

Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference

The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC)†

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Background: In the late 1990s, several professional organizations convened antiemetic guideline groups and published the findings of these expert panels. Each of these documents was based on analyses of the available published trials and provided nearly similar recommendations. Nonetheless, small differences in emetic risk categories and treatment recommendations led to confusion in antiemetics selection. With the emergence of new findings and agents since the guidelines were initially published, many of the oncology professional societies have updated the antiemetic guidelines.

Materials and methods: A literature review up to March 2004 was carried out using MEDLINE with evaluation of the evidence by an expert panel composed of 23 oncology professionals in clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology. The experts represented nine oncology professional societies and came from 11 different countries on four continents.

Results: Recommendations on antiemetic regimens to prevent emesis induced by high, moderate, low and minimal risk chemotherapy were suggested as well as management of anticipatory emesis. Furthermore, recommendations for refractory emesis, emesis induced by high-dose chemotherapy and radiotherapy and for antiemetics in children receiving chemotherapy were elaborated.

Conclusions: Recommendations about antiemetic prophylaxis in patients receiving treatment with chemo- and radiotherapy have been updated by representatives of nine oncological organizations.

Key words: acute emesis, aprepitant, delayed emesis, dexamethasone, 5-HT₃-receptor antagonists, metoclopramide

introduction

Despite progress in the last 20 years, vomiting and nausea continue to be significant side effects of cancer therapy. In the late 1990s, to define the optimal antiemetic prophylaxis in patients receiving treatment with chemotherapy and radiotherapy, several professional organizations convened guideline groups and published the finding of these expert panels. Each of these documents was based on analyses of the published trials and on the whole provided similar recommendations. Nevertheless, small differences in the number of emetic risk categories and in some treatment recommendations confused many individuals attempting to implement the guidelines.

With the emergence of new research findings and agents since the most recent guidelines, many of the oncology professional

societies have encouraged an update of the antiemetic guidelines. Therefore, in 2004 a new guideline process was initiated and conducted by representatives from nine oncology organizations: the American Society of Clinical Oncology (ASCO), Cancer Care Ontario (CCO), the Clinical Oncology Society of Australia (COSA), the European Oncology Nursing Society (EONS), the European Society of Medical Oncology (ESMO), the Multinational Association of Supportive Care in Cancer (MASCC), the National Comprehensive Cancer Network (NCCN), the Oncology Nursing Society (ONS) and the South African Society of Medical Oncology (SASMO). The MASCC served as the host organization.

The methodology for this guideline process was based on a literature review up to March 2004 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, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology. The experts represented the nine oncology

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professional societies mentioned above and came from 11 different countries on four continents.

The panel comprised 10 committees, each composed of five to seven members and 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. Each committee completed a literature search, as described, within their own topic, agreed on updated recommendations and prepared a draft position paper prior to the 3-day consensus meeting (29–31 March 2004). During the conference, the findings of each committee were presented by the chair to the entire expert panel. The panel then discussed the recommendations and determined the level of evidence and the level of confidence for the recommendation according to MASCC criteria [1]. For a guideline recommendation to be accepted, a consensus of at least 75% of the expert panelists was needed.

An updating process was also put into place: every 6 months, each of the committees will be queried by the chair to determine whether any member wishes to have new evidence evaluated for possible guideline revision. If the committee determines that the evidence is of sufficient value it will make a recommendation to all the expert panelists who will decide whether a guideline change should be made. An updating process has recently been completed with regard to recommendations for the prevention of emesis induced by moderately emetogenic chemotherapy. Updated guidelines can be found at the MASCC website (www.mascc.org).

emetogenicity of antineoplastic agents

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. Secondly, 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. A useful schema would provide enough information to be utilized for both of these purposes. A number of schemas have been proposed in which chemotherapy agents have been divided among three to five levels of emetic risk [1, 2]. The literature has been a very limited source of information in the development of these schemas, given the imprecise and inconsistent ways in which information on emesis and nausea has been recorded in most therapeutic trials. Most schemas have not differentiated between the various types of emesis, such as acute, delayed and anticipatory, none have addressed nausea and only a few have accounted for important treatment- and patient-related variables, such as chemotherapy dose, infusion rate, route of administration, sex, age and history of ethanol consumption [1, 2].

A new problem in emetic assessment is the growing use of oral cytotoxic and targeted agents. The distinction between acute and delayed emesis loses significance when an agent is given orally over a period of several days or weeks.

Hesketh et al. [3] have proposed a classification system for acute emesis that accounts for chemotherapy dose and standardizes the rate and route of chemotherapy administration. Chemotherapy agents were divided into five levels according to the expected frequency of emesis in the

absence of effective antiemetic prophylaxis. Given the paucity of objective data in the literature, however, this schema reflects primarily the opinions of the authors.

