Update and new trends in antiemetic therapy: the continuing need for novel therapies

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Chemotherapy-induced nausea and vomiting (CINV) continues to be one of the most feared side effects of chemotherapy. Inadequately controlled CINV can have a significant negative impact on quality of life and can in some cases compromise adherence to treatment. However, the repercussions of CINV for patients are often underestimated. Advances in our understanding of the physiology of CINV and the identification of risk factors have greatly contributed towards improvements in the control of CINV. A number of antiemetic agents are currently available for the prophylaxis and treatment of CINV, including 5-hydroxytryptamine 3 receptor antagonists corticosteroids, neurokinin 1 receptor antagonists, dopamine receptor antagonists, benzodiazepines, neuroleptics and cannabinoids. With the correct use of these agents, CINV can be prevented to a great extent; however, adherence to guidelines is disappointingly low. Furthermore, a significant number of patients still experience nausea and vomiting despite optimal treatment. More effective therapies are, therefore, greatly needed, with the ultimate goal of attaining complete control of CINV. This review focuses on the current understanding of CINV, problems associated with its management and the status of promising antiemetic therapies.

Key words: aprepitant, breakthrough, casopitant, CINV, NK\textsubscript{1} receptor antagonist, palonosetron

introduction

Nausea and vomiting continues to be a significant problem in patients receiving chemotherapy [1]. As well as being among the most distressing side effects of chemotherapy [2], chemotherapy-induced nausea and vomiting (CINV) can have a number of clinical implications for patients, including non-compliance with treatment, potential treatment curtailment, unwillingness or inability to eat and/or drink and nutritional deficits [1, 3]. CINV also significantly impairs patient daily functioning and health-related quality of life (HRQoL), as assessed by the Functional Living Index—Emesis. Without appropriate antiemetic prophylaxis, 70%–80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting. Therefore, effective management of CINV represents an extremely important part of patients’ overall care plan. The purpose of this article is to review the current understanding of CINV, problems associated with its management, the status of promising novel neurokinin-1 receptor antagonists (NK\textsubscript{1}-RA) and potential new indications and formulations of palonosetron and aprepitant.

classification and risk factors for CINV

CINV is classified into three distinct categories: acute onset—occurring within 24 h of initial administration of chemotherapy, delayed onset—occurring 24 h to several days after initial treatment and anticipatory CINV—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 or by inadequate antiemetic prophylaxis in the previous cycle of chemotherapy [2]. It is of note that the time definitions of the acute and delayed phases are somewhat arbitrary [4]. However, these time definitions are well established in clinical practice.

Some patients have a higher risk for developing CINV. Risk factors for developing CINV can be grouped into two basic categories: treatment related and patient related [1, 5]. Treatment-related factors, such as the type of chemotherapy, dosage of the chemotherapeutic agents used, and scheduling and route of administration, are fundamentally responsible for the risk of developing CINV. However, the contribution of individual patient variability resulting from patient-related risk factors, such as sex, age, prior history of CINV, emesis during pregnancy or motion sickness, alcohol use, tumour burden, anxiety, concomitant medication and medical conditions and inadequate hydration, should not be underestimated. Current guidelines only take into account the emetogenic potential of the chemotherapy itself. By not considering the numerous patient-related risk factors, the accuracy of emesis prediction is likely to be reduced, and thus, the propensity for inadequate prophylaxis increased.

Chemotherapeutic agents are classified into four emetic risk groups, as suggested by the Multinational Association of
mechanisms of emesis

Three key components involving areas in the hindbrain and the abdominal vagal afferents have been identified. Nowadays, it is thought that an anatomically discrete vomiting centre is unlikely to exist [5]. The locations of neurons that coordinate the bodily functions associated with emesis are spread throughout the medulla, supporting the notion that a central pattern generator coordinates the sequence of behaviours during emesis. The central pattern generator receives indirect input from both the (i) area postrema (chemoreceptor trigger zone (CTZ)) and (ii) abdominal vagus by means of the nucleus tractus solitarius.

