

MiniReview**Anti-Emetic Therapy in Cancer Chemotherapy: Current Status**

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Abstract: Nausea and vomiting are ranked as the most severe side effects to chemotherapy by cancer patients. Twenty years ago, treatment of nausea and vomiting from chemotherapy only had moderate effect and often unpleasant side effects. The drugs used included dopamine₂-receptor antagonists and corticosteroids alone or combined. This review summarizes the development of anti-emetic therapy, but will focus on the importance of two new classes of anti-emetics: the serotonin₃- and the neurokinin₁-receptor antagonists. Furthermore, evidence-based guidelines for the treatment of chemotherapy-induced nausea and vomiting will be given. The serotonin₃-receptor antagonists, the first group of drugs developed specifically as anti-emetics, have significantly improved the prophylaxis of chemotherapy-induced emesis especially in combination with a corticosteroid. The improvement in the prophylaxis of nausea with this combination is however modest. A new group of anti-emetics, the neurokinin₁-receptor antagonists, has now been developed, and the first drug, aprepitant, was marketed in 2003. Aprepitant increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against acute emesis induced by highly or moderately emetogenic chemotherapy and aprepitant is also active in the protection against delayed emesis. The importance of drug–drug interactions with anti-emetics and other drugs, especially cytotoxins, through their competition for cytochrome P450 enzymes, have been studied. At present, there is no evidence that such interactions are of major clinical importance. Evidence-based clinical guidelines are now available and regularly updated, but unfortunately clinical implementation is slow. Recommendations for some types of chemotherapy-induced emesis such as delayed emesis, is based on a low level of evidence. Furthermore, the majority of clinical trials include highly selected groups of patients not permitting definite conclusions for other and more heterogeneous patient groups. Development of new anti-emetics with other mechanisms of action is awaited with interest.

Nausea and vomiting are ranked by patients as two of the worst adverse effects of cancer chemotherapy [1]. Twenty-five years ago, nausea and vomiting were inevitable adverse effects of cancer chemotherapy, but the development of new and potent anti-emetics has led to a significant decrease in a number of patients suffering from chemotherapy-induced vomiting. Today, the majority of patients consider nausea as the main problem.

Chemotherapy-induced nausea and vomiting is divided in the acute and the delayed phase, occurring 0–24 hr and 24–120 hr after initiation of chemotherapy. Furthermore, some patients suffer from anticipatory nausea or vomiting in the last few days before chemotherapy, in particular those who have experienced nausea or vomiting during previous cycles of chemotherapy.

The risk of suffering from nausea and vomiting is dependent on the emetic potential of the chemotherapy, specific patient risk factors and on the anti-emetic treatment. Young age, female gender and vomiting during previous chemotherapy are the most potent risk factors, whereas large alcohol consumption seems to be protective. In table 1,

the emetic potential of the most common cytotoxins are given. Patients receiving chemotherapy with a high emetic potential (more than 90% risk) or a moderate emetic potential (30–90% risk) have been most frequently investigated. It should be recognized that not only the specific cytotoxin but also the dose and the combination with other cytotoxins are risk factors.

This review summarizes the development of anti-emetic therapy, but will focus on the importance of two new classes of anti-emetics, the serotonin₃- and the neurokinin₁-receptor antagonists. Furthermore, evidence-based guidelines for the treatment of chemotherapy-induced nausea and vomiting will be given.

Pathophysiology

The emetic reflex protects human beings from poisoning by digestion of toxic substances. Therefore, emesis is a natural consequence of treatment with most cancer chemotherapy. The understanding of the emetic reflex arch is complicated and subject to current changes.