Despite the limitations of the emetogenic classification schemas proposed to date, a working schema is necessary for treatment recommendations and defining the emetic risk in clinical trials. For this purpose, a modification of the schema of Hesketh et al. [3] based on the intrinsic emetogenicity of single agents is proposed. Intravenous chemotherapy agents are listed with division across four emetic risk groups: high, moderate, low and minimal (Table 1). A separate listing of oral agents is also proposed (Table 2). Since oral agents tend to be given daily for several days to several weeks, emetogenicity can only be judged for the entire period. Antiemetic regimens can differ from those recommended for single dose intravenous chemotherapeutic agents.

Table 1. Emetic risk of intravenous antineoplastic agents

Emetic risk (estimated incidence without prophylaxis)	Agent of emesis
High (>90%)	Cisplatin
	Mechlorethamine
	Streptozotocin
	Cyclophosphamide ≥ 1500 mg/m ²
	Carbustine
Moderate (30–90%)	Dacarbazine
	Oxaliplatin
	Cytarabine >1 gm/m ²
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m ²
	Doxorubicin
	Daunorubicin
	Epirubicin
	Idarubicin
Low (10–30%)	Irinotecan
	Paclitaxel
	Docetaxel
	Mitoxantrone
	Topotecan
	Etoposide
	Pemetrexed
	Methotrexate
	Mitomycin
	Gemcitabine
Minimal (<10%)	Cytarabine ≤ 100 mg/m ²
	5-Fluorouracil
	Bortezomib
	Cetuximab
	Trastuzumab
	Bleomycin
	Busulfan
	2-Chlorodeoxyadenosine
	Fludarabine
	Vinblastine
Vincristine	
Vinorelbine	
Bevacizumab	

prevention of acute emesis induced by high emetic risk chemotherapy

Previous recommendations suggest a combination of a 5-HT₃-receptor antagonist plus dexamethasone as the regimen of choice for the prevention of acute emesis in cisplatin-treated patients [1, 2].

Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK1) neurotransmitter receptor, the binding site of the regulatory peptide Substance P. Aprepitant has been studied extensively for the prevention of cisplatin-induced emesis. Several phase II double-blind studies showed added antiemetic activity when combined with a 5-HT₃-receptor antagonist plus dexamethasone [4].

Two phase III trials with identical design compared a standard two-drug regimen with ondansetron 32 mg plus dexamethasone 20 mg on day 1, followed by dexamethasone 8 mg twice a day on days 2–4 with a three-drug regimen of 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 days 2 and 3 [5, 6]. A reduced dose of dexamethasone was given in combination with aprepitant because a prior pharmacokinetic study found that aprepitant increased dexamethasone levels approximately two-fold.

The primary endpoint was complete response (no emesis, no use of rescue antiemetics) over the 5-day study period. In both studies complete response was superior with aprepitant (89% compared with 78% and 83% compared with 68% on day 1, 75% compared with 56% and 68% compared with 47% on days 2–5). Additional analysis confirmed that the aprepitant combination was significantly superior during six cycles of chemotherapy [7].

Therefore, to prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT₃-receptor antagonist,

dexamethasone and aprepitant given before chemotherapy is recommended (MASCC level of consensus: high; MASCC level of confidence: high).

The principles of 5-HT₃-receptor antagonist use to prevent acute vomiting and nausea induced by chemotherapy of high emetogenic risk are the following: (i) use the lowest tested fully effective dose, (ii) no schedule is better than a single dose given before chemotherapy, (iii) the antiemetic efficacy and adverse effects of these agents are comparable in controlled trials, (iv) intravenous and oral formulations are equally effective and safe; always use in combination with dexamethasone and administer before chemotherapy. Suggested therapeutically equivalent doses, schedules and route of administration of the 5-HT₃-receptor antagonists in the prevention of acute nausea and vomiting induced by highly emetic risk chemotherapy are reported in Table 3.

Concerning dexamethasone dose, the Italian Group for Antiemetic Research published a dose-finding study of dosages ranging from 4 to 20 mg, always given in combination with a 5-HT₃-receptor antagonist, in patients receiving cisplatin [8]. 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 previously noted, when used concomitantly with aprepitant, the 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’ [9]. This 125 mg dose was used in the randomized phase III comparison studies of aprepitant.