- CTZ: the CTZ is located in the area postrema at the bottom end of the fourth ventricle. The CTZ is a circumventricular organ that basically means that this structure lacks an effective blood-brain barrier and is able to detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The area postrema has afferent and efferent connections with underlying structures, the subnucleus gelatinosus and nucleus tractus solitarius, receiving vagal afferent fibres from the gastrointestinal tract.

- Abdominal vagal afferents: The abdominal vagal afferents appear to have the greatest relevance for CINV. A variety of receptors, including 5-hydroxytryptamine 3 (5-HT3), neurokinin-1 and cholecystokinin-1, are located on the terminal ends of the vagal afferents.

Following exposure to radiation or cytotoxic drugs, serotonin (5-HT) is released from enterochromaffine cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-HT3 receptors are located. The released serotonin activates vagal afferent neurons via the 5-HT3 receptors that leads ultimately to an emetic response mediated via the CTZ within the area postrema. Although the vagal nerve relays information to the area postrema, most of the sensory information from the vagal nerve is relayed to the tractus solitarius further interacting with the central pattern generator. At present, this vagal-dependent pathway is considered the primary mechanism by which most chemotherapeutic agents initiate acute emesis.

Substance P is a neuropeptide that acts as a neurotransmitter or neuromodulator within both the central and peripheral nervous system by preferentially binding to the NK-1 receptor. During the past two decades, multiple studies have suggested that substance P may also be a relevant neurotransmitter in CINV [8, 9]. In early studies, it could be shown that administration of substance P to dogs could induce emesis [10].

antiemetic agents

A wide variety of antiemetic agents are available for the prevention and treatment of CINV. Combination antiemetic regimens have become the standard of care for the control of CINV.

5-HT3 receptor antagonists

Antagonists inhibiting the actions of serotonin have been the most widely used antiemetics for the management of CINV over the past 20 years [5]. Five 5-HT3 receptor antagonists (5-HT3-RAs) are currently available in Europe and the United States: ondansetron, granisetron, tropisetron, dolasetron and, more recently, palonosetron. When given at equivalent doses for the prevention of acute emesis, 5-HT3-RAs have equivalent efficacy and safety and can be used interchangeably [5, 7]. Single-dose daily schedules have similar efficacy to multiple-dose daily schedules, and oral forms have been shown to be as effective as i.v. forms [6, 7]. As a class, 5-HT3-RAs are well tolerated; common adverse events include mild headache, transient elevation of hepatic aminotransferase levels and constipation [11].

All five currently available 5-HT3-RAs are effective in controlling acute CINV in patients receiving HEC or MEC regimens [3, 12–14]. Despite this, 5-HT3-RAs are not universally accepted as standard prophylactic therapy for delayed CINV [2, 13]. However, this might not be the case with palonosetron (see below). A meta-analysis from 2005 reported that 5-HT3-RAs (palonosetron was not included in the meta-analysis) did not significantly improve control of delayed CINV [11].

In view of this, current guidelines recommend that dexamethasone should be the agent of choice for delayed CINV associated with MEC [excluding regimens containing anthracycline (AC)/cyclophosphamide], with 5-HT3-RAs used as alternative agents [3, 7, 15].

neurokinin 1 receptor antagonists

The first NK1-RA aprepitant was first approved in 2003. They exert their antiemetic action through the inhibition of substance P in the emetic pathways in both the central and peripheral nervous systems. Aprepitant is currently the only agent available in this class, although a novel NK1, RA, namely casopitant, has shown clinical promise in phase III trials of patients receiving MEC and HEC. Other NK1-RAs, such as netupitant and rolapitant, are also under investigation [16, 17].