During the past 100 years, we have operated with terms as ‘the vomiting centre’ and the chemoreceptor trigger zone located in the lateral reticular formation and in the area postrema of the medulla oblongata, respectively [2,3]. The chemoreceptor trigger zone is located outside the blood-brain

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Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given

High (>90%)	Intravenous Cisplatin Mecloretamine, streptozocin, dacarbazine Cyclophosphamide >1500 mg/m ² Oral Procarbazine
Moderate (30–90%)	Intravenous Oxaliplatin Cytarabine >1000 mg/m ² Carboplatin Ifosfamide Cyclophosphamide <1500 mg/m ² Doxorubicin, epirubicin, daunorubicin, idarubicin Irinotecan Oral Cyclophosphamide, etoposide, temozolomide Vinorelbine, imatinib
Low (10–30%)	Intravenous Topotecan Gemcitabine Liposomal doxorubicin Mitoxantron Docetaxel, paclitaxel Etoposide Pemetrexed Methotrexate Mitomycin Fluorouracil Cytarabine <100 mg/m ² Bortezomib, cetuximab, trastuzumab Oral Capecitabine, fludarabine, topotecan
Minimal (<10%)	Intravenous Bleomycin Busulfan (not high dose) 2-chlorodeoxyadenosine Fludarabine Vincristine, vinblastine, vinorelbine Bevacizumab Oral Chlorambucil, hydroxyurea, methotrexate, gefitinib, erlotinib

Modified after the Multinational Association of Supportive Care guidelines [54].

barrier and therefore able to sense emetic stimuli from cytotoxins in the blood and in the spinal fluid. A number of receptors known to be involved in the emetic reflex arch have been demonstrated in the chemoreceptor trigger zone and the vomiting centre, including serotonin₃-, neurokinin₁-, dopamine₂-, muscarine-cholinergic receptors and others. Cytotoxins do not act by direct binding at these receptors [4], but rather by facilitating the release of transmitters such as serotonin, substance P and dopamine, which initiate the emetic reflex arch by stimulation of serotonin₃ (5-HT₃), neurokinin₁ (NK₁) and dopamine₂ (D₂) receptors, respectively. The development of specific and potent anti-emetics has led to a much better understanding of this process. Today, it is clear that only central NK₁ receptors are of importance, whereas both central and peripheral (in the gut) 5-HT₃ receptors participate in the emetic reflex. It has also been

demonstrated that another area of the medulla oblongata, the nucleus of the tractus solitarius, is important and probably contains the highest concentration of 5-HT₃ and NK₁ receptors in the brain [5]. Table 2 summarizes the most important receptors and transmitters known to be involved in the emetic reflex arch. Most anti-emetic agents act by binding at one of these receptors (antagonist), thereby preventing the (agonist) effect of the transmitters released, following administration of cancer chemotherapy. An exception from this, is the effect of cannabinoids such as dronabinol, that is exerted by agonism of cannabinoid₁ (CB₁) receptors. The mechanism of action of corticosteroids is unknown, but hypotheses such as modification of the capillary permeability of the chemoreceptor trigger zone, decrease in the inflammatory changes in the gut and participation in the release of endorphins have been suggested [6].

Table 2.

Transmitters and receptors known to be involved in the emetic reflex arch.

Transmitters	Receptors	Receptor subtypes relevant for the initiation of emesis
Serotonin	5-HT ₁ -5HT ₇	5-HT _{1A} 5-HT _{2A} 5-HT _{2C} 5-HT _{3A} 5-HT _{3B} 5-HT ₄
Substance P	NK ₁ -NK ₃	NK ₁
Dopamine	D ₁ -D ₅	D ₂ , D ₃
Endocannabinoids	CB ₁ , CB ₂	CB ₁

5-HT, serotonin; CB, cannabinoid; D, dopamine; NK, neurokinin.

Development and use of anti-emetics

Dopamine₂-receptor antagonists.

