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Review

Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment

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Abstract

Nausea and vomiting are considered as two of the most distressing side-effects of chemotherapy. Chemotherapy-induced nausea and vomiting have been classified into acute, delayed and anticipatory based on the time of onset. The frequency of nausea and vomiting depends primarily on the emetogenic potential of the chemotherapeutic agents used. With the introduction of the 5-HT_3 receptor-antagonists in combination with dexamethasone in the early 1990s approximately 70% of patients receiving highly emetogenic chemotherapy were protected from acute emesis. However, 40% of patients have symptoms in the delayed phase. Another group of antiemetics, the neurokinin-1-receptor-antagonists, have recently been introduced. The addition of neurokinin receptor (NK1 receptor)-antagonists to standard therapy significantly improves emesis protection in the acute and in particular in the delayed phase by approximately 20%. Due to these new developments, revised antiemetic guidelines have been set. Here, the most recent developments in antiemetic therapy, including these guidelines, are reviewed.

Keywords: Anti-emetic therapy; MASCC-guidelines; NCCN-guidelines; Chemotherapy; 5-HT_3 receptor-antagonists; Steroids; Neurokinin-1-receptor-antagonists

1. Introduction

The goal of antiemetic therapy is to abolish nausea and vomiting. Twenty years ago, nausea and vomiting were inevitable adverse events of chemotherapy and forced up to 20% of patients to postpone or refuse potentially curative treatment. The introduction of the 5-HT_3 receptor-antagonists in the 1990s dramatically reduced chemotherapy-induced emesis, particularly when used in combination with corticosteroids. Another group of antiemetics, the neurokinin receptor-antagonists, have recently been developed, and the first drug in this class, aprepitant, has been approved by the authoritative bodies of the Food Drug Administration (FDA) and European Union (EU). Studies have shown that patients benefit from the use of this drug in combination with standard antiemetic therapy, both in the acute and delayed setting of cisplatin-induced nausea and vomiting.

This article will review the most recent developments in antiemetic therapy including the results from the 2004 Perugia Consensus Conference on antiemetic therapy, the Multinational Association of Supportive Care in Cancer (MASCC guidelines) and the National Comprehensive Cancer Network (NCCN) guidelines from 2004 [1,2] and will present a practical treatment approach for antiemetic prophylaxis.

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Table 1
Categories of chemotherapy-induced nausea and vomiting

Acute nausea and vomiting
Within the first 24 h after chemotherapy
Mainly by serotonin (5-HT) release from the enterochromaffin cells
Delayed nausea and vomiting
24 h to 5 days after start of chemotherapy
Various mechanisms: mainly substance P-mediated, disruption of the blood–brain barrier, disruption of gastrointestinal motility, adrenal hormones [28]
Anticipatory nausea and vomiting
Occurrence is possible after 1 cycle of chemotherapy
Involves the element of classic-conditioning
In approximately 30% of patients by the fourth treatment cycle after experience of emetic episode(s)

2. Acute/delayed/anticipatory nausea and vomiting

Chemotherapy-induced nausea and vomiting usually are classified into 3 categories: acute onset, occuring within 24 h of the initial administration of chemotherapy; delayed onset, occuring 24 h to several days after initial treatment; and anticipatory nausea and vomiting, observed in patients whose emetic episodes are triggered by taste, odour sight, thoughts, or anxiety secondary to a history of poor response to antiemetic agents (Table 1).

3. Classification of the emetic-risk

The emetogenic potential of chemotherapeutic agents is the main risk factor for the degree of chemotherapy-induced nausea and vomiting. With regard to their emetogenic potential, chemotherapeutic agents are classified into 4 emetic risk groups: high, moderate, low and minimal (Table 2) [1]. Other risk factors, including young age, female gender, low alcohol intake, experience of emesis during pregnancy, impaired quality of life and previous experience of chemotherapy, are known to increase the risk of nausea and vomiting after chemotherapy [3,4].

4. Antiemetic agents

With modern antiemetic therapy, nausea and vomiting can completely be prevented in almost 70–80% of patients [5,6]. Combination antiemetic regimens have become the standard of care for the control of chemotherapy-induced nausea and vomiting.