Aprepitant is available for oral and as fosaprepitant in the i.v. administration form. It is recommended for use in the acute phase in combination with a 5-HT3-RA plus dexamethasone [7, 3, 15] and in combination with dexamethasone alone on days 2–3 for delayed emesis in HEC and AC-containing regimens in MEC. Aprepitant-containing regimens have been shown to significantly reduce acute and delayed emesis in patients receiving HEC [18–20] and MEC compared with regimens containing a 5-HT3-RA plus dexamethasone only [21].
Aprepitant is well tolerated. The most common low-grade adverse effects reported during clinical trials include headache, anorexia, fatigue, diarrhoea, hiccups and mild transaminase elevation [18–22]. In general, the incidence of adverse events reported with aprepitant plus 5-HT3-RA and dexamethasone is similar to that with 5-HT3-RA plus dexamethasone alone: headache, 8% versus 10%; anorexia, 12% versus 11%; asthenia/fatigue, 20% versus 17%; diarrhoea, 11% versus 12% and hiccups, 12% versus 9% [23]. Aprepitant is metabolised by cytochrome P450 (CYP) 3A4. It is a moderate inhibitor and an inducer of CYP3A4, as well as an inducer of CYP2C9 [24]. Therefore, possible interactions between aprepitant and other drugs have been investigated intensively. Aprepitant has been shown to cause a twofold increase in the area under the plasma concentration curve (AUC) of dexamethasone, which is a sensitive substrate of CYP3A4. Consequently, dexamethasone doses should be decreased by ~50% when used in combination with aprepitant [24–27]. Potential interactions with cytoxic drugs metabolised by CYP3A4 were intensively studied. In a study by Nygren et al. [28], aprepitant had no clinically significant effect on either the pharmacokinetics or the toxicity of standard doses of docetaxel in cancer patients, and the metabolism of cyclophosphamide is not significantly reduced in the presence of aprepitant [29]. Caution is recommended when warfarin is administered, as aprepitant induces its metabolism, causing low international normalised ratio values [23]. There is also a potential for interacting with several other agents, including phenytoin, itraconazole, terfenadine and oral contraceptives [24, 27]. However, after 5 years of clinical experience with aprepitant, the clinical relevance of these potential interactions appears to be rather low.

corticosteroids
Corticosteroids are an integral part of antiemetic therapy for acute and delayed CINV, although they are not approved as antiemetics [30]. When used in combination with other antiemetics, corticosteroids exert a booster effect, raising the emetic threshold. Dexamethasone is the most frequently used corticosteroid, although no study reports the superiority of one corticosteroid over another in terms of efficacy [12]. For the prevention of acute CINV, current guidelines recommend 20 mg (12 mg when administered with aprepitant) in HEC and a single dose of 8 mg dexamethasone (12 mg in the NCCN guidelines) for MEC [7, 3, 15]. While for the prevention of delayed CINV, the guidelines recommend 8 mg dexamethasone once daily with aprepitant on days 2–4 for HEC (aprepitant only on days 2–3) and 4 mg dexamethasone twice daily or 8 mg dexamethasone daily on days 2–3 for MEC [7, 3, 15].

Steroids are sometimes underutilised, owing to concerns regarding potential adverse events [30]. Usually, when used in the short term as antiemetic therapy, corticosteroids are well tolerated [1, 2]. However, a recent study of patients receiving dexamethasone for the prevention of delayed CINV reported the following adverse events in the week following chemotherapy: moderate-to-severe insomnia (45%), indigestion/epigastric discomfort (27%), agitation (27%), increased appetite (19%), weight gain (16%) and acne (15%) [31].