Before the introduction of cisplatin in the late 1970s, the only agents with some anti-emetic effect were D₂-receptor antagonists and corticosteroids. D₂-receptor antagonists can be divided into phenothiazines (chlorpromazine, prochlorperazine and metopimazine), butyrophenones (haloperidol and the derivative domperidone) and substituted benzamides (metoclopramide and alizapride). None of the D₂-receptor antagonists were originally developed as anti-emetics. They are only moderately effective when given in conventional doses and have significant adverse effects. Although metoclopramide is the most intensively investigated, the minimal effective dose has not been clearly defined. Old studies show that 20 mg orally, a commonly used dose, is probably no better than placebo [7]. A dose of 0.5 mg/kg patient has anti-emetic effect, but does induce extrapyramidal adverse effects, necessitating concomitant administration of an antihistamine, a benzodiazepine or an anticholinergic agent such as biperidene. The minimal effective dose of metopimazine is 15 mg [8] and the maximum tolerable dose is 30 mg orally four to six times a day [9]. In contrast to metoclopramide, metopimazine does not induce extrapyramidal adverse events, whereas orthostatic hypotension is the dose-limiting toxicity. Oral metoclopramide should therefore be dosed as 30 mg four times daily and metopimazine as 15–30 mg four times daily, when used in the treatment of chemotherapy-induced nausea and vomiting. Two studies have shown that metopimazine improves the anti-emetic effect of ondansetron [9,10]. The dopamine receptor antagonists are today primarily used as rescue anti-emetics in patients who suffer from nausea or vomiting despite treatment with anti-emetics as recommended by the evidence-based guidelines.

Corticosteroids.

The corticosteroids do not differ in anti-emetic effect, but dexamethasone is the one most intensively investigated.

In a meta-analysis, it was concluded that dexamethasone significantly decreases acute and delayed emesis and nausea. It was emphasized that no studies used dexamethasone in the delayed phase without having used dexamethasone in the acute phase, meaning that the protection after the initial 24 hr could be due to carry-over effect [11]. Corticosteroids are most often used in combination with other anti-emetics such as 5-HT₃-receptor antagonists and NK₁-receptor antagonists. The Italian Group for Antiemetic Research has defined the optimal dose of dexamethasone for acute emesis protection. In patients receiving cisplatin-based, highly emetogenic chemotherapy (HEC), a single intravenous dose of 20 mg is superior to lower doses [12], whereas in patients receiving moderately emetogenic chemotherapy (MEC), a single intravenous dose of 8 mg is as good as higher doses [13]. The adverse effects of corticosteroids, when used as anti-emetics, are usually tolerable and limited to insomnia, euphoria, facial flush and perineal itch. Some patients prefer other anti-emetics because of the weight gain often seen after corticosteroid administration. The use of corticosteroids as anti-emetics has recently been reviewed [14].

Cannabinoids.

Due to the adverse event profile, there are no routine indications for the use of cannabinoids as anti-emetics. Younger patients with insufficient effect of other anti-emetic therapy may benefit from the use of dronabinol [15].

Serotonin₃-receptor antagonists.

The first trial, demonstrating that high-dose metoclopramide is superior to placebo and prochlorperazine in prevention of cisplatin-induced emesis, was published in 1981 [16]. The understanding that the effect of high-dose metoclopramide was caused by antagonism at 5-HT₃ receptors and not by antagonism of D₂ receptors (as with low-dose metoclopramide) soon led to the development of more potent and specific 5-HT₃-receptor antagonists [17]. The 5-HT₃-receptor antagonists are today recommended as part of the anti-emetic combination for prophylaxis of acute nausea and vomiting in patients receiving MEC or HEC. In patients treated with cytotoxins of a low emetic potential (10–30% risk), they may be used as a single agent.

Ondansetron, granisetron, tropisetron, dolasetron and palonosetron are marketed in the USA and a number of European and other countries, whereas ramosetron and azasetron are marketed in Japan only. Palonosetron, the newest of these agents, has a very potent and specific binding at 5-HT₃ receptors and a half-life around 40 hr as compared to less than 10 hr for the other agents (table 3).

Ondansetron and granisetron were initially developed as 8 mg t.i.d. and 3 mg plus up to two additional doses within the first 24 hr after chemotherapy, respectively. Today, all these agents are primarily used as a single oral or intravenous dose (ondansetron can be given twice daily in patients receiving MEC). Originally ondansetron and granisetron were prescribed for up to 5 days after chemotherapy, but it is now recognized that the 5-HT₃-receptor antagonists are primarily effective

Table 3.

