Daily challenges in oncology practice. What do we need to know about antiemetics?

F. Roila, S. Fatigoni & G. Ciccarese
Medical Oncology Division, Silvestrini Hospital, Perugia, Italy

Introduction

Important progress has been achieved in the last 20 years in the prevention of chemotherapy-induced nausea and vomiting. The most efficacious prophylactic antiemetics will be discussed in relationship to the different types of emesis and to the different antineoplastic agents.

Chemotherapy-induced nausea and vomiting should be classified as acute, delayed or anticipatory.

Acute nausea and vomiting occur within the first 24 h after administration of chemotherapy. Delayed nausea and vomiting have been arbitrarily defined as occurring 24 h after chemotherapy administration. Anticipatory nausea and vomiting is a learned or conditioned response that typically occurs before the administration of chemotherapy in patients who have experienced acute and/or delayed nausea and vomiting in the previous courses of chemotherapy.

The emetogenic potential of antineoplastic agents varies. However, each classification is arbitrary because the emetogenic characteristics of many chemotherapeutic agents, such as frequency, intensity, duration and the latency to feeling nausea or vomiting after drug administration are unknown. Furthermore, the emetogenic potential of a single agent can vary if it is given in combination with other chemotherapeutic agents, and emesis is also influenced by dosage of the chemotherapeutic drug, the duration of its infusion and patients' characteristics, such as gender, age, a history of chronic alcohol intake, previous experience of emesis either during pregnancy or during earlier cancer treatment, or susceptibility to motion sickness. In the most recent classification [1], the emetogenic potential of a single intravenous antineoplastic drug is considered high (>90% incidence) for cisplatin, dacarbazine, carmustine, methotrexate and cyclophosphamide ≥1500 mg/m²; moderate (30–90%) for oxaliplatin, cyclophosphamide <1500 mg/m², ifosfamide, cytosine-arabinoside, anthracyclines, carboplatin, and irinotecan; low (10–30%) for paclitaxel, docetaxel, mitoxantrone, topotecan, gemcitabine, etoposide, teniposide, pemetrexed, methotrexate, mitomycin-C, fluorouracil, bortezomib, cetuximab and bevacizumab [1]. Oral antineoplastic agents have also been classified accordingly [1]: hexamethylmelamine and procarbazine are classified as highly emetogenic agents; cyclophosphamide, etoposide, temozolomide, vinorelbine and imatinib as moderate; capecitabine and fludarabine as low; and chlorambucil, hydroxyurea, l-phenylalanine mustard, 6-thioguanine, methotrexate, gefitinib and erlotinib as minimally emetogenic chemotherapy. Since oral agents tend to be given daily from several days to several weeks, emetogenicity can only be judged for the entire period without a distinction between acute and delayed emesis, and antiemetic regimens will tend to differ from those recommended for single dose intravenous chemotherapeutic agents.

No prospective randomized double-blind antiemetic studies have been carried out in patients treated with oral antineoplastic drugs. Therefore, the following suggestions, summarized in Table 1, are only for intravenously administered agents.

Prevention of nausea and vomiting induced by highly emetogenic chemotherapy

Acute nausea and vomiting

Before the introduction of the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists, an intravenous combination of high-dose metoclopramide and corticosteroids plus diphenhydramine or lorazepam was able to achieve complete protection from acute vomiting in about 60% of patients. 5-HT3-receptor antagonists used alone (ondansetron, granisetron, tropisetron, dolasetron) achieve complete protection from acute cisplatin-induced vomiting in 40–60% of patients. Several studies comparing the various 5-HT3 receptor antagonists have shown their equivalent efficacy and tolerability.

Furthermore, the combination of 5-HT3-receptor antagonists plus dexamethasone is superior to 5-HT3-receptor antagonists alone since it induces complete protection from acute emesis in about 70–90% of patients. A combination of 5-HT3-receptor antagonists plus dexamethasone versus a combination of high-dose metoclopramide and dexamethasone, plus diphenhydramine or lorazepam was evaluated in two large double-blind, randomized studies in patients treated with cisplatin [2, 3]. Complete protection from both vomiting and nausea was significantly superior with ondansetron plus dexamethasone and this regimen was better tolerated. Therefore a combination of a 5-HT3 receptor antagonist plus single dose dexamethasone was regarded as standard treatment until the introduction in clinical practice of aprepitant.
Substance P, an 11-amino acid neuropeptide located primarily within the gastrointestinal tract and the central nervous system, can induce emesis when injected into the ferret [4]. Substance P exerts its biological effects by binding to the neurokinin-1 (NK1) receptors. Aprepitant is a NK1 receptor antagonist that in animal models is able to antagonize a large spectrum of emetic stimulus such as those induced by apomorphine, morphine, copper sulfate, ipecac, radiation, chemotherapy, motion and anesthesis [4].

