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Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference

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introduction

Despite the relevant progress achieved in the last 20 years, vomiting and, especially, nausea, continue to be two of the most distressing side-effects of cancer chemotherapy. In the late 1990s several professional organizations published recommendations on the optimal antiemetic prophylaxis in patients submitted to chemotherapy and radiotherapy.

Subsequently, due to the emergence of new findings and new antiemetic agents since the first recommendations from 1997, representatives from several oncology societies met in Perugia, Italy, in 2004 and updated the antiemetic guidelines. On 20–21 June 2009 the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) organized the third Consensus Conference on antiemetics in Perugia. The results of this Conference are reported in this paper.

The methodology for the guideline process was based on a literature review through 1 June 2009 using MEDLINE (National Library of Medicine, Bethesda, MD, USA) and other databases, with evaluation of the evidence by an expert panel composed of 23 oncology professionals in clinical medicine, medical oncology, radiation oncology, surgical oncology, oncology nursing, statistics, pharmacy, pharmacology, medical policy and decision making. With the participating experts coming from 10 different countries, on five continents, we believe that this is the most representative and evidence-based guideline process that has yet been performed.

The panel comprised 10 committees dealing with major topics in this field (e.g. acute or delayed nausea and vomiting induced by highly emetogenic chemotherapy). Although prevention of acute and delayed nausea and vomiting induced by highly and moderately emetogenic chemotherapy (HEC and MEC) had specific committees, these worked finally together, as

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Conflict of interest: Dr Roila has reported that he is a member of the advisory board for Helsinn SA, that in the last years he participated in researches sponsored by GSK, Merck Sharp & Dhome and Helsinn and that he has been a speaker at satellite symposia for GSK, Merck Sharp & Dhome and Helsinn; Dr Herrstedt has reported that he is a member of the speakers' bureau for Merck; Dr Aapro has reported that he is a consultant for Helsinn, Merck, Novartis, Roche and Sanofi-Aventis; Dr Gralla has not reported any conflicts of interest; Dr Einhorn has reported that he holds stock in GlaxoSmithKline; Dr Ballatori has reported no conflicts of interest; Dr Bria has reported no conflicts of interest; Dr Clark-Snow has reported no conflicts of interest; Dr Espersen has reported no conflicts of interest; Dr Feyer has reported no conflicts of interest; Dr Grunberg has reported that he has served as a consultant to Helsinn, Merck, GlaxoSmithKline, SNBL and Prostrakan, he holds stock in Merck and has received lecture honoraria from Merck; Dr Hesketh has reported that he has received research funding from Eisai and Merck and that he serves as consultant on the advisory boards of Helsinn, Merck and GlaxoSmithKline; Dr Jordan has reported that she is a member of the speakers' bureau of MSD and Helsinn; Dr Kris has reported that he serves as a consultant to Merck and GlaxoSmithKline; Dr Maranzano has reported no conflicts of interest; Dr Molassiotis has reported that he has received honoraria from Roche UK Ltd, Merck, GlaxoSmithKline, Bayer-Schering and research grants from Roche UK Ltd and Merck; Dr Morrow has reported that he is a speaker for EISAI; Dr Olver has reported no conflicts of interest; Dr Rapoport has reported that he is a member of the Merck antiemetic advisory board; Dr Rittenberg has reported no conflicts of interest; Dr Saito has reported no conflicts of interest; Dr Tonato has reported no conflicts of interest; Dr Warr has reported that he is a member of the speakers' bureau and a consultant for Merck.

some of the issues are inseparable. Each committee was composed of five to seven members and each committee had one chair and co-chair. Each expert could be part of three or four committees but could only be a chair or co-chair of one committee. During the consensus conference the findings of each committe were presented by the chair to the entire expert panel. The panel then discussed the results and determined the level of evidence and the level of confidence for the recommendation according to ESMO and MASCC criteria.

To change the 2004 recommendations or for a new guideline recommendation to be accepted, a consensus of at least 66% of the expert panelists was needed. As a general rule, the panel considered changes of >10% to be sufficient to warrant changing a guideline, given that the evidence supported this magnitude of benefit.

antineoplastic agents emetogenicity

Defining the emetogenicity of chemotherapy agents is of value for at least two important reasons. First, such a classification can be used as a framework for defining antiemetic treatment guidelines. Second, it can provide a means for clinical investigators to attain a more precise definition of the emetogenic challenge that is being employed in an antiemetic trial. In the past, a number of classifications have been proposed in which chemotherapy agents have been divided into three to five emetogenic levels. The literature has provided a very limited source of useful information in the development of these classifications, given the imprecise, inconsistent and extremely limited ways in which information on emesis and nausea has been recorded in most therapeutic trials. Most classifications have not differentiated between the various types of emesis, such as acute, delayed and anticipatory, and few have accounted for important treatment- and patient-related variables, such as chemotherapy dose, rate and route of administration, gender, age and history of ethanol consumption.

Recently, a four-level classification of intravenous chemotherapy agents (high, moderate, low and minimal) has been accepted by the major organizations producing recommendations on antiemetics. At the 2009 Consensus Conference, this classification was left intact as was the basic principle that the emetogenic classification scheme should be used to describe single agents, since the potential variety of combination doses and schedules of even a few chemotherapeutic agents might defy meaningful classification. However, it was recognized that the commonly used combination of the moderately emetogenic agents cyclophosphamide and doxorubicin that forms the basis of many breast cancer regimens, did appear to create a particularly potent moderately emetogenic combination that commonly served as the basis for antiemetic clinical trials and that might require more aggressive antiemetic regimens.

