found for dietary counselling to meet macronutrient requirements in reducing the incidence of radiotherapy-related nausea and vomiting in adults ($n = 2$ studies; $n = 124$ participants; grade level: moderate). There was also moderate certainty in the beneficial effect of protein supplementation on nausea and vomiting incidence in adults during radiotherapy ($n = 2$ trials; $n = 124$ participants; grade level: moderate). A significant positive effect on the incidence and/or severity of CINV in adults was also found for dietary counselling and education to meet macronutrient requirements during ChT. Small or single studies have suggested a positive outcome from the use of a peppermint drink, scaly wood mushroom, chamomile, protein with ginger and a colourless, odourless diet (grade: low to very low).

PMRT and GI

A systematic review of six trials using PMRT alone and involving 288 patients showed a beneficial effect on CINV, particularly on the incidence and severity of delayed nausea and vomiting.[91] However, three studies were rated of low quality and three of moderate quality. No effects were found with the use of GI alone. Furthermore, a systematic review of seven good-quality randomised trials on the combination of GI with PMRT showed that the combination was effective in improving CINV outcomes.[92]

Other interventions

For all other interventions assessed, including inhalation aromatherapy, reflexology, abdominal massage and music therapy, no clear recommendations could be made due to poor-quality trials. For hypnosis, the data were mostly for paediatric patients, which was not the focus of the current guideline development, and while a positive effect was suggested in children and adolescents, a single study in adults showed no benefit.

Recommendations

General

- If a non-pharmacological intervention is considered, it should be used in addition to guideline-recommended antiemetic drug regimens when feasible and based on patient preference.

Ginger

- Due to conflicting evidence, no recommendation can be made for ginger as an adjuvant treatment to standard antiemetics [III, C].

Acupuncture and electroacupuncture

- The use of acupuncture or electroacupuncture, where appropriate and as an adjunct to standard antiemetics,

is suggested for the management of CINV, particularly acute vomiting. Any effects may be short-lived [II, B].

Acupressure and auricular acupressure

- No recommendation can be made for the use of acupressure or auricular acupressure due to conflicting evidence, while the use of non-invasive electrical stimulation is not recommended [III, C].

Food-based interventions

- Nutritional advice/education on healthy eating practices and personalised diet plans, delivered by a dietician or other health care practitioners, is suggested for the prevention and management of CINV [II, B].

PMRT and GI

- The adjunctive use of PMRT (alone or with GI) is suggested for the management of CINV [II, B].

PREVENTION OF RADIOTHERAPY- AND CHEMORADIOTHERAPY-INDUCED NAUSEA AND VOMITING

Risk classification

Radiotherapy-induced nausea and vomiting (RINV) are common and often undertreated symptoms among patients receiving radiotherapy. Acknowledged risk factors for RINV are especially the site of irradiation and the size of the radiation field.[93] The emetic risk of radiotherapy is divided into four risk levels: high, moderate, low and minimal (Table 5). The risk levels are categorised according to the site of radiation and do not account for other risk factors (e.g. field size). The risk classification is based on the incidence of emesis in clinical studies and expert opinions. In the setting of concomitant chemoradiotherapy (CRT), the risk level and corresponding prophylactic antiemetic recommendation are according to the antineoplastic modality with the highest emetic risk.

Antiemetic treatment—fractionated radiotherapy

Since the 2015 guidelines edition, three RINV clinical trials and one meta-analysis in patients receiving single fraction or fractionated radiotherapy have been published.

A meta-analysis published in 2017 by Li et al. assessed 17 RCTs for efficacy of antiemetic regimens in radiotherapy.[94] Among patients receiving radiotherapy to the abdomen/pelvis, the study found that prophylaxis with a 5-HT_3-RA was significantly more efficacious than placebo and dopamine RAs in both complete control of vomiting and complete control of nausea. Using 5-HT_3-RAs as prophylaxis was more efficacious compared with the use of 5-HT_3-RAs as rescue therapy and compared with prophylaxis with dopamine RAs plus DEX. The addition of DEX to a 5-HT_3-RA compared with a 5-HT_3-RA alone provides a modest improvement in prophylaxis of RINV. Among patients receiving total body irradiation, 5-HT_3-RAs were more effective than other agents (placebo, combination of metoclopramide, DEX and lorazepam). These findings are in accordance with the recommendations in the 2015 guideline update, which remains unchanged in the current update.

Palonosetron as RINV prophylaxis was explored in a pilot study including 75 patients receiving low or moderate emetic risk radiotherapy in a palliative setting.[95] In summary, compared with a historical cohort using ondansetron, complete control of nausea and vomiting was clinically significantly higher both during radiotherapy and in the 10 days after treatment. The results need to be confirmed in a larger-scale randomised setting to assess the efficacy and tolerability of multiple doses of palonosetron.

The efficacy of NK_1-RAs for RINV prevention remains widely unexplored. Two small clinical studies ($n = 20$ and 52, respectively) including NK_1-RAs for the prevention of RINV have been published.[96,97] In both studies, a proportion of the patients received concomitant ChT; hence, it is difficult to assess the impact of NK_1-RAs on RINV control.

Antiemetic treatment—concomitant CRT

Two randomised, double-blind, placebo-controlled antiemetic studies in CRT have been published since the 2015 update.