Furthermore, in a very recent double-blind randomised study in patients (n = 300) receiving AC/EC-based chemotherapy were treated with a single injection of palonosetron in combination with dexamethasone on day 1 [32]. On the following 2 days, one arm received dexamethasone and the other arm received placebo. Primary end point was complete response (CR) (no emesis and no rescue medication) in the overall (days 1–5) period. Overall CR was achieved in 53.7% in the palonosetron + dexamethasone days 1–3 group and in 53.6% in the palonosetron + dexamethasone day 1-only group. The authors concluded that in patients treated with a single injection of palonosetron on day 1 in combination with dexamethasone on day 1 only might be a sufficient treatment option also in view of the delayed phase. This approach should be further investigated also considering a potential treatment simplification strategy when given the antiemetic treatment just on day 1 as published by Grunberg et al. [33] and discussed below.

dopamine receptor antagonists
Prior to the introduction of 5-HT3-RAs, dopamine receptor antagonists formed the basis of antiemetic therapy [2]. These agents can be subdivided into phenothiazines, butyrophenones and substituted benzamides [1, 2]. One of the most frequently used benzamides is metoclopramide. Before establishing the 5-HT3-RAs in CINV prophylaxis, metoclopramide, usually at high doses and in combination with a corticosteroid, played a primary role in the management of acute CINV. However, in patients receiving cisplatin-based chemotherapy, the effects of conventional doses of metoclopramide are not significantly different from placebo. Consequently, current guidelines do not recommend metoclopramide for prevention of acute CINV.

Although not effective in the acute phase, metoclopramide in combination with corticosteroids has proven efficacy in the prevention of delayed CINV [34, 35]. Indeed, two studies have demonstrated that metoclopramide-containing regimens are more effective than corticosteroid monotherapy. In the study by the Italian group for antiemetic research, the combination of metoclopramide plus corticosteroid was shown to be as effective as 5-HT3-RA plus corticosteroid in the delayed phase (CR 60% versus 62%) [36]. Similar results were obtained in another study by Aapro et al. [37]. Consequently, metoclopramide was recommended for the prevention of delayed CINV by the first MASCC and former ASCO antiemetic guidelines [12]. However, in the updated MASCC/European Society for Medical Oncology (ESMO) and current ASCO guidelines, metoclopramide is no longer recommended for use in the prevention of delayed CINV [7, 15], due to the availability of more effective drugs, such as NK1-RA. The current ASCO guidelines recommend that metoclopramide be reserved for patients intolerant of or refractory to 5-HT3-RAs, dexamethasone and aprepitant [7].

benzodiazepines
Benzodiazepines can be useful additions to antiemetic regimens in certain circumstances. They are often used to treat anxiety and reduce the risk of anticipatory CINV. Benzodiazepines are
also used in patients with refractory and breakthrough emesis [1, 2].

cannabinoids
Cannabinoids (e.g. dronabinol and nabilone) possess weak antiemetic efficacy combined with potentially beneficial side effects, including sedation and euphoria. This makes them a useful adjunctive therapy in selected patients; in the ASCO and NCCN guidelines, cannabinoids are recommended for patients intolerant of or refractory to 5-HT\textsubscript{3}-RA or steroids and aprepitant [7, 3].

In a systematic review of the efficacy of oral cannabinoids in the prevention of nausea and vomiting, cannabinoids were found to be slightly better than dopamine receptor antagonists, including phenothiazines, haloperidol and metoclopramide. Despite this, their clinical utility was found to be generally limited by the high incidence of adverse events, such as dizziness, dysphoria and hallucinations [38].

new guidelines-based management of CINV
Pharmacological interventions for CINV are recommended based on the type of nausea and/or vomiting and the emetogenicity of the chemotherapy. Treatment guidelines for the prevention of acute and delayed CINV have been developed by a number of cancer societies (ASCO [7], MASCC/ESMO [15] and NCCN [3]), with a strong degree of concordance in their recommendations.

For acute emesis, the updated MASCC/ESMO guidelines recommend triple therapy with a 5-HT\textsubscript{3}-RA, corticosteroid (dexamethasone) and NK\textsubscript{1}-RA for HEC regimens. Triple therapy is also recommended for AC plus cyclophosphamide-containing regimens. In 'other MEC regimens', the updated MASCC/ESMO guidelines recommend the double therapy with a 5-HT\textsubscript{3}-RA (palonosetron preferred) and a corticosteroid (dexamethasone). In low emetogenic chemotherapy, a monotherapy with a corticosteroid (dexamethasone) is adequate and for minimal emetogenic chemotherapy, no prophylaxis is necessary [15].