Table 2. Emetic risk of oral antineoplastic agents

Emetic risk (estimated incidence of emesis without prophylaxis)	Agent
High (>90%)	Hexamethylmelamine
Moderate (30–90%)	Procarbazine
	Cyclophosphamide
	Etoposide
	Temozolomide
Low (10–30%)	Vinorelbine
	Imatinib
	Capecitabine
Minimal (<10%)	Fludarabine
	Chlorambucil
	Hydroxyurea
	L-Phenylalanine mustard
	6-Thioguanine
	Methotrexate
	Gefitinib
Erlotinib	

Table 3. Dose and schedule of antiemetic agents to prevent acute emesis induced by chemotherapy of high emetic risk

Antiemetic	Single daily dose given before chemotherapy	MASCC	
		Level of consensus	Level of confidence
5-HT ₃ receptor antagonists			
Ondansetron	Oral: 24 mg	Moderate	High
	i.v.: 8 mg or 0.15 mg/kg	High	High
Granisetron	Oral: 2 mg	High	High
	i.v.: 1 mg or 0.01 mg/kg	High	High
Tropisetron	Oral or i.v.: 5 mg	High	Moderate
Dolasetron	Oral: 100 mg	High	Moderate
	i.v.: 100 mg or 0.18 mg/kg	High	High
Palonosetron	i.v.: 0.25 mg	High	Moderate
Dexamethasone	Oral: 12 mg	High	High
	Oral: 20 mg ^a	High	Moderate
Aprepitant	Oral: 125 mg	High	High

^aOnly in patients not receiving aprepitant.

prevention of delayed emesis induced by high emetic risk chemotherapy

Nausea and vomiting developing more than 24 h after chemotherapy is termed delayed emesis.

Among agents of high emetic risk, cisplatin has been the most extensively studied with respect to its potential to induce delayed nausea and vomiting. A number of predictive factors have been identified for the development of delayed emesis [10]. By far the most important is the presence or absence of acute nausea and vomiting. Approximately three to four times 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 previous chemotherapy cycles, cisplatin dose, sex and age.

All patients receiving cisplatin should receive prophylactic antiemetics for at least 3 days.

5-HT₃-receptor antagonists have minimal to modest activity in the prevention of cisplatin-induced delayed emesis. Earlier studies have demonstrated efficacy for combinations of oral dexamethasone plus metoclopramide or dexamethasone plus oral ondansetron [11], although even with these combinations about 50% of patients suffer delayed nausea and/or vomiting.

Previous guidelines recommended a combination of dexamethasone and either a 5-HT₃-receptor antagonist or metoclopramide to prevent cisplatin-induced delayed emesis. More recent randomized trials, however, have questioned the relative contribution of 5-HT₃-receptor antagonists in this setting. Trials compared granisetron [12, 13] or ondansetron [14] combined with dexamethasone with dexamethasone alone. In all three studies the combination regimen was no better than dexamethasone alone.

Aprepitant efficacy against delayed emesis has been evaluated in the two double-blind studies reported previously [5, 6]. During the delayed phase (days 2–5), complete response rates on the aprepitant and standard arms were 75% and 68% compared with 56% and 47% in the two studies, respectively. Given the different antiemetic regimens employed for acute prophylaxis, one could 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. Subsequent analysis of the combined database from these two phase II trials strongly suggested that aprepitant provided protection against delayed vomiting regardless of response in the acute phase [15]. 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.

Therefore, the panel recommended that given the dependence of delayed emesis and nausea on acute antiemetic outcome, optimal acute antiemetic prophylaxis should be employed. For cisplatin, this includes a three-drug combination of aprepitant, a 5-HT₃-receptor antagonist and dexamethasone.

In patients receiving cisplatin treated with a combination of aprepitant, a 5-HT₃-receptor antagonist and dexamethasone to prevent acute vomiting and nausea, the combination of

dexamethasone and aprepitant is suggested to prevent delayed emesis, on the basis of its superiority to dexamethasone alone (MASCC level of consensus: moderate; MASCC level of confidence: high).

To date, no trials have compared this regimen for delayed emesis with our previous standard (dexamethasone combined with a 5-HT₃-receptor antagonist or metoclopramide).

After having analysed the results of the randomized trials comparing a 5-HT₃-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 our previous standard with dexamethasone plus aprepitant. The question remains whether the metoclopramide plus dexamethasone regimen for delayed emesis should be compared with aprepitant plus dexamethasone. Only a clinical trial directly comparing these two regimens could definitively assess their relative efficacy.

No studies have been published evaluating the optimal dose of dexamethasone for the prevention of delayed emesis 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 emesis induced by chemotherapy of moderate emetic risk

The standard antiemetic therapy for acute emesis in patients receiving chemotherapy of moderate emetic risk is a combination of a 5-HT₃-receptor antagonist plus dexamethasone (MASCC level of confidence: high; MASCC level of consensus: high) [1]. This recommendation was confirmed during the 2004 Perugia Consensus Conference.