Interesting results have been achieved with aprepitant in some phase II studies that suggest that NK1 antagonists combined with a 5-HT3 antagonist and dexamethasone seem to significantly increase complete protection from cisplatin-induced acute vomiting compared with a 5-HT3 antagonist and dexamethasone alone. Furthermore, phase II studies have shown that the NK1 antagonist combined with dexamethasone is significantly less efficacious than a 5-HT3 antagonist plus dexamethasone combination in the prevention of cisplatin-induced acute emesis [4].

For the identification of the optimal dose of apreptiant in cisplatin-treated patients, a randomized double-blind study evaluating oral pre-chemotherapy doses of aprepitant from 40 to 375 mg was carried out. This study concluded that a single 125 mg oral dose had ‘the most favorable benefit/risk profile’ [5].

Recently, two phase III studies [6, 7] have been published in which the standard treatment [ondansetron 32 mg intravenously (iv)] plus oral dexamethasone 20 mg in the first 24 h and oral dexamethasone 8 mg twice daily on days 2–4) was compared to an apreptiant regimen (oral aprepitant 125 mg plus ondansetron 32 mg iv and oral dexamethasone 12 mg in the first 24 h; oral apreptiant 80 mg plus oral dexamethasone 8 mg on day 2 and 3 and oral dexamethasone 8 mg on day 4). In the apreptiant arm the dexamethasone dose was reduced due to a pharmacokinetic interaction with apreptiant that increases its plasma level more than two-fold. In the first study 569 patients were enrolled [6]. Complete response (no vomiting and no rescue treatment) was significantly superior with apreptiant compared to the standard treatment (63% versus 43% on days 1–5, 83% versus 68% on day 1 and 68% versus 47% on days 2–5, respectively). Complete protection from nausea was also significantly superior with apreptiant.

In the second study 530 patients were enrolled. Aprepitant induced a significantly superior complete response when compared to standard treatment (73% versus 52% on days 1–5, 89% versus 78% on day 1 and 75% versus 56% on days 2–5) [7]. Complete response from nausea was not significantly different. In both studies adverse effects were mild and not significantly different between the two groups of patients. In conclusion, in both studies apreptiant significantly increased antiemetic efficacy and its combination with a 5-HT3 antagonist and dexamethasone should be considered the new standard option for the prevention of cisplatin-induced acute emesis.

A single intravenous/oral dose of a 5-HT3-receptor antagonist (ondansetron 8 mg/24 mg, granisetron 1 mg/2 mg, tropisetron 5 mg/5 mg, dolasetron 100 mg/100 mg), dexamethasone 12 mg orally plus apreptiant 125 mg orally are the recommended doses.

delayed nausea and vomiting

The incidence of cisplatin-induced delayed emesis is low in patients who did not have acute vomiting while it is substantial in patients who did. For this reason prevention of acute emesis is very important.

The combination of orally administered metoclopramide (0.5 mg/kg four times daily on days 2–5) plus dexamethasone (8 mg twice daily on days 2–3 and 4 mg twice daily on days 4–5) provides complete protection from delayed vomiting in around 50% of patients and it is superior to both dexamethasone and placebo [8]. Therefore, all patients submitted to cisplatin should receive prophylactic antiemetics for at least 3 days.

The 5-HT3 receptor antagonists used alone showed, at best, only a moderate activity against delayed emesis. Furthermore, the combination of granisetron or ondansetron plus dexamethasone is equivalent to dexamethasone alone [9–11]. A recent randomized study demonstrated equivalent prevention of delayed emesis by oral metoclopramide combined with intramuscular dexamethasone and oral ondansetron combined with intramuscular dexamethasone: complete protection from delayed vomiting was around 60% and complete protection from delayed nausea around 45–50% [12]. Due to its lower cost, metoclopramide plus dexamethasone was considered the standard option for the prevention of delayed emesis. In patients who did not tolerate metoclopramide the standard option was regarded as ondansetron in combination with dexamethasone.