As new antineoplastic agents have been developed, these have been added to the emetogenic classification schema. Such efforts continue to be hampered by the limited recording of 'common' toxicities such as emesis during antineoplastic drug development and the unregulated use of prophylactic antiemetics during antineoplastic drug development even before emetogenicity of the agents has been specifically established. Classification of new agents must therefore depend to a certain extent on expert opinion and on synthesis of various limited data sources, still allowing significant consensus but limiting confidence to that allowed by the quality of the underlying data. Table 1 represents the 2009 consensus on the emetogenic classification of commonly used intravenous antineoplastic agents. Numerous new agents have been added

Table 1. Emetogenic potential of intravenous antineoplastic agents

Degree of emetogenicity (incidence)	Agent
High (>90%)	Cisplatin
	Mechlorethamine
	Streptozotocin
	Cyclophosphamide ≥1500 mg/m^2
	Carmustine
	Dacarbazine
Moderate (30%–90%)	Oxaliplatin
	Cytarabine >1 gm/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin
	Daunorubicin
	Epirubicin
	Idarubicin
	Irinotecan
	Azacitidine
	Bendamustine
	Clofarabine
	Alemtuzumab
Low (10%–30%)	Paclitaxel
	Docetaxel
	Mitoxantrone
	Doxorubicin HCl liposome Injection
	Ixabepilone
	Topotecan
	Etoposide
	Pemetrexed
	Methotrexate
	Mitomycin
	Gemcitabine
	Cytarabine ≤1000 mg/m^2
	5-Fluorouracil
	Temsirolimus
	Bortezomib
	Cetuximab
	Trastuzumab
	Panitumumab
	Catumaxumab
Minimal (<10%)	Bleomycin
	Busulfan
	2-Chlorodeoxyadenosine
	Fludarabine
	Vinblastine
	Vincristine
	Vinorelbine
	Bevacizumab

since 2004, and some agents have been reclassified based on additional data.

The increasing use of oral agents (both cytotoxic agents and biologic agents) has created an additional challenge, since such agents tend to be used in extended regimens of daily oral use rather than the single bolus administration commonly seen with intravenous agents. Whether emetogenicity of such agents should be defined based on the acute emetogenicity of a single dose or the cumulative emetogenicity of a full course of chronic administration remains an issue for discussion. This is particularly critical since some of the newer agents may only become consistently emetogenic after a week or more of continuous administration, so that evaluation of only a single day would greatly underestimate the clinical concern. In general, emetogenic classification of oral agents has therefore been established based on that of a full course of therapy as clinically employed (Table 2). Chronic oral administration also erases the distinction between acute and delayed emesis so that definitions for oral agents must intrinsically differ from those of intravenous agents.

prevention of acute nausea and vomiting induced by highly emetogenic chemotherapy

Before the introduction of aprepitant, a combination of a 5-HT_3 receptor antagonist plus dexamethasone was the regimen of choice for the prevention of acute nausea and vomiting in cisplatin-treated patients.

Aprepitant, a potent and selective antagonist of the neurokinin $(NK)_1$ neurotransmitter receptor showed its antiemetic activity when added to a 5-HT_3 receptor antagonist plus dexamethasone in several phase II double-blind studies.

Subsequently, two phase III trials with identical design have been reported comparing standard therapy with ondansetron 32 mg plus dexamethasone 20 mg on day 1, followed by dexamethasone 8 mg twice a day on days 2–4 with ondansetron 32 mg, dexamethasone 12 mg and aprepitant 125 mg on day 1, followed by dexamethasone 8 mg daily on days 2–4 and aprepitant 80 mg on days 2 and 3. A third study used the same design, but ondansetron was continued in the control arm on days 2–4 in an oral dose of 8 mg twice daily. The dexamethasone dose was reduced in the aprepitant arms because a pharmacokinetic study found that aprepitant increased dexamethasone plasma concentrations resulting in an approximately twofold increase in AUC. Because the differential exposure to dexamethasone could theoretically confound the intrepretation of the efficacy of aprepitant a 40%–50% reduction of the oral dexamethasone dose was made in the aprepitant arms.

The primary endpoint was complete response (no emesis, no use of rescue antiemetics) over the 5-day study period. In all three studies complete response was significantly superior with aprepitant (73% versus 52%, $P < 0.001$; 63% versus 43%, $P < 0.001$; 72% versus 61, $P < 0.003$).

Casopitant, a new NK_1 receptor antagonist, has been evaluated in a phase II, double-blind, dose-ranging study in 493 patients receiving cisplatin-based chemotherapy. The addition of casopitant to ondansetron plus dexamethasone at doses of 50, 100 and 150 mg administered orally on days 1–3, significantly reduced emesis on days 1–5 (complete responses in 76%, 86%, 77% of patients, respectively, versus 60% with ondansetron and dexamethasone alone). In this study an exploratory arm using oral casopitant 150 mg only on day 1 obtained 75% complete responses.

A subsequent phase III study ($n = 810$) in patients receiving cisplatin-based chemotherapy compared the addition to ondansetron plus dexamethasone of casopitant as a 150-mg single oral dose, or the addition of casopitant as a 90-mg intravenous (i.v.) dose on day 1 followed by oral casopitant 50 mg on days 2 and 3, versus a control arm of ondansetron plus dexamethasone plus placebo. Complete response on days 1–5 was significantly superior with the addition of casopitant (86% and 80% versus 66%, $P < 0.0001$ and $P < 0.0004$, respectively).

After the completion of the Consensus Conference, GlaxoSmithKline decided to discontinue the regulatory filings for casopitant. Consequently, casopitant cannot be recommended by the consensus panel, but the results of the casopitant studies contribute to the conclusions about NK_1 receptor antagonists as a drug class.

Therefore, to prevent acute nausea and vomiting following chemotherapy of high emetic risk a three-drug regimen including single doses of a 5-HT_3 receptor antagonist,

Table 2. Emetogenic potential of oral antineoplastic agents[a]

Degree of emetogenicity (incidence)	Agent
High (>90%)	Hexamethylmelamine
	Procarbazine
Moderate (30%–90%)	Cyclophosphamide
	Temozolomide
	Vinorelbine
	Imatinib
Low (10%–30%)	Capecitabine
	Tegafur Uracil
	Fludarabine
	Etoposide
	Sunitinib
	Everolimus
	Lapatinib
	Lenalidomide
	Thalidomide
Minimal (<10%)	Chlorambucil
	Hydroxyurea
	L-Phenylalanine mustard
	6-Thioguanine
	Methotrexate
	Gefitinib
	Erlotinib
	Sorafenib

[a]Considerable uncertainty prevails for the emetogenic risk of oral agents.

dexamethasone and aprepitant given before chemotherapy is recommended [High, High] [I, A].