Subsequently, a double-blind study comparing oral aprepitant (125 mg) plus dexamethasone (12 mg) plus ondansetron (8 mg before and 8 mg 8 h after the chemotherapy) on day 1 and aprepitant 80 mg on days 2 and 3, with oral ondansetron (8 mg before and 8 mg 8 h after) plus dexamethasone (20 mg) on day 1 and ondansetron 8 mg twice on days 2 and 3 in 866 patients with breast cancer receiving cyclophosphamide ± doxorubicin or epirubicin has been published [16]. Complete response was superior with the aprepitant regimen compared with the control regimen (51% compared with 43%). Complete response on day 1 was also superior with aprepitant (76% compared with 69%, respectively). Adverse events were not significantly different between the two regimens. The superiority of the aprepitant combination was maintained throughout the four cycles of chemotherapy studied [17].

Therefore, the guidelines have been amended to incorporate this new information: women receiving a combination of an anthracycline plus cyclophosphamide represents a situation with a particularly high risk of vomiting and nausea. To prevent acute vomiting and nausea in these women, a three-drug regimen including single doses of a 5-HT₃-receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended (MASCC level of confidence: moderate; MASCC level of consensus: high).

No studies, so far, have investigated an aprepitant-based regimen in patients who receive chemotherapies of moderate emetic risk other than the combination of anthracycline plus cyclophosphamide. In these patients a 5-HT₃-receptor antagonist plus dexamethasone remains the antiemetic treatment of choice.

No clinically relevant differences have been found in the efficacy and tolerability between the 5-HT₃-receptor antagonists used for the prophylaxis of acute emesis induced by chemotherapy of moderate emetic risk. Furthermore, there is no difference in the efficacy of oral or iv administration of a 5-HT₃-receptor antagonist (palonosetron is only available as an iv formulation and is further discussed below). The optimum dose of dexamethasone is 8 mg [18] and of aprepitant 125 mg. Dose and schedule of antiemetics is shown in Table 4.

prevention of delayed emesis induced by chemotherapy of moderate emetic risk

Previous recommendations suggested that if patients have a significant probability of suffering delayed emesis, prophylactic treatment should be administered. In such a case, oral dexamethasone alone, a 5-HT₃-receptor antagonist alone or their combination, beginning 24 h after chemotherapy and continuing for a minimum of 72 h should be administered [1].

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 after chemotherapy [19]. These patients were randomized to placebo, dexamethasone or dexamethasone plus ondansetron. Dexamethasone was significantly superior to placebo in terms of the percentage of patients free of delayed vomiting or moderate to severe nausea (87% compared with 77%; *P* < 0.02). The combination of dexamethasone and ondansetron was not superior to dexamethasone alone (92% compared with 87%) and induced more constipation [19].

In patients who experienced vomiting or moderate to severe nausea on day 1 despite the optimal antiemetic prophylaxis of acute emesis, ondansetron plus dexamethasone was compared with dexamethasone alone in 87 patients. The combination was numerically but not statistically significantly superior to dexamethasone alone (41% compared with 23%).

Therefore, the panel recommended that patients who receive chemotherapy of moderate emetic risk known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis (MASCC level of confidence: high; MASCC level of consensus: high).

Oral dexamethasone is the preferred treatment (MASCC level of confidence: high; MASCC level of consensus: high) while the 5-HT₃-receptor antagonists may be used as an alternative (MASCC level of confidence: moderate; MASCC level of consensus: moderate).

Palonosetron is a 5-HT₃-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT₃ receptor antagonists. Two studies in patients treated with chemotherapy of moderate emetic risk demonstrated efficacy

Table 4. Dose and schedule of antiemetic agents to prevent acute emesis induced by chemotherapy of moderate emetic risk

Antiemetic	Single daily dose given before chemotherapy	MASCC	
		Level of consensus	Level of confidence
5-HT ₃ receptor antagonists			
Ondansetron	Oral: 16 mg (8 mg b.i.d.)	High	High
	i.v.: 8 mg or 0.15 mg/kg	High	Moderate
Granisetron	Oral: 2 mg	High	High
	i.v.: 1 mg or 0.01 mg/kg	High	High
Tropisetron	Oral : 5 mg	High	Low
	i.v.: 5 mg	High	Moderate
Dolasetron	Oral: 100 mg	High	Moderate
	i.v.: 100 mg	High	Moderate
	or 1.8 mg/kg		
Palonosetron	i.v.: 0.25 mg	High	High
Dexamethasone	i.v.: 8 mg	High	Moderate
Aprepitant	Oral: 125 mg	High	High

with a single intravenous dose of palonosetron 0.25 mg that was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases [20, 21]. In neither study were corticosteroids used. Somewhat surprisingly, a higher dose of palonosetron was less effective than a lower dose although still numerically superior to the comparator 5-HT₃-receptor antagonist.