4.1. 5-HT_3 receptor-antagonists

The 5-HT_3 receptor-antagonists are without doubt the most effective antiemetics in the prophylaxis of acute nausea and vomiting. The following five 5-HT_3 receptor-antagonists are currently available: ondansetron, granisetron, tropisetron, dolasetron and palonosetron (Table 3). More than 50 randomised trials have compared the clinical effect of two or more of these agents and have

Table 2
Emetogenic risk of chemotherapeutic agents

High (emesis risk > 90% without antiemetics)	
Carmustine	Lomustine (>60 mg/m^2)
Cisplatin	Mechlorethamine
Cyclophosphamide (>1500 mg/m^2)	Pentostatin
Dacarbazine, DTIC	Streptozotocin
Dactinomycin, Actinomycin D	
Moderate (emesis risk 30–90% without antiemetics)	
Altretamin	Irinotecan
Carboplatin	Lomustine (<60 mg/m^2)
Cyclophosphamide (<1500 mg/m^2)	Melphalan i.v.
Cyclophosphamide, per os	Mitoxantrone (>12 mg/m^2)
Cytarabine (>1 g/m^2)	Oxaliplatin
Daunorubicin	Procarbazine, per os
Doxorubicin	Temozolamide
Epirubicin	Treosulfan
Idarubicin	Trabectedin
Ifosfamide	
Low (emesis risk 10–30% without antiemetics)	
Aldesleukin (IL-2)	Mitomycin
Asparaginase	Mitoxantrone (<12 mg/m^2)
Bortezomib	Paclitaxel
Cetuximab	Pegasparaginase
Cytarabine (<1 g/m^2)	Pemetrexed
Docetaxel	Teniposide
Etoposide i.v., per os	Thiopeta
5-Fluorouracil	Topotecan
Gemcitabine	Trastuzumab
Methotrexate	
Minimal (emesis risk <10% without antiemetics)	
Bleomycin: Bevacizumab	Gifitinib
Busulfan	α-, β-, γ-Interferon
Capecitabine	Melphalan per os
Chlorambucil	Mercaptopurine
Cladribine	Methotrexate (<100 mg/m^2)
Cytarabine (<100 mg/m^2)	Rituximab
Erlotinib	Thioguanin
Fludarabine	Vinblastine
Hydroxyurea	Vincristine
Imatinib mesylate	Vinorelbine

Adapted from [1,9,29], i.v., intravenous; p.o., orally.

Table 3
Dose of 5-HT_3 receptor-antagonists

Drug	Route	Recommended dose per day
Ondansetron	p.o.	12–24 mg
	i.v.	8 mg (0.15 mg/kg)
Granisetron	p.o.	2 mg
	i.v.	1 mg (0.01 mg/kg)
Tropisetron	p.o.	5 mg
	i.v.	5 mg
Dolasetron	p.o.	100 mg
	i.v.	100 mg (1.8 mg/kg)
Palonosetron	i.v.	0.25 mg

Adapted from [1,2,9]. p.o., orally.

been unable to find clinically meaningful differences [7]. However, a meta-analysis conducted recently and presented at the American Society of Clinical Oncology (ASCO) 2004 meeting including more than 40 studies and comparing all of the available 5-HT_3 receptor-antagonists suggested a possible advantage for granisetron compared with tropisetron [8]. In consideration of the MASCC guidelines, it was stated that given at biologically equivalent doses, ondansetron, granisetron, dolasetron, tropisetron and palonosetron are equally efficacious, equally safe, and appear to be interchangeable [1,9,10]. The adverse effects of 5-HT_3 receptor-antagonists are generally mild, with headache and constipation being most commonly described.

When administering 5-HT_3 receptor-antagonists, the following statements should be taken into account:

- The lowest fully effective dose for each agent should be used; higher doses do not enhance any aspect of activity because of receptor saturation.
- The oral and intravenous routes are similarly effective.
- Single dose regimens are as effective as multiple dose regimens.
- Adverse effects of these agents are comparable.