The principles for use of 5-HT_3 receptor antagonists to prevent acute nausea and vomiting induced by chemotherapy of high emetogenic risk are the following: (i) use the lowest tested fully effective dose; (ii) no schedule better than a single dose beginning before chemotherapy; (iii) the adverse effects of these agents are comparable; (iv) intravenous and oral formulations are equally effective and safe; (v) give with dexamethasone and an NK_1 receptor antagonist beginning before chemotherapy [Moderate, High] [I, A].

Generally all agree that no differences between the 5-HT_3 receptor antagonists, dolasetron, granisetron, ondansetron, tropisetron exist in terms of efficacy. Recently two studies have compared palonosetron with ondansetron and granisetron in the prevention of cisplatin-induced acute nausea and vomiting. In the first study, two different doses (0.25 and 0.75 mg i.v.) of palonosetron have been compared with 32 mg i.v. of ondansetron. Only 67% of patients also received dexamethasone, as recommended by all consensus guideline groups. Complete response was not significantly different between the three arms. The second study, a double-blind study carried out in 1114 patients, compared palonosetron 0.75 mg i.v. with granisetron 40 μg/kg i.v., both combined with dexamethasone 16 mg i.v. followed by 8 mg i.v. (cisplatin-treated patients) or 4 mg orally (anthracyclines + cyclophosphamide-treated patients) on days 2–3. The complete response was similar in the first 24 h (75.3% versus 73.3%, respectively) but significantly superior with palonosetron on days 2–5 (56.8% versus 44.5%) and on days 1–5 (51.5% versus 40.4%). Despite some shortcomings of both studies (i.e. in the last study cisplatin- and non-cisplatin-treated patients were combined, doses of dexamethasone were different from those generally used for acute and delayed emesis prophylaxis) the similar results achieved in the first 24 h permit us to conclude that palonosetron induced more protection from delayed emesis than a single administration of granisetron before chemotherapy. These studies do not address the issue of whether palonosetron is superior to other 5-HT_3 receptor antagonists when an NK_1 receptor antagonist is used as recommended by guidelines. Therefore, it is concluded that more studies are necessary to determine whether palonosetron should be recommended as the 5-HT_3 receptor antagonist of choice in prevention of cisplatin-induced acute nausea and vomiting. These studies should include a NK_1 receptor antagonist.

Suggested doses, schedules and route of administration of the 5-HT_3 receptor antagonists in the prevention of acute nausea and vomiting induced by HEC are reported in Table 3. Of note, a recent meta-analysis of eight trials concluded that there is no difference in efficacy between the 0.25- and 0.75-mg doses of palonosetron.

Concerning dexamethasone dose, the Italian Group for Antiemetic Research published a dose-finding study of dosages ranging from 4 to 20 mg, always combined with a 5-HT_3 receptor antagonist, in patients receiving cisplatin. A single 20-mg dose before chemotherapy was recommended based on the observations that the 20-mg dose had the highest numerical efficacy and there was no difference in adverse effects between the doses tested. As stated before, when used concomitantly with aprepitant, dexamethasone dose should be reduced to 12 mg.

Concerning aprepitant, for the prevention of acute emesis induced by cisplatin chemotherapy, a randomized study evaluated oral prechemotherapy doses from 40 to 375 mg, and concluded that a single 125-mg oral dose had 'the most favorable benefit:risk profile'. This 125-mg dose was used in the randomized phase III comparison studies of aprepitant.

Recently fosaprepitant, a water-soluble phosphoryl prodrug for aprepitant, has been approved. When administered intravenously it is converted within 30 min into aprepitant. A dose of 115 mg of fosaprepitant was bioequivalent in its AUC to aprepitant 125 mg and can be used as parenteral alternative to oral aprepitant on day 1 of a 3-day oral aprepitant regimen.

Table 3. Antiemetic agents to prevent acute emesis induced by HEC in adults

		MASCC		ESMO	
Antiemetics	Single daily dose given before chemotherapy	Level of Consensus	Level of Confidence	Level of Evidence	Grade of Recommendation
5-HT_3 receptor antagonists					
Ondansetron	Oral: 24 mg	Moderate	High	I	A
	i.v.: 8 mg or 0.15 mg/kg	High	High	I	A
Granisetron	Oral: 2 mg	High	High	I	A
	i.v.: 1 mg or 0.01 mg/kg	High	High	I	A
Tropisetron	Oral or i.v.: 5 mg	High	Moderate	I	A
Dolasetron	Oral: 100 mg	High	Moderate	I	A
	i.v.: 100 mg or 0.18 mg/kg	High	High	I	A
Palonosetron	i.v.: 0.25 mg	High	Moderate	II	A
	Oral 0.50 mg	High	Moderate	II	A
Dexamethasone	Oral or i.v.: 12 mg[a]	High	High	I	A
Aprepitant	Oral: 125 mg	High	High	I	A
Fosaprepitant	i.v.: 115 mg	High	Moderate	II	A

[a]20 mg if aprepitant is not available. If dexamethasone is not available limited data suggest that prednisolone or methylprednisolone can be substituted at doses about 7 and 5 times higher respectively.