Serotonin₃ (5-HT₃)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [-log(Ki)]	Metabolism by CYP450 enzymes				t _{1/2} hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9 [†]	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. [†]In poor metabolizers 30 hr.

in the prophylaxis of acute emesis with limited or no efficacy in delayed emesis. Palonosetron might be an exception and it has been approved by the Food and Drug Administration (but not by the European Medicines Agency) in the treatment of delayed emesis from MEC.

Subsequent studies have shown that ondansetron is equal or superior to conventional-dose metoclopramide [18–20] and equal to dexamethasone [21] in patients receiving MEC and superior to high-dose metoclopramide against cisplatin-induced emesis [22,23]. Granisetron is superior to dexamethasone plus prochlorperazine in MEC [24] and equal to high-dose metoclopramide plus dexamethasone in patients receiving cisplatin-based chemotherapy [25].

Many randomized, double-blind trials have compared two or three of these agents, primarily ondansetron and granisetron. Three large studies found no significant differences between ondansetron and granisetron in patients treated with highly emetogenic, cisplatin-based chemotherapy [26,27] and MEC [28], respectively. Palonosetron has been compared to ondansetron and dolasetron in three randomized, double-blind trials. All were designed as non-inferiority trials and demonstrated that palonosetron was not inferior to dolasetron [29] and ondansetron [30] against emesis induced by MEC and to ondansetron in cisplatin-based chemotherapy [31]. Furthermore, in the MEC studies some of the evaluable parameters significantly favoured palonosetron.

Constipation and headache are drug class adverse effects and appear in around 10% of patients. There are no significant differences between the agents in adverse effects.

Neurokinin₁-receptor antagonists.

The NK₁-receptor antagonists are the second group of agents specifically developed for anti-emetic use. Substance P, the preferred ligand at NK₁ receptors, was isolated in 1931 [32], but not purified and sequenced before 1970 [33]. The first NK₁-receptor antagonist was found in 1984, but being a peptide it was too large to penetrate the blood-brain barrier, a necessity for NK₁-receptor antagonists to exert anti-emetic effect. The first non-peptide NK₁-receptor antagonist was developed in 1991, and the first clinical trial with one of these agents was published in 1997 [34].

A large number of NK₁-receptor antagonists have been investigated, but only aprepitant has been marketed, and only one other, casopitant, is so far in phase III. Studies have clearly demonstrated that NK₁-receptor antagonists

are not able to replace 5-HT₃-receptor antagonists [35], but are important additives [36].

During the development of aprepitant, it became clear that the dose of oral (and to a minor degree intravenous) corticosteroids had to be reduced due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Four phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy [37–39] or a combination of cyclophosphamide plus an anthracycline [40]. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 postcisplatin', was the primary end-point in all studies. Two of the HEC studies [37,38] used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2–4 with ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2–4 plus aprepitant days 2–3. In the Hesketh study [37], a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm was seen ($P < 0.001$), and in the Poli-Bigelli study [38] complete response rates were 62.7% versus 43.3% ($P < 0.001$). The most recently published HEC study [39] used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4. Again a statistically benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm ($P = 0.003$). In the first two studies, a difference of approximately 20% in complete response rates was seen. The reason for the smaller difference in the last study (11.4%) could be due to an effect of ondansetron days 2–4 in the control arm or that some of the prognostic risk factors (gender, alcohol consumption, history of emesis in pregnancy) favoured the control. In the first two HEC studies, patients were followed for up to six cycles of chemotherapy. During each of the cycles, the aprepitant-based arm was significantly superior to the control [41]. In the MEC study [40], a significant benefit in complete response of 9% was seen in the aprepitant arm ($P = 0.015$, response rates 50.8% versus 42.5%, respectively). If the components of complete response were divided into patients with no emesis and those without the need of rescue anti-emetics, a highly significant difference in the no vomiting rate was seen (76% versus 59%, $P < 0.001$), whereas there was no statistically significant difference in the number of patients who needed rescue anti-emetics.