In the absence of day 1 dexamethasone, single-dose palonosetron 0.25 mg is equal or superior to other 5-HT₃-receptor antagonists. However, superior efficacy in the setting of dexamethasone as recommended by the consensus guidelines has not been demonstrated. As with studies of other agents, it is possible that superiority in the initial 24 h explains much of the superiority observed in the delayed phase.

Administering aprepitant as part of a regimen incorporating dexamethasone and a 5-HT₃ receptor antagonist (see above) was associated with better results in delayed phases (complete response in 55% compared with 49% of patients on days 2–5) in one randomized trial in breast cancer patients receiving a combination of anthracycline plus cyclophosphamide [16]. Limitations of that study design do not allow conclusions about the benefit of continuing dexamethasone beyond day 1 in patients receiving aprepitant or the value of administering aprepitant beyond day 1. Therefore, the panel updated the recommendation stating that in these patients aprepitant or dexamethasone be used to prevent delayed emesis (MASCC level of confidence: moderate; MASCC level of consensus: high). In patients who do not receive aprepitant, the use of oral dexamethasone is recommended for the prevention of delayed emesis induced by chemotherapy of moderate emetic risk.

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.

prevention of emesis induced by chemotherapy of low or minimal emetic risk

For patients treated with low or minimally emetic risk chemotherapy there is little evidence from clinical trials supporting the choice of any 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 a single agent such as dexamethasone 8 mg is suggested for the prophylaxis of acute emesis in patients receiving agents of low emetic risk (MASCC level of confidence: no confidence possible; MASCC level of consensus: moderate).

For patients receiving minimal emetic risk chemotherapy, no prophylactic antiemetic treatment should be routinely administered before chemotherapy in patients without a history of nausea and vomiting (MASCC level of confidence: no confidence possible; MASCC level of consensus: high).

Finally, the panel recommended that no prophylactic treatment should be administered for the prevention of delayed emesis induced by low or minimal risk emetic chemotherapy.

prevention of emesis induced by multiple-day chemotherapy

Few studies have been carried out with this type of chemotherapy. The intravenous combination of a 5-HT₃-receptor antagonist plus dexamethasone has been shown to induce about 55–83% complete protection from vomiting during the 3–5 days of cisplatin administration and this combination has proved superior to intravenous high-dose metoclopramide plus dexamethasone, alizapride plus dexamethasone or a 5-HT₃-receptor antagonist alone [1].

In these patients a phase III study compared two different schedules of dexamethasone (administered on days 1 and 2 compared with days 4 and 5) combined with ondansetron. There was no difference in nausea or vomiting during the 5 days of chemotherapy (22).

With daily 5-HT₃ receptor antagonist and dexamethasone prophylaxis patients receiving five consecutive days of cisplatin for testicular cancer generally have little or no nausea or vomiting during the first 3 days of chemotherapy. The worst nausea is seen on days 4 and 5 as well as on days 6, 7 and 8. Whether this reflects delayed nausea from the earlier days or whether there are other mechanisms involved is not clear. Strategies to prevent delayed nausea and vomiting for multiple-day cisplatin courses should be similar to those utilized for

single-day high-dose cisplatin. The current recommendation is to employ oral dexamethasone as a single 20 mg dose on each day of cisplatin administration (days 1–5) and then dexamethasone 8 mg orally twice on days 6 and 7 and 4 mg twice on day 8.

Therefore, patients receiving multiple-day cisplatin should receive a 5-HT₃-receptor antagonist plus dexamethasone for acute nausea and vomiting and dexamethasone for delayed nausea and vomiting (MASCC level of confidence: high; MASCC level of consensus: high).

The optimal dose of the 5-HT₃-receptor antagonist and dexamethasone, as well as the role of aprepitant in these patients, remains to be defined.

refractory and breakthrough emesis

'Refractory emesis' is generally defined as emesis occurring despite the use of antiemetic prophylaxis during the previous cycle of chemotherapy [1]. Breakthrough emesis represents vomiting that occurs on any day of treatment despite the administration of optimal antiemetic prophylaxis.

Breakthrough emesis is treated with rescue antiemetics given on the demand of a patient. No randomized trials have investigated breakthrough emesis, and only a few randomized double-blind trials have investigated antiemetics in patients with refractory emesis.

Different approaches have been utilized such as switching to a different 5-HT₃-receptor [23] or adding other agents such as dopamine antagonists, benzodiazepines or neuroleptic agents such as haloperidol or phenothiazines. Palonosetron is a new 5-HT₃-receptor agent and whether the substitution of this would be beneficial is unknown. Likewise, the same is true for the NK1 antagonist aprepitant. Novel agents such as olanzapine could also be considered [24]. Olanzapine has action in multiple dopaminergic, serotonergic, muscarinic and histaminic receptor sites.