Table 4. Antiemetic agents to prevent acute emesis induced by MEC in adults

Antiemetic	Single daily dose given before chemotherapy	MASCC		ESMO	
		Level of Consensus	Level of Confidence	Level of Evidence	Grade of Recommendation
5-HT_3 receptor antagonists					
Ondansetron	Oral: 16 mg (8 mg b.i.d.)	High	High	I	A
	i.v. 8 mg or 0.15 mg/kg	High	Moderate	III	B
Granisetron	Oral 2 mg	High	High	I	A
	i.v. 1 mg or 0.01 mg/kg	High	High	I	A
Tropisetron	Oral 5 mg	High	Low	III	B
	i.v. 5 mg	High	Moderate	III	B
Dolasetron	Oral 100 mg	High	Moderate	II	A
	i.v. 100 mg or 1.8 mg/kg	High	Moderate	II	A
Palonosetron	i.v. 0.25 mg	High	High	I	A
	Oral 0.5 mg	High	Moderate	II	A
Dexamethasone	Oral or i.v. 8 mg[a]	High	Moderate	II	A
Aprepitant	Oral 125 mg	High	Moderate	II	A
Fosaprepitant	i.v. 115 mg	High	Moderate	II	A

If dexamethasone is not available limited data suggest that prednisolone or methylprednisolone can be substitued at doses about seven and five times higher, respectively.

At the time of the Consensus Conference (June 2009), no clinical trials had compared the efficacy of intravenous fosaprepitant with oral aprepitant. An update of ESMO/MASCC recommendations for prophylaxis of chemotherapy-induced nausea and vomiting is given in Table 5.

prevention of delayed nausea and vomiting induced by highly emetogenic chemotherapy

Nausea and vomiting developing more than 24 h after chemotherapy administration is arbitrarily termed delayed nausea and vomiting. A number of predictive factors have been identified for the development of delayed nausea and vomiting. By far the most important is the presence or absence of acute nausea and vomiting. Approximately twice as many patients experiencing emesis during the first 24 h after cisplatin will develop delayed emesis as compared with patients with no acute emesis. Other factors with prognostic importance include protection against nausea and vomiting in prior chemotherapy cycles, cisplatin dose, gender and age.

All patients receiving cisplatin should receive antiemetics to prevent delayed nausea and vomiting.

Aprepitant efficacy against delayed emesis has been evaluated in the three double-blind studies previously discussed. During the delayed phase (days 2–5), complete response rates on the aprepitant and standard arms were 75%, 68% and 74% versus 56%, 47% and 63% in the three studies, respectively. Given the different antiemetic regimens employed for acute prophylaxis, one can question whether a significant component of the improved efficacy of the aprepitant-containing arms during the delayed phase was due to a carryover effect from the different control rates during day 1. A subsequent analysis of the combined database from two of these phase III trials suggested that aprepitant provided protection against delayed vomiting regardless of response in the acute phase. In patients with acute vomiting, the proportion of patients with delayed vomiting was 85% and 68% on the control and aprepitant arms, respectively. In patients with no acute vomiting, the proportion with delayed vomiting was 33% and 17% on the control and aprepitant arms, respectively.

Recent trials with casopitant have raised some questions about the efficacy of the NK_1 receptor antagonists administered on days 2–3 after cisplatin chemotherapy. A phase II and phase III study both demonstrated similar efficacy of casopitant when administered on day 1 only or for three consecutive days.

Therefore, the panel recommended that given the dependence of delayed emesis and nausea on acute antiemetic outcome, optimal acute antiemetic prophylaxis should be employed. In patients receiving cisplatin treated with a combination of aprepitant, a 5-HT_3 receptor antagonist and dexamethasone to prevent acute vomiting and nausea, the combination of dexamethasone and aprepitant is suggested to prevent delayed nausea and vomiting, on the basis of its superiority to dexamethasone alone [High, Moderate] [II, A].

To date, no trials have compared this regimen for delayed emesis with the previous standard treatments (dexamethasone combined with metoclopramide or a 5-HT_3 receptor antagonist).

After having analysed the results of the randomized trials comparing a 5-HT_3 receptor antagonist plus dexamethasone with dexamethasone alone in the prevention of cisplatin-induced delayed emesis several panelists felt no need to initiate a trial to formally compare the previous standard of dexamethasone plus a 5-HT_3 receptor antagonist with dexamethasone plus aprepitant. The question remains whether metoclopramide plus dexamethasone should be compared with aprepitant plus dexamethasone. Only a clinical trial in which all patients receive the same antiemetic prophylaxis for acute

Table 5. Chemotherapy-induced emesis: emetic risk levels and new MASCC and ESMO guidelines

Risk level	Chemotherapy	Antiemetic guidelines	MASCC Level of Scientific Confidence/Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
High (>90%)	Cisplatin and other HEC (see Tables 1 and 2)	Day 1: 5-HT_3 receptor antagonist + DEX + (fos)aprepitant	High/high	I/A
		Days 2–3: DEX + aprepitant	High/Moderate	II/A
		Day 4: DEX	High/Moderate	
Moderate (30%–90%)	AC	Day 1: 5-HT_3 receptor antagonist + DEX + (fos)aprepitant[a]	High/High	I/A
		Days 2–3: aprepitant	Moderate/Moderate	II/B
	Non-AC MEC (see Tables 1 and 2)	Day 1: Palonosetron + DEX	Moderate/Moderate	II/B
		Days 2–3: DEX days 2–3	Moderate/Moderate	II/B
Low (10%–30%)	See Tables 1 and 2	Day 1: DEX or 5-HT_3 or dopamine receptor antagonist	No confidence possible/ Moderate	III, IV/D
		Days 2–3: no routine prophylaxis		
Minimal (<10%)	See Tables 1 and 2	Day 1: no routine prophylaxis	No confidence possible/high	V/D
		Days 2–3: no routine prophylaxis		

DEX, dexamethasone; AC, combination of an anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

[a](fos)aprepitant: either i.v. or oral form of the NK1 receptor antagonist.

For doses of day 1 see Tables 3 and 4. The dose of aprepitant for days 2 and 3 is 80 mg. The optimal duration and dose of dexamethasone in the delayed phase has not been defined.