4.2. Steroids

The mechanisms by which steroids exert their anti-emetic activity are not fully understood. Steroids are considered to be effective and safe antiemetics. When used in combination with other anti-emetics, they appear to exert a booster effect in raising the emetic threshold. Theoretical concerns that steroids may interfere with the antitumour effects of chemotherapy through immunsuppressive mechanisms have not been confirmed in clinical trials [11]. In one study by Kemeny and colleagues [12] the addition of dexamethasone to floxuridine into the hepatic artery in patients with colorectal cancer significantly improved tolerance and showed a trend towards improved survival. It is not evident that there is any difference between the different steroids,

Table 4
Dose of steroids

Drug	Route	Recommended dose per day (mg)
		Moderate/High
Dexamethasone	p.o.	8/20
	i.v.	
Methylprednisolone	p.o.	40–125/40–125
	i.v.	

but dexamethasone appears to be the most intensively investigated (Table 4). For prevention of acute emesis an 8 mg single dose of dexamethasone for moderately emetogenic chemotherapy and 20 mg for highly emetogenic chemotherapy should be the doses of choice [1,13,14].

Side-effects are usually dependent on the dose and duration of therapy and include insomnia and hyperglycemia.

4.3. Neurokinin-1-(NK1)receptor-antagonists

Aprepitant represents a new class of anti-emetic. It is a potent selective, central nervous system (CNS)-penetrant, oral non-peptide antagonist of the NK1 receptor. Aprepitant has recently been approved by the United States (US) FDA and by the EU authorities to be used in acute and delayed emesis resulting from highly emetogenic chemotherapy, including cisplatin (FDA) or cisplatin-based therapy (EU). It has been shown in several studies to augment the antiemetic activity of the combination of the 5-HT_3 receptor-antagonist and dexamethasone to inhibit both, acute and, particularly, delayed emesis in cisplatin-based chemotherapy. Furthermore a randomised study of patients receiving moderately emetogenic chemotherapy showing superiority of the triple combination of a 5-HT_3 receptor-antagonist, dexamethasone and aprepitant used in the first 24 h followed by aprepitant alone for another 2 days. Whereas, the recently released MASCC-guidelines (April 2004) recommend aprepitant only for cisplatin-based chemotherapy a revision including aprepitant as well in the moderate emetogenic setting is expected soon. However, the NCCN guidelines already recommend aprepitant for moderate emetogenic chemotherapy in selected patients in combination with a 5-HT_3 receptor-antagonist plus dexamethasone [2].

Concerning the dose, a randomised study established the most favourable risk profile of aprepitant at doses of 125 mg orally (p.o.) on day 1 and 80 mg p.o. on days 2 and 3 (Table 5) [15].

Table 5
Dose of neurokinin-1-receptor-antagonist

Drug name	Route of administration	Recommended dose
Aprepitant	p.o.	125 mg day 1, 80 mg days 2 + 3

Aprepitant is eliminated primarily by metabolism of CYP3A4 and is a substrate and moderate inhibitor of CYP3A4 [16]. Therefore, possible interactions between aprepitant and other drugs have been investigated intensively. A 2-fold increase in the area under concentration curve (AUC) of dexamethasone, as a sensitive substrate of CYP3A4, could be demonstrated when it was combined with aprepitant. Therefore, the dose of dexamethasone should be reduced by approximately 50% when aprepitant is coadministered. As such, a potential risk of interaction with cytotoxic drugs metabolised by CYP3A4 may occur. So far, preliminary data from an ongoing trial have shown no interaction between docetaxel (metabolised by CYP3A4) and aprepitant [16]. In clinical trials in general, patients treated with aprepitant do not have a statistically different incidence of adverse events from those receiving placebo.

4.4. Dopamine receptor antagonists

Dopamine receptor antagonists were the basis of antiemetic therapy from the 1950s to the early 1980s, but their efficacy as single agents is relatively low. They can be divided into phenothiazines (e.g., promethazine and metopimazine), butyrophenones (e.g., haloperidol and droperidol) and substituted benzamides (e.g., metoclopramide and alizapride).

Metoclopramide has been most intensively investigated and possesses antiemetic activity when given in conventional doses to patients receiving mildly or moderately emetogenic chemotherapy [17]. However, in patients receiving cisplatin-based chemotherapy, conventional doses of metoclopramide are not significantly different from placebo. Today, it is recognised that the effect of high-dose metoclopramide in patients receiving cisplatin is due to antagonism at the 5-HT_3 receptors [18]. Adverse effects are mainly extrapyramidal symptoms, especially in higher doses, sedation and orthostatic hypotension.