A few trials have investigated patients with refractory emesis defined as emesis in the previous cycle of chemotherapy. In two randomized trials, metopimazine improved the efficacy of ondansetron and of ondansetron plus methylprednisolone [25, 26].

prevention of anticipatory emesis

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 [1]. More recent studies showed that the incidence of anticipatory nausea and vomiting is much less than observed in older studies which used less satisfactory antiemetic prophylactic treatments (less than 10% of anticipatory nausea and less than 2% of anticipatory vomiting). The risk of anticipatory nausea and vomiting increases with the number of cycles received and the symptoms may persist for a long time after the completion of chemotherapy. If post-chemotherapy nausea and vomiting do not occur then anticipatory nausea and vomiting are very unlikely. Patient characteristics, such as age < 50 years, nausea and vomiting after the last chemotherapy, susceptibility to

motion sickness, experiencing ‘sweating’ or ‘generalized weakness’ after the last treatment, can predict the occurrence of anticipatory nausea and vomiting [27, 28].

A relationship has also been demonstrated between emotional distress and expectations [29]. Once it develops, anticipatory nausea and vomiting is difficult to control by pharmacological means. Therefore, the panel recommended that the best management of anticipatory emesis is the best possible control of acute and delayed emesis (MASCC level of confidence: high; MASCC level of consensus: high).

Behavioural therapies involving desensitization can be used to treat anticipatory nausea and vomiting effectively (MASCC level of confidence: high; MASCC level of consensus: high) but unfortunately their use will remain difficult to implement as most patients are treated in settings where the necessary expertise is not available.

Benzodiazepines reduce anticipatory nausea and vomiting but their efficacy decreases as chemotherapy treatment continues (MASCC level of confidence: moderate; MASCC level of consensus: moderate).

prevention of emesis induced by high-dose chemotherapy

There are little data on the use of antiemetics for patients receiving high-dose chemotherapy, mainly phase II studies of a 5-HT₃-receptor antagonist alone or combined with dexamethasone. Nausea and vomiting in this setting are triggered by multiple causes including antibiotics, narcotic analgesics that are used for mucositis, as well as the chemotherapy-induced nausea and vomiting. In addition, the use of total body irradiation can be a confounding factor. Cross-comparison of studies are difficult due to the varied regimens and different patient populations.

Three small randomized trials involving the 5-HT₃-receptor antagonists have been published in which ondansetron was shown to be superior to metoclopramide and droperidol, granisetron showed similar efficacy to that of standard antiemetic therapy and a continuous infusion of chlorpromazine was comparable to but more toxic than a continuous infusion of ondansetron [1]. In these studies, however, complete protection from nausea and vomiting was achieved in only a small proportion of patients and, therefore,

controlling nausea and vomiting in patients receiving high-dose chemotherapy and stem cell transplantation remains an unmet need. Standard therapy appears to be a 5-HT₃-receptor antagonist with dexamethasone. Neither palonosetron nor aprepitant has been studied in these patients.

prevention of radiotherapy-induced emesis

As many as 40–80% of patients undergoing radiotherapy will experience nausea and/or vomiting depending on the site of irradiation. Many individuals receive fractionated radiotherapy which can involve up to 40 fractions over a 6–8 week period and prolonged symptoms of nausea and vomiting could affect quality of life. Furthermore, uncontrolled nausea and vomiting may result in patients delaying or refusing further radiotherapy. Nausea and vomiting are often underestimated by radiation oncologists.

The incidence and severity of nausea and vomiting depend on radiotherapy-related factors (single and total dose, fractionation, irradiated volume, radiotherapy techniques) and patient-related factors (sex, general health of the patient, age, concurrent or recent chemotherapy, psychological state, tumour stage). However, the observational trial by the Italian Group for Antiemetic Research in Radiotherapy (IGARR) provided evidence that the irradiated site (upper abdomen), radiation field size (>400 cm²) and previous chemotherapy were the only significant risk factors [30].

Previous antiemetic guidelines (MASCC, ASCO, ASHP, NCCN) for the use of antiemetics in radiotherapy vary considerably in 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, with 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 [31, 32]. Using the site of irradiated area as the basis for stratification the proposed guidelines are divided into four levels of risk: high, moderate, low and minimal emetogenic risk (Table 5). They offer guidance to prescribing physicians for effective antiemetic therapies in radiotherapy-induced nausea and vomiting (Table 5).