If the NK_1 receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist.

emesis could definitively assess the relative efficacy of these two regimens in the delayed phase.

No studies have been published evaluating the optimal dose of dexamethasone for the prevention of delayed nausea and vomiting induced by cisplatin. Aprepitant should be used as a single 80-mg oral dose on days 2 and 3 after cisplatin administration.

prevention of acute nausea and vomiting induced by moderately emetogenic chemotherapy

At the 2004 Perugia Antiemetic Conference, the consensus recommendation for patients receiving MEC was the use of a combination of a 5-HT_3 receptor antagonist plus dexamethasone as standard antiemetic prophylaxis. The only exception was in the setting of an anthracycline combined with cyclophosphamide (AC) regimen where the addition of aprepitant was recommended based upon a study conducted in 866 breast cancer patients. Additional studies reported since the 2004 conference provide further insight into the role of palonosetron and NK_1 receptor antagonists in this setting.

In earlier studies two different doses (0.25 and 0.75 mg i.v.) of palonosetron have been compared, in two double-blind studies, with ondansetron and dolasetron. In these studies both 0.25 and 0.75 mg of palonosetron were non-inferior to ondansetron and dolasetron, respectively. The 0.25-mg dose of palonosetron was superior to ondansetron and dolasetron as concerns several secondary parameters, but the 5-HT_3 receptor antagonists were not given according to guideline recommendations (no dexamethasone for the prophylaxis of acute emesis and no prophylaxis for delayed emesis was administered). A more recent double-blind study, already described, carried out in 1114 patients receiving either cisplatin or the combination of an anthracycline and cyclophosphamide, compared single doses of palonosetron with granisetron, both combined with dexamethasone administered on days 1–3. The complete response was similar in the first 24 h but significantly superior with palonosetron on days 2–5 and on days 1–5.

With respect to the NK_1 receptor antagonists, several studies have been reported since the 2004 Perugia conference with relevance to patients receiving MEC. A study evaluating the addition of aprepitant to a 5-HT_3 receptor antagonist and dexamethasone in breast cancer patients receiving AC failed to demonstrate an advantage for the NK_1 antagonist. However, given the small sample size this study was underpowered.

A recent, large phase III randomized, gender stratified, double-blind trial in 848 patients receiving a broad range of MEC regimens (non-AC or AC) with a variety of tumour types showed superiority of an aprepitant triple regimen compared with a control regimen of ondansetron and dexamethasone. The primary efficacy endpoint was the proportion of patients reporting no vomiting during the 5 days (0–120 h) following initiation of chemotherapy. Significantly more patients in the

aprepitant group reported no vomiting compared with the control group: 72.6% versus 62.1%. Also in the acute and delayed phases, significantly more patients in the aprepitant group reported no vomiting compared with the control group (92% versus 83.7% and 77.9% versus 66.8%, respectively). The key secondary endpoint was the overall complete response (no emetic episodes and no administration of rescue therapy) during the 5 days following initiation of chemotherapy. Significantly more patients in the aprepitant group reported complete response compared with the control group (68.7% versus 56.3%). In addition, significantly more patients in the aprepitant group reported complete response compared with the control group in both the acute and delayed phases (89.2% versus 80.3% and 70.8% versus 60.9%, respectively). No significant differences in the incidence of adverse events were identified. This study confirms and reinforces the results from the first phase III MEC study in breast cancer patients treated with AC chemotherapy. A *post-hoc* analysis demonstrated superiority for the addition of aprepitant in both the AC and non-AC populations. Given the heterogeneity of chemotherapy in the non-AC population and the use of a *post-hoc* analysis, this trial is not regarded as sufficiently compelling to recommend the standard use of aprepitant with the initial cycle of non-AC chemotherapy.

Recently, casopitant has been evaluated in a phase II, double-blind, dose-ranging study in 719 patients submitted to MEC. The addition of casopitant to ondansetron plus dexamethasone at doses of 50, 100 and 150 mg administered orally on days 1–3, significantly reduced emesis on days 1–5 (complete responses in 81%, 79%, 85% of patients, respectively, versus 70% with ondansetron and dexamethasone alone). In this study an exploratory arm using oral casopitant 150 mg only on day 1 obtained 80% complete responses.

A subsequent phase III study has been carried out in 1933 breast cancer patients submitted to AC-based chemotherapy. All patients received dexamethasone 8 mg i.v. on day 1 and oral ondansetron 8 mg twice daily on days 1–3. Patients were randomized to a control arm (placebo), a single oral dose casopitant arm (150 mg oral day 1), a 3-day oral casopitant arm (150 mg p.o. day 1 + 50 mg p.o. days 2–3), or a 3-day i.v./oral casopitant arm (90 mg i.v. day 1 + 50 mg p.o. days 2–3). The primary endpoint was the proportion of patients achieving complete response in the first 120 h after the initiation of chemotherapy. A significantly greater proportion of patients in the single-dose oral casopitant arm, 3-day oral casopitant arm and 3-day i.v./oral casopitant arm achieved complete response (73%, 73% and 74%, versus 59%, respectively). There was no difference during the first 24 h in the number of patients with complete response. The study did not demonstrate a reduced proportion of patients with nausea in those receiving casopitant.

In conclusion, to prevent acute nausea and vomiting induced by non-AC MEC a combination of palonosetron plus dexamethasone is recommended as standard prophylaxis [Moderate, Moderate] [II, B]. Women receiving a combination of anthracycline plus cyclophosphamide represents a situation with a particularly great risk of nausea and vomiting. To prevent acute nausea and vomiting in these women, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended [High, High] [I, A]. If aprepitant is not available women receiving a combination of anthracycline plus cyclophosphamide should receive a combination of palonosetron plus dexamethasone [Moderate, Moderate] [II, B].

