Chapter 17
State of the Art of Antiemetic Therapy

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Abstract Despite relevant progress achieved in the last 20 years for the prevention of chemotherapy-induced emesis, nausea and vomiting continue to be among the most distressing adverse events induced by chemotherapy. Emesis is a complex phenomenon, and the precise mechanism by which chemotherapy induces nausea and vomiting is not well known. Many neurotransmitters are involved, and several antiemetic drugs are available. The complete control of vomiting could be achieved in about 70–90 % of patients with the better combination of antiemetic drugs.

Recently, international guidelines to prevent chemotherapy-induced nausea and vomiting have been updated, and it is very important to know these recommendations and to use them in our clinical practice correctly. However, several aspects of antiemetic therapy will be clarified in the coming years: the improvement of nausea control, the best prophylaxis of delayed emesis induced by multiple days of cisplatin, the prevention of nausea and vomiting induced by high-dose chemotherapy, the control of emesis induced by chemoradiation therapy, and the emesis in children.

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Introduction

Significant progress has been achieved in the last years for the prevention of chemotherapy-induced nausea and vomiting. Nevertheless, vomiting and especially nausea continue to be the most important chemotherapy-induced side effects, with significant consequences for patients' quality of life and patients' adherence to chemotherapy.

For these reasons, it is very important in clinical practice to know the different risks of emesis induced by different chemotherapeutic agents, the antiemetic drugs available, and the international antiemetic guidelines.

In the 1990s several professional organizations published recommendations for antiemetic treatment in patients submitted to chemotherapy and radiotherapy. In the following years these recommendations have been updated, and the last update was published in 2010 [1], after the third Consensus Conference on Antiemetics, organized in Perugia, Italy, on June 20–21, 2009 by the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC). The majority of suggestions (Table 17.1) refer only to intravenous agents, because no randomized trial has been carried out in patients receiving oral antineoplastic agents. Recently, the American Society of Clinical Oncology (ASCO) guidelines have been updated, and these recommendations are similar to the European guidelines [2]. The National Comprehensive Cancer Network (NCCN) antiemetic guidelines have been updated as well, but it is important to remember that these recommendations, as opposed to the ESMO-MASCC and ASCO recommendations, are opinion-based rather than evidence-based [3].

Table 17.1 ESMO and MASCC guidelines for the prevention of chemotherapy-induced emesis

Emetogenic potential	Chemotherapy	Recommendations
High (>90 %)	Cisplatin (see Table 17.2)	Day 1: 5-HT3 antagonist + dex + (fos) aprepitant
		Days 2–3: dex + aprepitant
		Day 4: dex
Moderate (30–90 %)	AC	Day 1: 5-HT3 antagonist + dex + (fos) aprepitant[a]
		Days 2–3: aprepitant
	Non-AC (see Table 17.2)	Day 1: palo + dex
		Days 2–3: no routine prophylaxis
Low (10–30 %)	See Table 17.2	Day 1: dex or 5-HT3 antagonist or dopamine-receptor antagonist
		Days 2–3: no routine prophylaxis
Minimal (<10 %)	See Table 17.2	Day 1: no routine prophylaxis
		Days 2–3: no routine prophylaxis

Abbreviations: *Dex* dexamethasone, *AC* anthracycline and cyclophosphamide combination, *palo* palonosetron

[a]If an NK1 receptor antagonist is not available for AC chemotherapy, palonosetron should be the preferred 5-HT3 receptor antagonist

Definition and Classification

Nausea is the perception that emesis may occur; it can be judged only by the patient. The incidence of nausea correlates with the incidence of vomiting, but nausea generally occurs

more frequently than vomiting. Vomiting is forcing the stomach contents up through the esophagus and out of the mouth; it may occur with or without nausea. Chemotherapy-induced nausea and vomiting should be classified as acute, delayed, and anticipatory arbitrarily, based on the time of onset: acute nausea and vomiting occur within the first 24 h after chemotherapy; delayed nausea and vomiting occur 24 h after chemotherapy; anticipatory nausea and vomiting occur before chemotherapy, usually in patients with acute and/or delayed nausea and vomiting experiences, in the previous courses of chemotherapy. When the patient comes back to receive the following cycle of chemotherapy, emesis could be induced by the smells, sights, and sounds of the treatment room.