In the phase II double-blind trials apreptiant produced some interesting activity against cisplatin-induced delayed emesis [4].

In the two phase III trials complete response on days 2–5 was significantly superior with apreptiant plus dexamethasone than with dexamethasone alone [6, 7] and according to the Multinational Association of Supportive Care in Cancer (MASCC) guidelines [1] this regimen should be the standard in patients receiving a combination of apreptiant, a 5-HT3 antagonist and dexamethasone for the prevention of cisplatin-induced acute emesis. The recommended doses are 80 mg orally of apreptiant on days 2 and 3 and 8 mg orally dexamethasone on days 2, 3 and 4.

Unfortunately, in both apreptiant phase III studies the treatment of choice for cisplatin-induced delayed emesis was not used. Therefore, to define the role of apreptiant in the prophylaxis of cisplatin-induced delayed emesis it is necessary to carry out further studies in which all patients receive the same combination of apreptiant plus a 5-HT3 antagonist plus dexamethasone for the prevention of cisplatin-induced acute emesis, and, starting from 24 h after cisplatin administration, patients should be randomized to receive dexamethasone plus metoclopramide (or ondansetron) or dexamethasone plus metoclopramide (or ondansetron) plus apreptiant.

prevention of nausea and vomiting induced by moderately emetogenic chemotherapy

acute nausea and vomiting

Dexamethasone or methylprednisolone achieved about 60–80% complete protection from acute vomiting induced by
moderately emetogenic chemotherapy. Corticosteroids are equivalent or superior in terms of efficacy to repeated low doses of metoclopramide, but they are better tolerated.

Various 5-HT3 receptor antagonists have been shown to be superior to metoclopramide, alizapride or phenothiazines. When used alone, the percentage of complete protection from vomiting with 5-HT3 receptor antagonists varies from 50% to 70%.

In two randomized, double-blind studies ondansetron or granisetron were compared with dexamethasone used at high and repeated doses. Both the 5-HT3 receptor antagonists and dexamethasone were found to be equally effective in the control of acute nausea and vomiting (complete control around 70%), but dexamethasone achieved better control of delayed nausea and vomiting [13, 14].

Before the introduction of the NK1 receptor antagonists, the standard option for the prevention of acute emesis induced by moderately emetogenic chemotherapy was the combination of dexamethasone plus a 5-HT3 receptor antagonist [13, 15]. Complete protection from acute vomiting was shown to be superior in patients treated with a combination of dexamethasone plus granisetron (93%) compared with dexamethasone or granisetron alone (around 70%) [13]. In another study, ondansetron 8 mg iv plus dexamethasone 16 mg iv single-dose achieved over 90% complete control from acute emesis [15].

Palonsetron is a potent and selective 5-HT3-receptor antagonist with a high affinity for the 5-HT3 receptors. Its mean plasma elimination half-life of about 40 h is substantially longer than that of ondansetron (4–6 h), granisetron (5–8 h), tropisetron (7 h) and dolasetron (7 h).

Two studies in patients treated with moderately emetogenic chemotherapy demonstrated efficacy with a single intravenous dose of palonosetron 0.25 mg that was equal to or better than a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phase [16, 17].

In the first study carried out in 563 patients, a complete response on day 1 was obtained in 81% of patients receiving 0.25 mg, 73% in those receiving 0.75 mg of palonosetron and in 69% of those receiving ondansetron [16]. On day 2–5 the complete response rate was 74%, 65% and 55% while on day 1–5 it was 69%, 59% and 50%, respectively. The difference between palonosetron 0.25 mg and ondansetron on day 1 and on day 2–5 was statistically significant.

In the second study carried out in 569 patients, a complete response on day 1 was achieved respectively by 63% and 57% of patients receiving 0.25 and 0.75 mg of palonosetron and by 53% of those receiving dolasetron 100 mg iv [17]. On day 2–5 and on day 1–5 complete response was significantly better with both doses of palonosetron (54%, 57% and 39%, and 46%, 47% and 34%, respectively).