No clinically relevant differences in tolerability between the 5-HT_3 receptor antagonists used for the prophylaxis of acute emesis induced by MEC have been found. Furthermore, there is no difference in the efficacy of oral or i.v. administration of a 5-HT_3 receptor antagonist. The optimal dose and schedule of antiemetics is shown in Table 4.

prevention of delayed nausea and vomiting induced by moderately emetogenic chemotherapy

A few comparative studies have been published, in which oral ondansetron, dolasetron or oral dexamethasone were better than placebo or no treatment in the prevention of delayed nausea and vomiting induced by MEC. Unfortunately all of these studies possessed methodological pitfalls. Consequently, the Italian Group for Antiemetic Research evaluated the role of dexamethasone alone or combined with ondansetron on days 2–5 in 618 patients who had no emesis and either no or mild nausea in the first 24 h. These patients were randomized to placebo, dexamethasone or dexamethasone plus ondansetron. Dexamethasone was statistically significantly superior to placebo in terms of the percentage of patients free of delayed vomiting or moderate to severe nausea (87% versus 77%) while the combination of dexamethasone and ondansetron was not significantly superior to dexamethasone alone (92% versus 87%) and induced more constipation.

In the group of patients who experienced vomiting or moderate to severe nausea on day 1 despite optimal acute antiemetic prophylaxis, ondansetron plus dexamethasone was compared with dexamethasone alone in 87 patients. The combination was numerically but not statistically significantly superior to dexamethasone alone (41% versus 23%). The small sample size could have limited the ability to detect clinically important differences in this subgroup of patients.

Therefore, the panel recommended that patients who receive MEC known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis [High, High] [I, A].

In patients receiving chemotherapy of moderate emetic risk that does not include a combination of anthracycline plus cyclophosphamide and in which palonosetron is recommended, multiday oral dexamethasone treatment is the preferred treatment for the prevention of delayed nausea and vomiting [Moderate, Moderate] [II, B].

After the publication of the Warr study aprepitant has been considered superior to a 5-HT_3 receptor antagonist in the prevention of delayed emesis induced by MEC in breast cancer patients receiving a combination of anthracycline plus cyclophosphamide treated with a combination of aprepitant,

a 5-HT3 antagonist and dexamethasone to prevent acute nausea and vomiting. Therefore, the panel updated the recommendation stating that in these patients aprepitant should be used to prevent delayed nausea and vomiting [Moderate, Moderate] [II, B] (Table 5). It should be emphasized that it is not known whether dexamethasone is as effective as aprepitant or if aprepitant plus dexamethasone would be even better.

The optimal duration and dose of dexamethasone have not been defined. Aprepitant is used at doses of 80 mg orally on days 2 and 3 (Table 4).

prevention of nausea and vomiting induced by multiple-day cisplatin chemotherapy

Only a few small studies have been carried out with this type of chemotherapy schedule. The intravenous combination of a 5-HT_3 receptor antagonist plus dexamethasone has been shown to induce ~55%–83% complete protection from vomiting during the 3–5 days of cisplatin administration and this combination has proved superior to i.v. high-dose metoclopramide plus dexamethasone, alizapride plus dexamethasone and to a 5-HT_3 receptor antagonist alone.

Using a combination of a 5-HT_3 receptor antagonist plus dexamethasone, patients receiving consecutive 5 days of cisplatin for testicular cancer will have little or no nausea or vomiting during the first 3 days of chemotherapy. The worst nausea is seen on day 4 and day 5 as well as on days 6, 7 and 8. Whether this all reflects delayed nausea from days 1 and 2 is unknown. Strategies for delayed nausea and vomiting for multiple-day cisplatin courses should be utilized similarly to single-day high-dose cisplatin.

Patients receiving multiple-day cisplatin should receive a 5-HT_3 receptor antagonist plus dexamethasone for acute nausea and vomiting and dexamethasone for delayed nausea and vomiting [High, High] [II, A].

The optimal dose of the 5-HT_3 receptor antagonist as well as of dexamethasone remains to be identified. It should be emphasized that the 20 mg of dexamethasone often used on each day of chemotherapy is only verified in patients receiving single-day higher doses of cisplatin-based chemotherapy (≥50 mg/m^2). It is not known whether a lower dose given on days 1–5 (in an attempt to decrease side-effects) will be as good as the 20-mg dose. No randomized trial has compared the use of aprepitant plus a 5-HT_3 receptor antagonist plus dexamethasone with the 5-HT_3 receptor antagonist plus dexamethasone alone. The possible role of the NK_1 receptor antagonists in this setting therefore remains undefined.

prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential

For patients treated with low or minimally emetogenic chemotherapy there is little evidence from clinical trials supporting the choice of a given antiemetic therapy or of any treatment at all. In fact, in these subgroups it is difficult to identify those patients at risk for developing nausea and vomiting.

Furthermore, the accurate assessment of the degree of nausea and or vomiting of these agents has not been well documented, nor are there prospective trials that clearly outline the incidence and severity of nausea and vomiting for each drug. It has been suggested that both physicians and nurses through direct observation and follow-up of patient reports of nausea and vomiting episodes may provide perhaps the most reliable method of assessing overall emetogenicity of chemotherapy agents of low or minimal emetogenicity.

Nonetheless, the panel recommended that patients with no prior history of nausea and vomiting who receive chemotherapy of low emetic potential as an intermittent schedule should be treated with a single antiemetic agent such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, as prophylaxis [No confidence possible, Moderate] [III; IV expert consensus, D].

For patients submitted to minimally emetogenic chemotherapy no antiemetic treatment should be routinely administered before chemotherapy in patients without a history of nausea and vomiting [No confidence possible, High] [V and expert consensus, D].

Finally, the panel recommended that no prophylactic treatment should be administered for the prevention of delayed emesis induced by low or minimally emetogenic chemotherapy. In these two last conditions, if nausea and vomiting occurs, in subsequent cycles, single-agent antiemetics can be used as above.

refractory nausea and vomiting and rescue antiemetic therapy

Antiemetics are most effective when used prophylactically, since emesis in progress is much more difficult to suppress and raises the spectre of an added component of anticipatory nausea or vomiting on future treatment cycles. It is therefore preferable to use maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure.