Table 5. Radiation emetic risk level and prevention of radiotherapy-induced emesis

Risk level	Irradiated area	Antiemetic guidelines	MASCC evidence (level of scientific confidence/level of consensus)
High (>90%)	Total body irradiation	Prophylaxis with 5-HT ₃ -receptor antagonists + dexamethasone	High/high Moderate/high
Moderate (60–90%)	Upper abdomen	Prophylaxis with 5-HT ₃ -receptor antagonists	High/high
Low (30–59%)	Lower thorax region and pelvis	Prophylaxis or rescue with 5-HT ₃ -receptor antagonists	Moderate/high
	Cranium (radiosurgery) and craniospinal		Low/high
Minimal (<30)	Head and neck, extremities, cranium and breast	Rescue with dopamine receptor antagonists or 5-HT ₃ -receptor antagonists	Low/high

antiemetics in children receiving cancer chemotherapy

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

When tested specifically in children, metoclopramide, phenothiazines and cannabinoids had only moderate efficacy and significant side effects, most notably sedation and extrapyramidal reactions. Ondansetron and granisetron have been shown to be superior to chlorpromazine and to metoclopramide combined with dexamethasone and were less toxic. As in adults the combination of a 5-HT₃-receptor antagonist with dexamethasone was shown to be more efficacious than a 5-HT₃-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-HT₃-receptor antagonist and dexamethasone (MASCC level of confidence: moderate; MASCC level of consensus: high).

The optimal dose and scheduling of the 5-HT₃-receptor antagonists has been evaluated in nine trials [33]. Unfortunately, these studies are insufficient to identify the optimal oral and intravenous doses of the 5-HT₃-receptor antagonists in children. In clinical practice, typically used doses follow the adult mg/kg regimens (i.e. ondansetron 0.15 mg/kg and granisetron 0.01 mg/kg).

Only one study has compared different 5-HT₃-receptor antagonists in children and no trials specifically evaluated antiemetic drugs in the prevention of delayed and anticipatory emesis.

conclusions

The 2004 Perugia Consensus Conference on antiemetics updated recommendations for the use of antiemetics in cancer patients receiving different chemotherapeutic and radiotherapy regimens and reconciled the guidelines of different professional organizations.

The major findings, since the publication of the first MASCC [1] and ASCO [2] antiemetic guidelines in 1998/1999, are from (i) studies investigating the new 5-HT₃-receptor antagonist, palonosetron [18, 19], (ii) studies investigating the NK1-receptor antagonist aprepitant [5–7, 9, 15–17] and (iii) studies defining the optimum doses of dexamethasone for the prevention of acute emesis induced by moderately [18] and highly [8] emetogenic chemotherapy, respectively. Palonosetron is an effective new 5-HT₃-receptor antagonist. Studies of this agent evaluating its effectiveness compared with guideline-recommended antiemetic regimens are necessary to fully define its role in emesis management. The use of the NK1-receptor antagonist aprepitant has now been included in the recommendations for the prevention of emesis induced by chemotherapy of moderate and high emetic risk.

We anticipate that the results of this meeting will provide useful information to our colleagues in helping to standardize antiemetic prophylaxis worldwide. We realize that the

elaboration of evidence-based recommendations is only the beginning of a process. The greater challenge is successfully implementing the recommendations. Recognizing the rapid changes that can occur in the antiemetic field, we have also established a process for updating the guidelines every 6 months. We hope this process will provide practitioners with timely evidence-based recommendations which will further minimize the extent of nausea and vomiting experienced by cancer patients.

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references

1. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy and radiotherapy-induced emesis: results of Perugia Consensus Conference. *Ann Oncol* 1998; 9: 811–819.
2. Gralla RJ, Osoba D, Kris MG et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *J Clin Oncol* 1999; 17: 2971–2994.
3. Hesketh PJ, Kris MG, Grunberg SM et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997; 15: 103–109.
4. Hesketh PJ. Potential role of the NK1 receptor antagonists in chemotherapy-induced nausea and vomiting. *Support Care Cancer* 2001; 9: 350–354.
5. Hesketh PJ, Grunberg SM, Gralla RJ et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients

- receiving high-dose cisplatin – the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003; 21: 4112–4119.
6. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003; 97: 3090–3098.
 7. de Witt R, Herrstedt J, Rapoport B et al. The oral NK₁ antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III trials. *Eur J Cancer* 2004; 40: 403–410.
 8. Italian Group for Antiemetic Research. Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. *J Clin Oncol* 1998; 16: 2937–2942.
 9. Chawla SP, Grunberg SM, Gralla RJ et al. Establishing the dose of the oral NK₁ antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 2003; 97: 2290–2300.
 10. Tavorath R, Hesketh PJ. Drug treatment of chemotherapy-induced delayed emesis. *Drugs* 1996; 52: 639–648.
 11. The Italian Group for Antiemetic Research. Ondansetron versus metoclopramide, both combined with dexamethasone, in the prevention of cisplatin-induced delayed emesis. *J Clin Oncol* 1997; 15: 124–130.
 12. Goedhals L, Heron JF, Kleisbauer JP et al. Control of delayed nausea and vomiting with granisetron plus dexamethasone or dexamethasone alone in patients receiving highly emetogenic chemotherapy: A double-blind placebo-controlled study. *Ann Oncol* 1998; 6: 661–666.
 13. Latreille J, Pater J, Johnston D et al. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy. *J Clin Oncol* 1998; 16: 1174–1178.
 14. Tsukada H, Hirose T, Yokoyama A et al. Randomized comparison of ondansetron plus dexamethasone with dexamethasone alone for the control of delayed cisplatin-induced emesis. *Eur J Cancer* 2001; 37: 2398–2404.
 15. Warr DG, Grunberg SM, Gralla RJ et al. The oral NK₁ antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: Pooled data from 2 randomised, double-blind, placebo-controlled trials. *Eur J Cancer* 2005; 41: 1278–1285.
 16. Warr DG, Hesketh PJ, Gralla RJ et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol* 2005; 23: 2822–2830.
 17. Herrstedt J, Muss HB, Warr DG et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer* 2005; 104: 1548–1555.
 18. Roila F, Basurto C, Bosnjak S et al. Randomized, double-blind, dose-finding study of dexamethasone in preventing acute emesis induced by anthracyclines, carboplatin or cyclophosphamide. *J Clin Oncol* 2004; 22: 725–729.
 19. Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. *N Engl J Med* 2000; 342: 1554–1559.
 20. Gralla R, Lichinitser M, Van der Vegt S et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol* 2003; 14: 1570–1577.
 21. Eisenberg P, Figueroa-Vadillo J, Zamora R et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT₃-receptor antagonist: results of a phase III, single-dose trial versus dolasetron. *Cancer* 2003; 98: 2473–2482.
 22. Fox SM, Einhorn LH, Cox E et al. Ondansetron vs ondansetron, dexamethasone, and chlorpromazine in the prevention of nausea and vomiting associated with multiple-day cisplatin chemotherapy. *J Clin Oncol* 1993; 11: 2391–2395.
 23. deWit R, de Boer AC, van Linden GHM et al. Effective cross-over to granisetron after failure to ondansetron, a randomized double-blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. *Br J Cancer* 2001; 85: 1099–1101.
 24. Passik SD, Loehrer PJ, Navari RJ et al. A phase I trial of olanzapine (Zyprexa) for the prevention of delayed emesis in cancer patients receiving chemotherapy: A Hoosier Oncology Group study. *Proc ASCO* 2002; 21: 374.
 25. Herrstedt J, Sigsgaard T, Boesgaard M et al. Ondansetron plus metopimazine compared with ondansetron alone in patients receiving moderately emetogenic chemotherapy. *N Engl J Med* 1993; 328: 1076–1080.
 26. Lebeau B, Depierre A, Giovanni M et al. The efficacy of a combination of ondansetron, methylprednisolone and metopimazine in patients previously uncontrolled with a dual antiemetic treatment in cisplatin-based chemotherapy. *Ann Oncol* 1997; 8: 887–892.
 27. Morrow GR. Clinical characteristics associated with the development of anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment. *J Clin Oncol* 1984; 2: 1170–1176.
 28. Morrow GR, Lindke J, Black PM et al. Predicting development of anticipatory emesis in cancer patients: prospective examination of eight characteristics. *J Pain Symptom Manage* 1991; 6: 215–223.
 29. Montgomery GH, Bovbjerg DH. Expectations of chemotherapy-related nausea: emotional and experiential predictors. *Ann Behav Med* 2003; 25: 48–54.
 30. The Italian Group for Antiemetic Research in Radiotherapy. Radiation-induced emesis: a prospective observational multicenter Italian trial. *Int J Radiat Oncol Biol Phys* 1999; 44: 619–625.
 31. Feyer PCh, Maranzano E, Molassiotis A et al. Radiotherapy-induced nausea and vomiting (RINV): antiemetic guidelines. *Support Care Cancer* 2005; 13: 12–128.
 32. Maranzano E, Feyer PCh, Molassiotis A et al. Evidence-based recommendations for the use of antiemetics in radiotherapy. *Radiother Oncol* 2005; 76: 227–233.
 33. Roila F, Feyer P, Maranzano E et al. Antiemetics in children receiving chemotherapy. *Support Care Cancer* 2005; 13: 129–131.