Unfortunately, in these two studies less than 5% of patients received dexamethasone combined with a 5-HT3 antagonist and therefore superior efficacy in the setting of dexamethasone as recommended by the MASCC guidelines was not demonstrated [1].

Furthermore, 30–60% of enrolled patients were pretreated and may have had mild nausea in previous courses, and although the distribution of pretreated patients was similar among the three arms, it was not known if the distribution among the three arms of patients with mild nausea was also similar.

In addition, no patients received a prophylaxis for delayed emesis in either study and this can also influence the results. 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. Somewhat surprisingly, a higher dose of palonosetron was less effective than a lower dose although it was still quantitatively superior to the 5-HT3-receptor antagonist.

In conclusion, the role of palonosetron with respect to the old 5-HT3 antagonists remains to be verified when both are combined with dexamethasone in the first 24 h and with the recommended therapies for delayed emesis in subsequent days.

Recently, a double-blind study comparing oral aprepitant (125 mg) plus dexamethasone (12 mg) plus ondansetron (8 mg before and 8 mg 8 h after chemotherapy) on day 1 and aprepitant 80 mg on day 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 day 2 and 3 in 866 patients with breast cancer receiving cyclophosphamide/docetaxel or epirubicin or paclitaxel has been published [18]. Overall complete response on day 1–5 was significantly superior with the aprepitant regimen than with the control regimen (51% versus 42%). Complete response on day 1 and on days 2–5 was also significantly superior with aprepitant (76% versus 69% and 55% versus 49%, respectively). Adverse events were not significantly different between the two regimens. The superiority of the aprepitant combination was maintained throughout the entire duration of chemotherapy treatment (four cycles) [19].

Therefore, to prevent acute vomiting and nausea in women receiving a combination of anthracycline plus cyclophosphamide, a three-drug regimen including single-doses of a 5-HT3 antagonist, dexamethasone, and aprepitant given before chemotherapy is recommended. In this case recommended doses are 125 mg orally of aprepitant, 8 mg orally of dexamethasone and a 5-HT3 antagonist intravenously (as before, for the prevention of acute emesis induced by cisplatin) or orally (ondansetron 8 mg b.i.d., granisetron 2 mg, tropisetron 5 mg, dolasetron 100 mg) before chemotherapy. Of course, in patients who receive moderately emetogenic chemotherapy, not including a combination of anthracycline plus cyclophosphamide, a 5-HT3 antagonist plus dexamethasone still remains the antiemetic treatment of choice.

**delayed nausea and vomiting**

The incidence of delayed vomiting/mild-to-severe nausea is low (delayed vomiting 12% delayed nausea 14%) in patients who did not have acute vomiting or acute moderate-to-severe nausea, while it increases (delayed vomiting 55%, delayed nausea 75%) in patients who did [20]. Three comparative studies have been published, in which oral ondansetron (8 mg twice daily on days 2–5), or dolasetron (200 mg orally), or oral dexamethasone (4 mg twice daily on days 2–5) were better than placebo or no treatment [21–23]. Unfortunately, for all of these studies some methodological criticisms can be made.

The results of a double-blind randomized study carried out in patients receiving moderately emetogenic chemotherapy for the
first time have recently been published [24]. In this study all patients received ondansetron combined with dexamethasone (the treatment of choice) for prophylaxis of acute emesis. Patients were then divided into two groups: those who did not have either acute vomiting or moderate-to-severe nausea (low risk group) and patients who had one or both (high risk group). Patients in the low risk group were then randomly assigned to one of the following regimens given on days 2–5 after the start of chemotherapy: oral placebo, 4 mg of dexamethasone given orally twice daily, or 8 mg of ondansetron in combination with 4 mg of dexamethasone, given orally twice daily. Patients in the high risk group were randomly assigned to receive oral dexamethasone alone or in combination with ondansetron at the same doses as those used in the low risk group. Among the 618 patients in the low-risk group there was significantly more complete protection from delayed vomiting and moderate-to-severe nausea in patients who received ondansetron plus dexamethasone (92%) and dexamethasone alone (87%) than in those who received placebo (77%). In these patients ondansetron significantly increased the incidence of constipation. Of the 87 patients in the high-risk group complete protection was achieved in 41% of those treated with ondansetron plus dexamethasone (92%) and dexamethasone alone (87%) than in those who received placebo (77%). In these patients ondansetron significantly increased the incidence of constipation. Of the 87 patients in the high-risk group complete protection was achieved in 41% of those treated with ondansetron plus dexamethasone and in 23% treated with dexamethasone alone, and there was no statistically significant difference. In conclusion, all patients submitted to moderately emetogenic chemotherapy should receive prophylactic antiemetics for delayed emesis. The recommended dose of dexamethasone is 4 mg orally two times daily on days 2–4 [24]. As the only phase III study [25] aprepitant has been shown superior to a 5-HT3 receptor antagonist in the prevention of delayed emesis induced by moderately emetogenic chemotherapy, we need to identify the role of aprepitant in the prevention of delayed emesis induced by moderately emetogenic chemotherapy.