There are no clear-cut definitions of the terms 'rescue antiemetic therapy' and 'refractory emesis'. Rescue antiemetic treatment is generally understood to be antiemetics given on demand to a patient with breakthrough emesis. No randomized double-blind trials have investigated antiemetics in this setting.

A few trials have investigated patients with refractory emesis defined as emesis in the previous cycle of chemotherapy, but without emesis before the subsequent cycle of chemotherapy. A number of approaches have been utilized including switching to a different 5-HT_3 receptor antagonist or adding other agents such as dopamine antagonists or benzodiazepines.

In two randomized trials, metopimazine improved the efficacy of ondansetron and of ondansetron plus methylprednisolone. Both pharmacological interventions such as cannabinoids and olanzapine, which act in multiple dopaminergic, serotonergic, muscarinic and histaminic receptor sites, and non-pharmacologic interventions, such as acupuncture, could be considered. More recently, some studies have documented antiemetic activity of the NK_1 receptor antagonists in patients who did not achieve complete

protection from emesis when treated with dexamethasone and a serotonin receptor antagonist alone.

prevention of anticipatory nausea and vomiting

Anticipatory nausea and vomiting is widely believed to be a learned response to chemotherapy that develops in up to 20% of patients by the fourth treatment cycle. More recent studies showed that the rate of anticipatory nausea and vomiting is much less than observed in older studies that used less satisfactory antiemetic prophylactic treatments (<10% of anticipatory nausea and <2% of anticipatory vomiting). The risk of anticipatory nausea and vomiting tends to increase with the number of cycles received and the symptoms may persist for a long time after the completion of chemotherapy. If postchemotherapy nausea and vomiting do not occur then anticipatory nausea and vomiting are unlikely to develop. Patient characteristics, such as age <50 years, nausea and vomiting after the last chemotherapy, susceptibility to motion sickness, anxiety, expectations of post-treatment nausea, experiencing sweating after the last treatment, can predict the occurrence of anticipatory nausea and vomiting.

Once it develops, anticipatory nausea and vomiting is difficult to control by pharmacological means. Therefore, the panel recommended that the best approach to the treatment of anticipatory emesis is the best possible control of acute and delayed emesis [High, High] [II, B].

Behavioural therapies, in particular progressive muscle relaxation training, systematic desensitization and hypnosis, can be used to effectively treat anticipatory nausea and vomiting [High, High] [II, B] but unfortunately their use will remain difficult to implement as most patients are treated in settings where the needed expertise is not available.

Benzodiazepines are the only drugs that reduced the occurrence of anticipatory nausea and vomiting but their efficacy tended to decrease as chemotherapy treatment continued [Moderate, Moderate] [II, B].

prevention of nausea and vomiting induced by high-dose chemotherapy

There are still very few data on the effective use of modern antiemetics for patients treated with high-dose chemotherapy with stem cell support. Most reports involve phase II studies of a 5-HT_3 receptor antagonist alone or combined with dexamethasone. A major difficulty in evaluating patients in this setting is the multi-factorial nature of the nausea and vomiting. In addition to chemotherapy, other contributing causes of emesis include prophylactic antibiotics, narcotic analgesics and in some patients the use of total body irradiation. Cross-comparison of studies is difficult due to the varied regimens and different patient populations and tumour types. Most patients have experienced emesis with prior chemotherapy or irradiation.

Three small randomized trials involving the 5-HT_3 receptor antagonists have been published in which (i) ondansetron was shown to be superior to metoclopramide and droperidol, (ii) granisetron showed similar efficacy to standard antiemetic therapy and (iii) a continuous infusion of chlorpromazine was comparable to but more toxic than a continuous infusion of ondansetron.

A phase II study in 42 patients submitted to high-dose chemotherapy and stem cell transplantation evaluated the activity of an antiemetic regimen consisting of a 5-HT_3 receptor antagonist, dexamethasone and aprepitant. The complete response rate was 42.9%.

In summary, complete protection from nausea and vomiting is currently achieved in a minority of patients receiving high-dose chemotherapy and stem cell transplantation. The use of a 5-HT_3 receptor antagonist with dexamethasone represents the current standard of care. Randomized studies evaluating the efficacy of aprepitant added to standard therapy are necessary.

prevention of radiotherapy-induced nausea and vomiting

As many as 50%–80% of patients undergoing radiotherapy will experience nausea and/or vomiting depending on the site of irradiation. Fractionated radiotherapy may involve up to 40 fractions over a 6- to 8-week period and prolonged symptoms of nausea and vomiting could adversely affect quality of life. Furthermore uncontrolled nausea and vomiting may result in patients delaying or refusing further radiotherapy.

Incidence and severity of nausea and vomiting depend on radiotherapy-related factors (irradiated site, single and total dose, fractionation, irradiated volume, radiotherapy techniques) and patient-related factors (gender, general health of the patient, age, concurrent or recent chemotherapy, psychological state, tumour stage).

Current antiemetic guidelines (MASCC, ASCO, NCCN) for the use of antiemetics in radiotherapy are quite different when classifying radiation emetogenic risk categories and giving indications for the use of antiemetic drugs. This diversity of recommendations reflects the limited amount of high-level evidence available (few randomized studies and a small number of patients entered in each trial). The panel proposed new guidelines that summarize the updated data from the literature and take into consideration the existing guidelines. According to the irradiated area (the most frequently studied risk factor), the proposed guidelines divide these areas into four levels of emetogenic risk: high, moderate, low and minimal emetogenic (Table 6). In fact, the emetogenicity of radiotherapy regimens and recommendations for the appropriate use of antiemetics are given in regard to the applied radiotherapy or radiochemotherapy regimen. The updated guidelines offer guidance to the treating physicians for effective antiemetic therapies in radiotherapy-induced nausea and vomiting (Table 6).

antiemetics in children receiving cancer chemotherapy

Only a few studies have been carried out in children on the prevention of chemotherapy-induced emesis and it is inappropriate to assume that all results obtained in adults can be directly applied to children, since metabolism and side-effects of drugs may be different.