Patients in this study were followed for up to four cycles of anthracycline plus cyclophosphamide chemotherapy, and the aprepitant-based arm was again significantly superior to the control arm during all cycles [42]. The sustained non-vomiting rate (patients, who did not have a single vomiting episode during any of the four cycles) was 63% in the aprepitant arm as compared to 39% in the control ($P < 0.001$). The conclusion is, therefore, that aprepitant significantly improves the effect of ondansetron plus dexamethasone in patients receiving a combination of cyclophosphamide plus an anthracycline.

The most frequent adverse events described in the phase III studies were fatigue, anorexia, dyspepsia, constipation, diarrhoea and hiccups.

Risk of drug–drug interactions with the use of anti-emetics

Patients receiving antineoplastic therapy in many cases have advanced or metastatic disease. Besides treatment with one or more antineoplastic drugs, this implies concomitant treatment with supportive care drugs such as anti-emetics, analgesics, neuroleptic drugs, antidepressants, anticoagulants, laxatives, corticosteroids, antibiotics and complementary medicines. Furthermore, the median age of cancer patients is in their 60s, thus with a considerably risk of other chronic diseases such as cardiovascular, gastrointestinal and rheumatologic diseases requiring additional medication. This patient group also has a high risk of age-related decrease in hepatic and renal function, resulting in a decrease in metabolism and excretion of many drugs. Overall, there is a 3–10-time increase in adverse drug reactions in older patients compared to younger [43]. Consequently, the polypharmacy in the older increases the risk of interactions significantly.

Interactions between anti-emetics and antineoplastic drugs.

Dopamine₂-receptor antagonists. Some of the D₂-receptor antagonists can possess antineoplastic activity or enhance cytotoxic drug activity. These studies have primarily been carried out *in vitro* or in animals, but generally such interactions have only been sparsely investigated [44].

Corticosteroids. No clinically relevant data.

Serotonin receptor₃ antagonists. There are differences in the metabolism of these drugs, especially in their interaction with the CYP system (table 3). Granisetron is metabolized by CYP3A4 (no enzyme inhibition), tropisetron by CYP2D6 (weak enzyme inhibition) with a minor contribution from CYP3A4 in poor metabolizers, dolasetron by CYP2D6 (weak enzyme inhibition by hydrodolasetron) and CYP3A4, ondansetron by CYP3A4, CYP2D6 (moderate enzyme inhibition), CYP1A1 and CYP1A2 (moderate enzyme inhibition) and palonosetron by CYP2D6, CYP3A4 and CYP1A2 (no enzyme inhibition on any of the three CYP), respectively [43]. Granisetron does not interfere with the metabolism of paclitaxel and docetaxel, both metabolized

by CYP3A4 enzymes *in vitro*, and granisetron did not interfere with the efficacy of cisplatin in a mouse model. Three clinical studies investigated the possible interaction between ondansetron and cyclophosphamide and two studies interactions between ondansetron and cisplatin. The pharmacokinetics of cyclophosphamide was changed (significant decrease in the area under the plasma-concentration curve (AUC)) in two studies but not in a third, whereas the pharmacokinetics of cisplatin was changed (AUC decreased) in one study, but not in another [44].

Substance P receptor antagonists. The NK₁-receptor antagonist aprepitant is primarily eliminated by metabolism of CYP3A4 with minor contributions from CYP1A2 and CYP2C19. Aprepitant is a substrate and a moderate inhibitor of CYP3A4 and an inducer of CYP2C9. A pharmacokinetic study has shown no interaction between docetaxel (metabolized by CYP3A4) and aprepitant [45]. In two phase III trials [37,38], a total of 1092 patients were randomized and 517 received chemotherapy metabolized by CYP3A4 in combination with cisplatin. There was a minor increase in adverse events in this group compared to the group that did not receive chemotherapy metabolized by CYP3A4, but no significant difference between those who received aprepitant ($n = 266$) and those who did not ($n = 251$), (30.1% versus 28.3%). The incidence of infections was, however, higher in the aprepitant group than in the standard therapy group (15.4% versus 10.0%) [46].