Table 1. Recommended antiemetic prophylaxis

<table>
<thead>
<tr>
<th>Emetogenic potential of chemotherapy (see text)</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong> (i.e., cisplatin)</td>
<td></td>
</tr>
<tr>
<td>Acute emesis</td>
<td>Aprepitant 125 mg po + Dexamethasone 12 mg po + 5-HT3 receptor antagonist (iv or orally; see text)</td>
</tr>
<tr>
<td>Delayed emesis</td>
<td>Aprepitant 80 mg po on day 2–3 + Dexamethasone 8 mg po on day 2–4 or Metoclopramide 20 mg po qid on day 2–4 + Dexamethasone 8 mg po bid on day 2–4</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
</tr>
<tr>
<td>Breast cancer pts receiving anthracylines + cyclophosphamide</td>
<td>Aprepitant 125 mg po + Dexamethasone 12 mg po + 5-HT3 receptor antagonist (iv or orally; see text)</td>
</tr>
<tr>
<td>Acute emesis</td>
<td>Aprepitant 80 mg po day 2–3 or Dexamethasone 4 mg po bid day 2–4</td>
</tr>
<tr>
<td>Delayed emesis</td>
<td>Dexamethasone 8 mg po or iv + 5-HT3 receptor antagonist (iv or orally; see text)</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td></td>
</tr>
<tr>
<td>Breast cancer pts receiving anthracylines + cyclophosphamide</td>
<td>Dexamethasone 8 mg po or iv or Metoclopramide 10–20 mg po or iv</td>
</tr>
<tr>
<td>Acute emesis</td>
<td>Dexamethasone 8 mg po or iv or Metoclopramide 10–20 mg po or iv</td>
</tr>
<tr>
<td>Delayed emesis</td>
<td>No prophylaxis</td>
</tr>
<tr>
<td><strong>Minimal</strong></td>
<td></td>
</tr>
<tr>
<td>Acute emesis</td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>Delayed emesis</td>
<td>No prophylaxis</td>
</tr>
</tbody>
</table>

**prevention of acute and delayed nausea and vomiting induced by low or minimally emetogenic chemotherapy**

For patients treated with low or minimal 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.

Nonetheless, MASCC has recommended a single agent, such as dexamethasone 8 mg for the prophylaxis of acute emesis in patients receiving low emetic risk agents [1].

For patients receiving minimally emetic risk chemotherapy, no prophylactic antiemetic treatment should be routinely administered before chemotherapy in patients without a history of nausea and vomiting.

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

**prevention of chemotherapy-induced anticipatory nausea and vomiting**

Anticipatory nausea and vomiting develops in around 30% of patients by the fourth treatment course. These figures refer to the pre-5-HT3 receptor antagonist era. In fact, more recent
studies have shown that the incidence of anticipatory nausea and vomiting is much less than that observed in older studies which used less satisfactory antiemetic prophylactic treatments (less than 10% of anticipatory nausea and less than 2% of anticipatory vomiting). If post-chemotherapy nausea and vomiting do not occur then anticipatory nausea and vomiting are very unlikely. Once they develop, anticipatory nausea and vomiting cannot be controlled by antiemetics, including even the 5-HT3 receptor antagonists. Optimal treatment of anticipatory emesis is first of all optimal treatment of acute/delayed nausea and vomiting. Benzodiazepines reduce anticipatory nausea and vomiting but their efficacy decreases as chemotherapy treatment continues. Behavioral interventions such as desensitization, counter-conditioning and hypnosis can be used to treat anticipatory nausea and vomiting.

references