Table 6. Radiotherapy-induced emesis: emetic risk levels and new MASCC and ESMO guidelines[a]

Risk level	Irradiated area	Antiemetic guidelines	MASCC Level of Scientific Confidence/Consensus	ESMO Level of Evidence/ Grade of Recommendation
High (>90%)	Total body irradiation, total nodal irradiation	Prophylaxis with 5-HT_3 receptor antagonists + DEX	High/High (for the addition of DEX: Moderate/High)	II/B (for the addition of DEX: III/C)
Moderate (60–90%)	Upper abdomen, HBI, UBI	Prophylaxis with 5-HT_3 receptor antagonists + optional DEX	High/High (for the addition of DEX: Moderate/High)	II/A (for the addition of DEX: II/B)
Low (30%–60%)	Cranium, craniospinal, H&N, lower thorax region, pelvis	Prophylaxis or rescue with 5-HT_3 receptor antagonists.	Moderate/High (for rescue: Low/High	III/B for rescue: IV/C
Minimal (<30%)	Extremities, breast	Rescue with dopamine receptor antagonists or 5-HT_3 receptor antagonists	Low/High	IV/D

HBI, half body irradiation; UBI, upper body irradiation; H&N, head and neck; DEX, dexamethasone.
[a]In concomitant radiochemoterapy the antiemetic prophylaxis is according to the chemotherapy-related antiemetic guidelines of the corresponding risk category, unless the risk of emesis is higher with radiotherapy than chemotherapy.

Overall, metoclopramide, phenothiazines and cannabinoids only had moderate efficacy and significant side-effects, most notably marked sedation and extrapyramidal reactions. Ondansetron and granisetron have been shown to be superior to chlorpromazine, dimenhydrate and to metoclopramide combined with dexamethasone and were less toxic. As in the adult population the combination of a 5-HT_3 receptor antagonist with dexamethasone was shown to be more efficacious than a 5-HT_3 receptor antagonist alone. Therefore, all paediatric patients receiving chemotherapy of high or moderate emetogenic potential should receive antiemetic prophylaxis with a combination of a 5-HT_3 receptor antagonist and dexamethasone [Moderate, High] [III, B].

The optimal dose and scheduling of the 5-HT_3 receptor antagonists has been evaluated in several trials. Unfortunately, these studies are small and it is difficult to identify the optimal oral and intravenous doses of 5-HT_3 receptor antagonists in children. In clinical practice, established doses for ondansetron are 5 mg/m^2 or 0.15 mg/kg and for granisetron 0.01 mg/kg or 10 μg/kg once a day.

Only two studies involving a limited number of patients have compared different 5-HT_3 receptor antagonists in the paediatric population, and no studies specifically evaluated antiemetic drugs in the prevention of chemotherapy-induced delayed and anticipatory emesis.

conclusions

The 2009 ESMO–MASCC Consensus Conference on antiemetics updated the classification of the antineoplastic agents according to their emetogenic potential and the recommendations for the prophylaxis of nausea and vomiting induced by different chemotherapeutic and radiotherapeutic regimens (Tables 5 and 6).

The consensus panel had several lively discussions and not all recommendations were unanimous. A few panel members argued that palonosetron should be the preferred 5-HT_3 receptor antagonist in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. The majority of the panel concluded, however, that the two studies available were not sufficient to support this recommendation. Another discussion concerned patients receiving MEC. Quite a few panel members (30%) were not convinced that the current studies support a recommendation of using palonosetron as the preferred 5-HT_3 receptor antagonist in MEC. Due to accumulating data since the 2004 Consensus Meeting, 70% of the panelists agreed to recommend palonosetron as the preferred 5-HT_3 receptor antagonist in non-AC MEC. The consensus panel recommends that a combination of aprepitant, a 5-HT_3 receptor antagonist and dexamethasone is used in the prophylaxis of nausea and vomiting induced by AC chemotherapy (Table 5). Because no randomized study has investigated palonosetron in combination with a NK_1 receptor antagonist, no specific 5-HT_3 receptor antagonist is to be preferred in combination with a NK_1 receptor antagonist in AC chemotherapy. The majority (70%) of the panel wanted to state that palonosetron should be preferred in AC chemotherapy if a NK_1 receptor antagonist is not available.

Control of vomiting has markedly improved during the last years. Therefore in the future attention should shift to control of nausea, at present the greatest remaining emetogenic challenge. In fact, although vomiting and nausea seem to appear and respond in parallel, they are not the same phenomena. While vomiting can be objectively measured in terms of number of emetic episodes, nausea is a subjective phenomenon that requires different measurement tools and definitions. It has also been recognized that the standard primary endpoint for emetogenic trials, complete response, is defined as 'no vomiting and no use of rescue medication' and does not specifically refer to nausea or protection from nausea at all. Preliminary clinical trials of several agents have also suggested that just as some agents may be more effective against acute vomiting and some against delayed vomiting, other agents may be more effective against nausea than against

vomiting and vice versa. Identification and characterization of antinausea agents and rational inclusion of these agents into antiemetic regimens may be the primary challenge in coming years.

Besides nausea, additional problems of antiemetic therapy such as prophylaxis of cisplatin-induced delayed nausea and vomiting, nausea and vomiting induced by high-dose chemotherapy and nausea and vomiting induced by combined chemoradiation as well as antiemetics in children remain unsolved. Therefore, more research on these topics is necessary as is the development of new antiemetics, thereby leading to an improvement in quality of life in patients treated with chemotherapy and/or radiotherapy.

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note

MASCC Level of Confidence and MASCC Level of Consensus are given in square brackets, followed by Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology also in square brackets.

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