Several factors may influence the incidence and severity of chemotherapy-induced emesis.

Some are patient-related: gender, age (females and young patients more frequently have nausea and vomiting), history of alcohol intake, history of emesis during pregnancy or due to motion sickness, and anxiety. Other factors are therapy-related: chemotherapy type and dose, infusion rate, and route of administration. However, the most important factor is the presence or absence of acute nausea and vomiting and emesis in previous courses of chemotherapy.

The emetogenic potential of antineoplastic agents should be classified as high (>90 % incidence), moderate (30–90 %), low (10–30 %), and minimal (<10 %). However, every classification is arbitrary, because many characteristics of emetogenic potential (frequency, intensity, duration, latency) are not so well known for many chemotherapeutic agents, especially oral antineoplastic agents (Table 17.2).

Pathogenesis of Chemotherapy-Induced Emesis

Emesis is a complex side effect, and the precise mechanisms by which chemotherapy induces nausea and vomiting are not well known. There are probably two principal pathways,

Table 17.2 Emetogenic potential of intravenous and oral antineoplastic agents

Emetogenic potential	Intravenous agents	Oral agents
High (>90 %)	Cisplatin	Hexamethylmelamine
	Mechlorethamine	Procarbazine
	Streptozotocin	
	Ciclofosfamide ≥1,500 mg/m^2	
	Carmustine	
	Dacarbazine	

(continued)

TABLE. 17. 2 (continued)

Emetogenic potential	Intravenous agents	Oral agents
Moderate (30–90 %)	Oxaliplatin	Cyclophosphamide
	Cytarabine > 1 g/m^2	Temozolomide
	Carboplatin	Vinorelbine
	Ifosfamide	Imatinib
	Cyclophosphamide < 1,500 mg/m^2	
	Doxorubicin	
	Daunorubicin	
	Epirubicin	
	Idarubicin	
	Irinotecan	
	Azacitidine	
	Bendamustine	
	Clofarabine	
	Alentuzumab	

Low (10–30 %)	Paclitaxel	Capecitabine
	Docetaxel	Tegafur uracil
	Mitoxantrone	Fludarabine
	Doxorubicin HCl liposome injection	Etoposide
	Ixabepilone	Sunitinib
	Topotecan	Everolimus
	Etoposide	Lapatinib
	Pemetrexed	Lenalidomide
	Methotrexate	Thalidomide
	Mitomycin	
	Gemcitabina	
	Cytarabine ≤ 1,000 mg/m^2	
	5-Fluorouracil	
	Temsirolimus	
	Bortezomib	
	Cetuximab	
	Trastuzumab	
	Panitumumab	
	Catumaxumab	

(continued)

TABLE. 17. 2 (continued)

Emetogenic potential	Intravenous agents	Oral agents
Minimal (<10 %)	Bleomycin	Chlorambucil
	Busulfan	Hydroxyurea
	2-Chlorodeoxyadenosine	L-Phenylalanine mustard
	Fludarabine	6-Thioguanine
	Vinblastine	Methotrexate
	Vincristine	Gefitinib
	Vinorelbine	Erlotinib
	Bevacizumab	Sorafenib

central and peripheral [4], and some mechanisms of activation are described in the following sections.

Central Pathway

The principal mechanism is the activation of the chemoreceptor trigger zone (CTZ), located in the area postrema in the brain. The CTZ works through the release of various neurotransmitters, including substance P, dopamine, serotonin, histamine, norepinephrine, apomorphine, neurotensin, angiotensin II, gastrin, and vasopressin. These neurotransmitters activate the vomiting center, located in the brain, near the CTZ. The CTZ can receive and transmit information from/to the other central and peripheral sites.

The nucleus of tractus solitarius, an area of the medulla oblongata, also plays an important role, because it probably contains the highest concentration of serotonin type 3 (5-HT3) and neurokinin 1 (NK1) receptors in the brain.

Moreover, there may be a cortical mechanism, with direct or indirect (psychogenic) cerebral activation; for example, patients with previous experience of nausea and vomiting are more likely to have emesis.