For delayed emesis, the updated MASCC/ESMO guidelines recommend in patients receiving HEC, a combination of a corticosteroid (dexamethasone) and NK\textsubscript{1}-RA. For AC-based regimen, aprepitant as a monotherapy should be given. In other MEC regimens, a corticosteroid (dexamethasone) or a 5-HT\textsubscript{3}-RA alternatively, when palonosetron was not preferred for the primary prophylactic treatment, are the agents of choice. In low and minimal emetogenic chemotherapy, no prophylaxis is necessary.

Despite the availability of treatment guidelines, there is evidence that adherence to and implementation of treatment recommendations are less than optimal [2] and that actual clinical practice is lagging behind current guidelines for the use of prophylactic antiemetics [7].

Emesis that occurs despite optimal preventative treatment is termed refractory or breakthrough emesis. Breakthrough emesis is often challenging to reverse [4]; the general principle of breakthrough treatment is to give an additional agent as needed from a different drug class—rectal or i.v. therapy is most common, as the oral route is seldom feasible, due to ongoing vomiting [15]. Uncontrolled CINV has a severe detrimental impact on the HRQoL of the patient [39]. Uncontrolled CINV can also limit the clinical utility of chemotherapy in clinical practice. Furthermore, failure to control CINV has been shown to lead to 25%–50% of patients delaying or refusing possibly life-saving chemotherapy [40].

new trends and recent developments in antiemesis
palonosetron
Palonosetron is a novel 5-HT\textsubscript{3}-RA with a binding affinity for the 5-HT\textsubscript{3} receptor ~100-fold greater than other 5-HT\textsubscript{3}-RAs, including ondansetron, granisetron and dolasetron. It also has a significantly longer elimination half-life of ~40 h. Furthermore, palonosetron exhibits allosteric interactions and triggers 5-HT\textsubscript{3} receptor internalisation [41].

Clinical trials have shown that as a single agent, palonosetron offers better control of CINV compared with currently available 5-HT\textsubscript{3}-RAs (Table 1). In two-phase III MEC trials, single-dose i.v. palonosetron have suggested possible higher efficacy compared with ondansetron or dolasetron for both acute and delayed CINV [43, 44]. Even though they showed statistically better results for palonosetron, both studies were designed as non-inferiority trials. In a further phase III trial, palonosetron was reported to be as effective as ondansetron in preventing acute CINV in patients receiving HEC. When administered in combination with dexamethasone in the same study, a subgroup analysis revealed that palonosetron was reported to be more effective than ondansetron plus dexamethasone [42].

The efficacy of palonosetron plus dexamethasone versus granisetron plus dexamethasone was recently evaluated in patients receiving cisplatin-based or AC plus cyclophosphamide-based regimens by Saito et al. In this phase III study, prevention of CINV with palonosetron and granisetron was comparable at the end of day 1. However, palonosetron demonstrated superior long-lasting CINV prevention in the delayed phase; CR rate was 56.8% with palonosetron/dexamethasone versus 44.5% with granisetron/ dexamethasone ($P < 0.0001$) [46]. Further studies are necessary to evaluate palonosetron in combination with a NK-1-RA in this setting as recommended by the guidelines.

The combination of palonosetron and dexamethasone has also been evaluated in patients receiving multiple-day cisplatin-based chemotherapy; response rates were high in both the acute and delayed phases. Overall, multiple-dose palonosetron was well tolerated; the most commonly reported side effects were mild headache and constipation in 17.1% and 9.8% of patients, respectively [47].