Interactions between different anti-emetics.

The potential metabolic interactions between anti-emetics have primarily been investigated as part of the development of the NK₁-receptor antagonist aprepitant.

Dexamethasone and methylprednisolone are sensitive substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism. When methylprednisolone is given in combination with aprepitant the intravenous dose can be reduced by 25% and the oral dose by 50% to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant [44]. Dexamethasone is an inducer of CYP3A4, but concomitant administration of dexamethasone and ondansetron has no clinically relevant impact on the AUC of aprepitant.

Granisetron is metabolized through CYP3A4 and ondansetron is metabolized in part by CYP3A4. Concomitant administration of aprepitant, dexamethasone and ondansetron increases the AUC of ondansetron by 15% compared to administration without aprepitant. The aprepitant dose was approximately three times higher than the dose chosen for phase III studies, and it was concluded that the increase in ondansetron AUC was without clinical relevance [47]. Co-administration of aprepitant, in the doses used for phase III studies, is without effect on the pharmacokinetics of oral granisetron. Interactions between aprepitant and dolasetron or aprepitant and tropisetron have not been investigated,

but interactions are not likely, because CYP2D6 is the major contributor in the metabolism of both drugs.

Interactions between anti-emetics and other drugs.

Dopamine₂-receptor antagonists. Dopamine₂-receptor antagonists such as phenothiazines (e.g. chlorpromazine, prochlorperazine) and butyrophenones (e.g. haloperidol) enhance the sedative effect of hypnotics, antihistamines, alcohol and analgesics. Use of phenothiazines in combination with antihypertensives increases the antihypertensive effect. Metoclopramide decreases the effect of L-dopa, and these two drugs should not be combined.

Corticosteroids. The effect of corticosteroids may be decreased by concomitant administration of barbiturates, antihistamines, phenytoin and rifampin due to increased metabolism caused by induction of CYP3A4 [43,44]. A well-known problem with corticosteroid therapy is the reduced effect of insulin and oral hypoglycaemic agents.

Serotonin₃-receptor antagonists. The 5-HT₃-receptor antagonists are only involved in a few drug interactions. Drugs that are inductive of the CYP450 enzyme system such as phenytoin increase the metabolic clearance of tropisetron, necessitating an increase in the tropisetron dose. Two possible drug–drug interactions resulting in decreased anti-emetic effect and dysphoria have been described with the selective serotonin re-uptake inhibitor fluoxetine and ondansetron. Cimetidine (inhibitor of the CYP450 enzyme system) decreases and rifampin (inducer of the CYP450 enzyme system) increases clearance of dolasetron, but these small changes are not considered of clinical importance.

Substance P receptor antagonists. Aprepitant is a substrate of CYP3A4. The combination of aprepitant and ketoconazole (a strong inhibitor) results in a five-time increase in aprepitant AUC compared to aprepitant alone. Diltiazem (a moderate inhibitor) increases AUC of aprepitant by a factor 2, but was studied at doses of aprepitant higher than those used for prophylaxis of chemotherapy-induced nausea and vomiting. Caution should therefore be taken, when aprepitant is combined with strong inhibitors of CYP3A4, whereas the minor pharmacokinetic changes with aprepitant and moderate inhibitors seem to be clinically insignificant. The strong inducer of CYP3A4 (and of other CYP's), rifampin, lowers the AUC of aprepitant 11 times and co-administration therefore might decrease the anti-emetic effect.

Aprepitant is also an inducer of CYP2C9 and might result in lower plasma concentrations of drugs metabolized by CYP2C9. This could be of clinical significance for drugs metabolized by CYP2C9, having a narrow therapeutic index, such as warfarin and phenytoin.

It should be recognized that many of these interaction risks were found as part of a programme for continuous (several weeks) administration of aprepitant. Today, aprepitant is only recommended for 3-day use every 3 weeks. In patients with continuous need of anti-emetics, such as for example

patients receiving conditioning chemotherapy for allogeneic transplantation plus cyclosporin to avoid graft-versus-host reaction, aprepitant can be used, but should be monitored with cyclosporin blood concentrations.