4.5. Benzodiazepines

Benzodiazepines can be a useful addition to antiemetic regimens in certain circumstances. Trials with lorazepam have shown a high degree of patient acceptance. As such, they serve to reduce anxiety and reduce the risk of anticipatory nausea. Lorazepam may add a small degree of objective anti-emetic efficacy. However, this property is so limited that the use of lorazepam as a single-agent antiemetic is not recommended. A double-blind randomised study showed that its known anti-anxiety effects can be quite prominent in the chemotherapy administration setting when added to effective antiemetic combinations [19]. Lorazepam is the preferred agent for anticipatory nausea and vomiting.

4.6. Cannabinoids

Cannabinoids (e.g. dronabinol) are thought to exert antiemetic activity at the cannabinoid receptor, likely located in the brain stem [20]. In a systematic review of the efficacy of oral cannabinoids in the prevention of nausea and vomiting, it was found that cannabinoids were slightly better than conventional antiemetics (e.g., metoclopramide, phenothiazines, haloperidol). However, their usefulness was generally limited by the high incidence of toxic effects such as dizziness, dysphoria and hallucinations. Accordingly, dronabinol is recommended for consideration in the treatment of breakthrough or refractory emesis. Doses in the range of 5–10 mg/m^2, every 3–4 h, orally, appear to be among the most useful [21].

4.7. Antihistamines

Antihistamines have been administered both as antiemetics and adjunctive agents to prevent dystonic reactions with dopamine antagonists. Studies with diphenhydramine or hydroxyzine in the prevention of chemotherapy induced nausea and vomiting have not shown any antiemetic activity for these drugs [9].

In palliative care, the antihistamines have a role in the treatment of nausea thought to be mediated by the vestibular system. Side-effects of antihistamines include drowsiness, dry mouth, and blurred vision.

5. Recommendations

Focused on the new MASCC guidelines from 2004 and NCCN Guidelines from 2004, the following treatment options are recommended (Table 6) [1,2]. The appropriate antiemetic regimen is based on the emesis risk categories (Table 2).

5.1. Prevention of acute nausea and vomiting

High risk of emesis: For agents in the high-risk category, the MASCC and NCCN guidelines suggest unanimously a combination of 5-HT_3 receptor-antagonist, dexamethasone and aprepitant within the first 24 h.

Moderate risk of emesis: Due to a lack of published randomised studies in the moderate emetogenic setting when creating the guidelines, conflicting recommendations are present. The NCCN guidelines recommended aprepitant already in selected patients for the moderate emetogenic chemotherapy in combination with a 5-HT_3 receptor-antagonist plus dexamethasone. However, the actual MASCC guidelines recommend a 5-HT_3 receptor-antagonist plus dexamethasone without aprepitant because of a lack of published studies at the time of the Perugia Consensus Conference. Considering the pos-

Table 6
Antiemetic prevention based on the emesis risk category according to the MASCC and NCCN-guidelines

Emesis risk	Acute (day 1)	Followed by	Delayed (days 2–5)
High	5-HT_3 + Dex + NK1	→	Dex + NK1
Moderate	5-HT_3 + Dex + NK1 in selected patients or 5-HT_3 + Dex	→	Dex alone or 5-HT_3 alone or metoclopramide alone or DEX + NK1 in selected patients
Low	Dex	→	None
Minimal	None	→	None

Adapted from [1,2]. 5-HT_3: 5-HT_3 receptor-antagonist, Dex: dexamethasone, NK1: neurokinin-1- receptor antagonist.

itive results from the most recent study in the moderate emetogenic setting showing a significantly better emesis control with aprepitant presented at the annual ASCO meeting in 2004, a revision of the MASCC guidelines including aprepitant is expected soon [22].

Low risk of emesis: Both guidelines recommend unanimously the use of a steroid alone.

Minimal risk of emesis: It is suggested that, for patients treated with agents of low emetic risk, no antiemetic drug should be routinely administered before chemotherapy.

5.2. Prevention of delayed nausea and vomiting

Trials have indicated that between 60 to nearly 90% of patients receiving cisplatin will experience delayed emesis if not given preventive antiemetics. Despite the efficacy of 5-HT_3 receptor-antagonists in the initial 24 h period after the start of chemotherapy, the therapeutical role in the delayed phase is rather limited [23]. The recommended treatment options for the delayed phase according to the MASCC and NCCN guidelines are shown in Table 6.