The potential possibility of dexamethasone sparing regimens when using palonosetron is discussed above [32].

aprepitant
single-day application. In a small non-randomised study ($n = 41$), the efficacy of a single day 3 drug regimen of dexamethasone 20 mg p.o., palonosetron 0.25 mg i.v. and
aprepitant 285 mg was evaluated in patients receiving MEC (mostly AC based) [33]. Complete overall response (no vomiting and no use of rescue medication d1-5) was achieved in 51% of patients, including 76% in the acute and 66% in the delayed phase. No unexpected major adverse events were seen. Further studies are urgently warranted to directly compare a brief and extended antiemetic regimen. Brief antiemetic regimens may lead to an improved patients adherence, guidelines adherence and improved quality of life.

‘other MEC’. In a recent large randomised study, the addition of aprepitant in combination with ondansetron and dexamethasone was tested in patients receiving a broad range of chemotherapies [48]. Of the 848 randomised patients, 429 patients received a non-AC-based regimen (e.g. oxaliplatin-, carboplatin-, irinotecan-based regimens) and 403 an AC-based regimen (16 patients were excluded). The primary end point was no vomiting during the 5 days after chemotherapy. Considering all patients, no vomiting in the overall phase was seen in 76.2% in the aprepitant group and 62.1% in the control group (ondansetron and dexamethasone) (P < 0.001). Among those patients receiving non-AC-based chemotherapy regimens, more patients in the aprepitant group reported no vomiting in the overall phase (83.2% versus 71.3%, post hoc analysis). To further elucidate the potentially beneficial role of aprepitant in the other MEC setting, more studies are warranted especially in view of inclusion in the MASCC/ESMO guidelines [15]. In the actual NCCN guidelines, aprepitant is recommended in selected patients in this setting [3].

**multiple-day chemotherapy.** Prophylactic treatment with a 5-HT₁-RA plus dexamethasone remains the standard of care for patients receiving multiple-day chemotherapy. As stated by the updated MASCC/ESMO guidelines, the role of NK₁-RA has yet to be defined due to a lack of randomised studies [15]. In a recent study of patients receiving multiple-day MEC (n = 40) or HEC (n = 38), the addition of aprepitant to the standard combination revealed superior efficacy compared with historical controls [49]. A complete overall response (day 1 until 5 days after cessation of chemotherapy) was seen in 57.9% and 72.5% of patients receiving HEC and MEC, respectively. The aprepitant regimen evaluated was well tolerated over 5–7 days; tolerability was comparable with a 3-day aprepitant regimen.

**high-dose chemotherapy.** The additional use and value of aprepitant in high-dose chemotherapy (HDC) were presented on several posters but these results are so far not fully published and will therefore be not discussed here [50–54]. In a very recent non-randomised study, the efficacy of the triple combination therapy with aprepitant in 42 patients receiving HDC was evaluated, which revealed superior efficacy compared with historical control [55]. However, analogous to multiple-day chemotherapy prophylactic treatment with a 5-HT₁-RA plus dexamethasone remains the standard of care for patients receiving HDC due to a lack of randomised studies in this setting [15].

**fosaprepitant**
In the large (n > 2000) phase III EASE (evaluation of fosaprepitant in single-dose schedule) study, the efficacy of a single i.v. dose of 150 mg fosaprepitant only on day 1 in comparison to the oral 3-day aprepitant regimen was tested in patients receiving HEC [56]. Both groups received concomitant standard antiemetic treatment with ondansetron and dexamethasone. The primary end point was CR (defined as no vomiting and no use of rescue therapy) during the overall phase (120 h following initiation of cisplatin therapy). CR in the overall phase was achieved by 71.9% [95% confidence interval (CI) 69.1–74.5] of patients in the fosaprepitant group compared with 72.3% (95% CI 69.6–74.9) in the aprepitant group. The determination that the fosaprepitant 150 mg single i.v. regimen is equally effective as the aprepitant 3-day oral regimen allows more convenient administration of the NK₁-RA in the near future.