The GAND-emesis study was a well-designed randomised, double-blind, phase III trial ($n = 246$) comparing once-weekly antiemetic regimens of fosaprepitant 150 mg or placebo on day 1, both combined with palonosetron (day 1) and DEX (days 1-4) for the prevention of chemo (C)-RINV in patients with cervical cancer. Patients were

Table 5. Radiotherapy emetic risk levels and antiemetic guideline

Emetic risk level	Area of treatment	Antiemetic guideline	Level of evidence/grade of recommendation
High	Total body irradiation	Prophylaxis with a 5-HT_3-RA + DEX	II/B (for the addition of DEX: III/C)
Moderate	Upper abdomen, craniospinal	Prophylaxis with a 5-HT_3-RA + optional DEX	II/A (for the addition of DEX: II/C)
Low	Brain	Rescue with DEX	IV/B
	Head and neck, thorax, pelvis	Rescue with DEX, a dopamine-RA or a 5-HT_3-RA	IV/B
Minimal	Extremities, breast	Rescue with DEX, a dopamine RA or a 5-HT_3-RA	IV/B
Concomitant RT and weekly cisplatin 40 mg/m^2	Acute NV: Prophylaxis day 1 before administration of cisplatin with a 5-HT_3-RA, DEX and aprepitant/fosaprepitant. Delayed NV: DEX days 2-4		II/B
Concomitant CRT	In concomitant CRT the antiemetic prophylaxis is according to the chemotherapy-related antiemetic guidelines of the corresponding risk category, unless the risk of emesis is higher with RT than chemotherapy		IV/D

5-HT_3, 5-hydroxytryptamine$_3$; CRT, chemoradiotherapy; DEX, dexamethasone; NV, nausea and vomiting; RA, receptor antagonist; RT, radiotherapy.

treated with fractionated radiotherapy and concomitant weekly cisplatin 40 mg/m^2.[98] The primary endpoint was the 'sustained no emesis' rate (SNE; completely free from emesis during 5 weeks of CRT). The study found an SNE rate of 49% for the placebo group compared with 66% for the fosaprepitant group (subhazard ratio 0.58, 95% CI 0.39-0.87, $P = 0.008$). The study proved the superiority of the addition of an NK_1-RA to a 5-HT_3-RA and DEX in the setting of weekly cisplatin concomitant to radiotherapy.

Olanzapine (10 mg daily on days 1-5) compared with fosaprepitant (150 mg on day 1), both in combination with palonosetron—DEX, was explored in a placebo-controlled clinical trial in patients ($n = 101$) treated for locally advanced head and neck cancer or locally advanced oesophageal cancer receiving radiotherapy and concomitant cisplatin (>70 mg/m^2) on day 1 and 5-fluorouracil (750 mg/m^2) once daily for 4 days.[99] Efficacy was assessed only for the 120 h following the first cycle of ChT, and the primary endpoint was CR overall (120 h), for which there was no difference between groups (76% and 74% for the olanzapine and fosaprepitant groups, respectively). Due to the study design, the study reports on CINV rather than RINV.

Recommendations for prevention of radiotherapy- and CRT-induced nausea and vomiting

New recommendations for prevention of radiotherapy- and CRT-induced nausea and vomiting

A summary is given in Table 5. A single study was identified to impact the guidelines update for C-RINV,[98] providing specific recommendations for prophylaxis during weekly cisplatin 40 mg/m^2 concomitantly to fractionated radiotherapy (Table 5).

None of the published data on RINV since 2015 has influenced the current update of the RINV antiemetics recommendations. However, the recommendation for the 'low emetic risk' category was changed from 'prophylaxis' to 'rescue', while the drugs of choice remain unchanged (Table 5). The evidence for a prophylaxis recommendation for 'low emetic risk' level is lacking, and the expert panel estimated that the majority of patients would be overtreated when using prophylaxis. Given the low risk, it was decided to adjust the recommendation to 'rescue' antiemetics.

SUMMARY

The 2015 MASCC—ESMO guideline for the prevention of ChT- and RINV was updated based on a literature search from 1 June 2015 through 31 January 2023. Thirty-four multidisciplinary experts reviewed the literature. The most important updates were as follows:

1) Recommendation to use olanzapine as part of the prophylaxis for patients receiving HEC;
2) Recommendation of a 1-day DEX schedule in patients treated with AC, carboplatin or other MEC;
3) Suggestion to include an NK_1-RA in the antiemetic regimen for women aged ≤50 years receiving oxaliplatin;
4) Suggestion to use olanzapine for breakthrough CINV;
5) For the first time providing suggestions for the use of some integrative and non-pharmacological therapies; and
6) Recommending aprepitant or fosaprepitant as part of the weekly antiemetic regimen in women treated with fractionated radiotherapy and concomitant weekly cisplatin.

This review also emphasises the risk of overuse and underuse of antiemetics. Consequently, the recommendation of including an NK_1-RA in the antiemetic regimen for carboplatin was withdrawn for carboplatin < AUC 5.

There are still unsolved issues such as the dosing and schedule of olanzapine and the best way to use DEX in patients treated with cisplatin. Furthermore, we know very little about how to prevent nausea and vomiting induced by oral agents or by the relatively new class of agents, the ADCs, of which a few seem to be moderately emetogenic (Table 3).

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