High risk of emesis: In two Phase III studies an average increase of 20% complete response rates was achieved in patients receiving apreptiant plus standard antiemetic therapy in comparison to standard antiemetic therapy plus placebo only [5,6]. On that basis, both panels suggested the combination of dexamethasone and aprepitant to prevent delayed emesis in cisplatin-based chemotherapy (MASCC) and highly emetogenic chemotherapy (NCCN).

Moderate risk of emesis: As stated for the acute emesis, there are different recommendations in the delayed setting as well. In the NCCN guidelines, aprepitant is already recommended in selected patients for moderate emetogenic chemotherapy in combination with dexamethasone. The MASCC guidelines suggest dexamethasone alone or a 5-HT_3 receptor-antagonist alone. In contrast to the NCCN guidelines metoclopramide is no longer recommended by the MASCC guide-lines.

Low and minimal risk of emesis: No regular preventive use of antiemetics for delayed emesis is suggested for patients receiving these chemotherapeutic agents.

5.3. Treatment of anticipatory nausea and vomiting

Prevention of chemotherapy-induced vomiting is seen as the best strategy for preventing anticipatory nausea and vomiting [24]. If it occurs, anticipatory nausea and vomiting should be managed by psychological techniques (e.g., behavioural therapy with systematic desensitisation). An alternative to or addition to psychological techniques is the use of benzodiazepines, in particular lorazepam. [1,9].

5.4. Management of breakthrough nausea and vomiting

Breakthrough nausea and vomiting is defined as an event that happens in spite of optimal preventative treatment. Treatment of breakthrough symptoms is referred to as rescue therapy. If optimal treatment has been given as prophylaxis, repeated dosing of the same agents is unlikely to be successful [25]; an addition of a dopamine receptor antagonist might be useful. Anecdotal reports indicate that various interventions that sedate patients may be of value in cases of breakthrough emesis. These comprise the use of benzodiazepines and neuroleptic agents, as suggested by the ASCO guidelines [9].

5.5. Refractory nausea and vomiting

Refractory nausea and vomiting refers to nausea or vomiting, or both, that recurs in subsequent cycles of therapy when all previous preventive and rescue treatments have failed. In one trial of granisetron failing with metoclopramide, dexamethasone and ondansetron indicated a response to alternative 5-HT_3 receptor-antagonists in 53–60% of cases [26]. These findings suggest a possible patient variability in response to the setrons. The reason may be an interindividually different hepatic metabolisation of the 5-HT_3 receptor-antagonists. Thus, tropisetron, dolasetron and palonosetron are mainly metabolised by the genetically polymorphic cytochrome P450 enzyme, 2D6. Ondansetron is metabolised partially through CYP2D6, as well as through cytochrome P450 enzymes, 3A4, 2E1, and 1A2. Ultrafast metabolisers for 2D6 show a lower maximal blood concentration and shorter half-life for tropisetron than poor metabolisers do [27].

5.6. Multiple-day chemotherapy

A considerable number of chemotherapeutic protocols are given over more than one day, of which the 5-day cisplatin represents the classical example. If after 24 h the same drug, i.e., cisplatin is given both an acute and eventually a delayed stimulus is generated. The expert panel creating the MASCC guidelines recommended for multiple–day cisplatin the use of a 5-HT_3 receptor-antagonist in combination with dexamethasone for acute nausea and vomiting and dexamethasone alone for delayed nausea and vomiting [1].

The use of a NK-1-receptor antagonist will probably add to the observed efficacy when the single day observations are extrapolated to the multiple day setting. However, no study is available to formally prove this proposal.

6. Conclusions

With the introduction of the neurokinin-1-receptor antogonist, a further step forwards in the prevention of nausea and vomiting has been made. With the triple combination therapy of a 5-HT_3 receptor-antagonist, neurokinin-1-receptor antogonist and dexamethasone, vomiting can be prevented in approximately 70–80% of patients receiving highly emetogenic therapy. Preventing emesis is a high priority for patients and to obtain optimal control, the results from antiemetic research must be transferred to clinical practice. Unfortunately, guidelines designed to define optimal care in this setting are often not followed in daily practice leading to suboptimal control of nausea and vomiting. One barrier to the implementation of guidelines is the underestimation of delayed nausea and vomiting by nurses and physicians. In spite of major improvements in controlling emesis after chemotherapy the effectiveness of the available antiemetic prophylaxis for nausea is still limited.

Conflict of interest statement

None declared.

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