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### Table 1. Palonosetron versus ondansetron, dolasetron and granisetron: details of cisplatin-based and non-cisplatin-based studies and efficacy results

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Study</th>
<th>No. of patients</th>
<th>Dose on day 1 (mg)</th>
<th>Control</th>
<th>Acute complete response (%)</th>
<th>Delayed complete response (%)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td></td>
<td></td>
<td>Palonosetron</td>
<td>Ondansetron</td>
<td>Dolasetron</td>
<td>Granisetron</td>
<td>Palonosetron</td>
<td>Comparator</td>
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<tr>
<td>HEC</td>
<td>Aapro et al. [42]</td>
<td>667</td>
<td>0.25 and 0.75</td>
<td>32</td>
<td>–</td>
<td>–</td>
<td>Blind</td>
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<tr>
<td>MEC</td>
<td>Gralla et al. [43]</td>
<td>563</td>
<td>0.25 and 0.75</td>
<td>32</td>
<td>–</td>
<td>–</td>
<td>Blind</td>
</tr>
<tr>
<td></td>
<td>Eisenberg et al. [44]</td>
<td>569</td>
<td>0.25 and 0.75</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>Blind</td>
</tr>
<tr>
<td>HEC/MEC</td>
<td>Saito et al. [45]</td>
<td>1114</td>
<td>0.75&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>40 μg/kg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Blind</td>
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</table>

<sup>a</sup>Palonosetron 0.25 (except Saito study) versus comparator.
<sup>b</sup>Including cisplatin and AC-, epirubicine- and cyclophosphamide-based chemotherapy.
<sup>c</sup>Combined with 16 mg dexamethasone i.v. day 1 and 8 mg i.v. (cisplatin based)/4 mg p.o. (AC/EC based) on days 2 and 3.

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HEC, highly emetogenic chemotherapies; MEC, moderate emetogenic chemotherapy; NS, not significant.
Casopitant is a potent, selective, small-molecule, non-peptide competitive NK₁-RA, which is administered orally or i.v. In preclinical studies, a single dose of casopitant was shown to significantly inhibit the number of retching and vomiting episodes, in a dose-related manner, in both cisplatin-induced acute and delayed emesis [57].

The results of two large-scale phase III trials corroborate the phase II findings in patients receiving MEC or HEC (Table 2) [58, 59]. In patients receiving AC-based MEC, CR rates with single-dose oral, 3-day oral/oral and 3-day i.v./oral casopitant regimens were superior to active control; the overall CR improved from 59% in the control arm to 73% in the casopitant single oral dose treatment group, 74% in the casopitant 3-day i.v./oral treatment group and 73% in the casopitant 3-day oral treatment group ($P < 0.0001$) [59].

In patients receiving cisplatin-based HEC, casopitant as either a single oral dose or a 3-day i.v./oral regimen in combination with dexamethasone and ondansetron was found to be significantly superior to 5-HT₃-RA plus dexamethasone therapy alone in the prevention of HEC-induced CINV during the overall, acute and delayed phases: 86% of patients in the single oral dose casopitant arm ($P < 0.001$) and 80% of patients in the 3-day i.v./oral casopitant arm ($P < 0.001$) achieved CR, in both the acute and delayed phases [58].

Safety analyses have shown that casopitant is generally well tolerated and does not confer any additional toxicity above and beyond that seen with 5-HT₃-RA plus dexamethasone therapy [58, 59]. The most common adverse events in clinical trials are nausea (11%), constipation (12%), fatigue (13%), anaemia (13%) and neutropaenia (12%) [59, 60].

Casopitant is metabolised by cytochrome CYP3A4, which is analogous to aprepitant. It is also a moderate inhibitor and an inducer of CYP3A4 and an inducer of CYP2C9 [61]. A 21% increase in oral dexamethasone AUC has been observed when coadministered with oral casopitant and ondansetron, although

### Table 2. Casopitant: results of phase III clinical trials in patients receiving moderately and highly emetogenic chemotherapy [61, 63]