Evidence-based guidelines

The huge number of anti-emetic trials, carried out during the last 20 years and the development of new and more effective anti-emetics have resulted in clinical guidelines from a number of societies and organizations.

The Multinational Association of Supportive Care in Cancer (MASCC) Guidelines Consensus Conference in 2004 included representatives from nine different organizations, including the American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). Consequently, the recommendations in the MASCC, ASCO and ESMO guidelines are almost identical. A summary of the latest update of the MASCC recommendations for prevention of acute and delayed nausea and vomiting are given in table 4.

MASCC [48], ASCO [49], ESMO [50] and the Canadian Consensus Group have all developed evidence-based guidelines. Other guidelines from opinion leaders have been published by the National Comprehensive Cancer Network (NCCN) and the American Society of Health-System Pharmacists.

Evidence-based guidelines are dependent on the number and quality of clinical trials. This implies that recommendations differ from being at a high scientific level based on randomized double-blind trials, to a low scientific level based on a few non-comparative trials only. Furthermore, the literature in some settings is too limited to permit evidence-based recommendations. For example, data on the need for anti-emetic prophylaxis in patients receiving chemotherapy of a low emetic potential (risk 10–30%) are very sparse, as are the number and quality of studies in the children. In patients receiving multiple-day chemotherapy, the recommendation is to give patients anti-emetics for acute emesis on each day of chemotherapy, and continue 1–2 days with anti-emetics as for delayed emesis.

Guidelines are of little value, if they are unknown to the potential users. It is therefore important to ensure that guidelines are updated frequently and available in different languages to facilitate local implementation.

Persistent problems and potential new anti-emetics

Patients receiving anti-emetic prophylaxis according to the guidelines are usually protected from vomiting during the first 1–3 courses of chemotherapy. Nausea and loss of appetite are the main problems for the majority of patients. It should be noted that the doses of anti-emetics are defined in studies using emesis as the primary end-point. It is therefore unknown if higher doses than recommended of for example corticosteroids increase the effect against nausea.

A number of new NK₁-receptor antagonists are in phase I–II studies. Casopitant has completed phase II, and the

Table 4.

Summary of the recommendations in the MASCC guidelines [2].

Prophylaxis of acute nausea and vomiting	
Emesis risk group	Anti-emetics*
High	Serotonin antagonist + dexamethasone + aprepitant
Anthracycline + cyclophosphamide (AC)	Serotonin antagonist + dexamethasone + aprepitant
Moderate (other than AC)	Serotonin antagonist + dexamethasone
Low	Dexamethasone
Minimal	No routine prophylaxis
Prophylaxis of delayed nausea and vomiting	
Emesis risk group	Anti-emetics*
High	Dexamethasone + aprepitant
Anthracycline + cyclophosphamide (AC)	Aprepitant or dexamethasone
Moderate (other than AC)	Dexamethasone, a serotonin antagonist may be used as an alternative
Low	No routine prophylaxis
Minimal	No routine prophylaxis

*Recommended doses of anti-emetics are given in reference [48].

results of two phase III studies are awaited. Gabapentin, midazolam and olanzapine are potential new anti-emetics. The most promising seems to be olanzapine with very high complete response rates of both nausea and vomiting, when combined with a 5-HT₃-receptor antagonist and a corticosteroid [51]. Grhelin, a peptide secreted by the gastric mucosa, increases the gut motility, protects the gastric mucosa against (e.g. ethanol) and increases appetite. In a study using the ferret as a model, grhelin decreased the number of vomiting episodes induced by cisplatin [52].

Little is known about why anti-emetics are ineffective in some patients. A recent study demonstrated that lack of anti-emetic effect could be due to a specific deletion variation on the 5-HT_{3B} receptor gene [53]. Further studies exploring the possibility of prescribing anti-emetics on a pharmacogenetic basis are needed.

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