<table>
<thead>
<tr>
<th>Emetogenic potential</th>
<th>Antiemetic regimen</th>
<th>Complete response</th>
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<tr>
<td></td>
<td>Day 1</td>
<td>Days 2–3</td>
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<tr>
<td>High ($n = 810$)</td>
<td>Control</td>
<td>Dexamethasone 2 × 8 mg p.o.</td>
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<td>Placebo; ondansetron 32 mg i.v.; dexamethasone 20 mg p.o.</td>
<td>Casopitant 90 mg i.v.; ondansetron 32 mg i.v.; dexamethasone 12 mg p.o.</td>
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<th>Complete response</th>
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<tr>
<td></td>
<td>Day 1</td>
<td>Acute phase (%)</td>
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<tr>
<td>High ($n = 810$)</td>
<td>Control</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Casopitant day 1: 90 mg i.v.; days 2–3: 50 mg p.o.</td>
<td>94$^{a}$</td>
</tr>
<tr>
<td></td>
<td>Casopitant day 1 only: 150 mg</td>
<td>95$^{a}$</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Casopitant day 1: 90 mg i.v.; days 2–3: 50 mg p.o.</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Casopitant day 1 only: 150 mg</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Casopitant day 1: 150 mg p.o.; days 2–3: 50 mg p.o.</td>
<td>89</td>
</tr>
</tbody>
</table>

$^{a}P < 0.0001$ versus control; $^{b}P = 0.0004$ versus control; $^{c}P = 0.0044$ versus control; $^{d}P = 0.0165$ versus control; $^{e}P < 0.0001$ versus control.

HEC, highly emetogenic chemotherapy.
Olanzapine, an atypical antipsychotic drug, has potential antiemetic properties due to its ability to bind at several receptors involved in the CINV pathways. In vitro and in vivo receptor binding studies showed that olanzapine exhibited a rich binding profile with high affinity for dopamine D1–D5, 5HT2A, 5HT3, 5HT6, muscarinic, alpha1-adrenergic and histamine H1 receptors [62, 63]. Adverse effects reported are typical of those seen with other antipsychotics and include sleepiness, dizziness, weight gain and dry mouth [1].

In two phase II studies, olanzapine demonstrated effective prevention of both acute and delayed CINV in patients receiving HEC or MEC [64, 65]. Consequently, olanzapine is cited in the MASCC/ESMO and NCCN guidelines as a potential treatment option for refractory and breakthrough emesis [3]. The latest small study (n = 50) compared olanzapine with aprepitant both combined with dexamethasone and palonosetron in the prevention of CINV in highly emetogenic and AC-based chemotherapy [66]. In this study, the olanzapine regimen (O) showed comparable results to the aprepitant regimen (A) in regard to acute [100% (O) versus 90% (A)], delayed [77% (O) versus 73% (A)] and overall [77% (O) versus 73% (A)] CR. However, for a phase III study, the sample size of 50 patients is underpowered and therefore too small to draw any firm conclusions. Therefore, the results have to be interpreted with great caution. Further studies are currently underway to further elucidate its role in CINV prophylaxis.

**conclusions**

Substantial progress has been made over the past two decades in the prevention and treatment of CINV. Of the various antiemetics currently available, 5-HT3-RAs, NK1-RAs and corticosteroids are the most effective agents. While the majority of patients gain complete protection from these therapies, a significant number still experience nausea and vomiting. A need exists for greater adherence to recommended treatment guidelines as well as more effective antiemetics especially in regard to nausea. The concept of single-day antiemetic prophylaxis should further be investigated. Further research is also warranted to assess the efficacy of antiemetic combination therapies (including e.g. aprepitant, palonosetron, olanzapine) in multiple-day chemotherapy, HDC and ‘other’ moderate emetogenic chemotherapy (e.g. oxaliplatin, carboplatin, irinotecan).

While continued research strives to attain the optimal antiemetic therapy, complete control of CINV, especially nausea, should be an optimistic goal for most patients receiving chemotherapy.

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**disclosure**

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nausea and vomiting associated with highly emetogenic preparative regimens prior to stem cell transplantation. Blood 2009; 114: (Abstr 2267).