Peripheral Pathway

It is activated primarily by the damage of gastrointestinal mucosa with release of neurotransmitters or by the direct activation of peripheral neurotransmitter receptors. Serotonin plays a central role: it is released by enterochromaffin cells, and it activates the serotonin type 3 (5-HT3) receptors along the vagus nerve in the gastrointestinal tract.

Many chemotherapeutic agents can induce taste and smell alterations, which may lead to nausea and vomiting.

The vestibular system also may be involved in chemotherapy-induced emesis, and patients with a history of motion sickness are more likely to have chemotherapy-induced emesis.

Antiemetic Drugs

Several antiemetic drugs are available, and the optimal combination can achieve vomiting control in about 80–90 % of patients, with minimal side effects. The most important agents are reported as follows [5, 6]:

1. Corticosteroids (Dexamethasone, Methylprednisolone). Their antiemetic mechanism is still unclear; they probably work without the blockage of specific neurotransmitters. Their adverse events as antiemetic drugs may be limited to insomnia, euphoria, facial flush, increased appetite, and anal pruritus when administered rapidly. They can decompensate diabetes or reactivate gastrin/duodenal ulcers, but these side effects are unlikely in short-term use, and their use is contraindicated only in cases of diabetic ketoacidosis and active peptic ulcers.
2. 5-HT3 Receptor Antagonists (Granisetron, Ondansetron, Palonosetron, Tropisetron). They block the serotonin type 3 receptors, both central and peripheral (in the small bowel). Palonosetron, the newest of these agents, has a potent and selective 5-HT3 antagonist action with a plasma-elimination half-life of about 40 h, longer than that of ondansetron (4–6 h), granisetron (5–8 h), tropisetron (7 h), and dolasetron (7 h). Constipation and headaches are drug-class adverse effects and appear in about 10 % of patients. All the 5-HT3-receptor antagonists have similar tolerability.
3. NK1 Receptor Antagonists (Aprepitant, Fosaprepitant). The NK1 antagonists are the most recent antiemetic agents, introduced about 10 years ago. This receptor is usually bound by substance P. The 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, by binding the NK1 receptor. The NK1 antagonists are able to antagonize this effect of substance P and also the emetic stimulus induced by morphine, chemotherapy, radiation, and anesthesia. They usually are well tolerated.

4. NK1 receptor antagonists present several drug-drug interactions, because they are metabolized by the cytochrome P-450 isoenzyme 3A4 (CYP3A4), the major metabolic pathway for drugs in humans [7]. NK1 antagonists may decrease, for example, the plasmatic level of oral contraceptives and tolbutamide; they may increase the plasmatic level of benzodiazepines and corticosteroids, which require a dose reduction of around 50 %; they can influence the plasmatic level of warfarin. They can also influence the metabolism of some chemotherapeutic agents (docetaxel, vinorelbine), but generally dose adjustments are not required. Therefore, it is very important to verify the drug-drug interactions during antiemetic treatment.
5. Dopamine Antagonists (Metoclopramide, Domperidone, Prochlorperazine, Aloperidol). They have antiemetic activity by the blockage of dopamine receptors. Metoclopramide may induce extrapyramidal adverse effects, especially in young women when used at high dosage.
6. Benzodiazepines (Lorazepam, Alprazolam). They are useful as combination therapy, for their sedative, anxiolytic, and amnesic effects. They may induce somnolence.

Nausea and Vomiting Induced by Highly Emetogenic Chemotherapy

Prevention of Acute Emesis

Before the introduction of aprepitant, a combination of a 5-HT3 receptor antagonist plus dexamethasone was indicated for the prevention of acute nausea and vomiting in cisplatin-treated patients.

Aprepitant showed antiemetic activity in several phase II double-blind studies and in two phase III trials with an identical design. The two phase III studies, published in 2003 [8, 9], compared ondansetron, 32 mg, plus dexamethasone, 20 mg on day 1, followed by dexamethasone, 8 mg twice a day on days 2–4, with the combination of ondansetron, 32 mg; dexamethasone,

12 mg; and aprepitant, 125 mg on day 1, followed by dexamethasone, 8 mg daily on days 2–4, and aprepitant, 80 mg on days 2 and 3. In the first study 530 patients were enrolled and in the second, 569 patients.

The dexamethasone dose was reduced in the aprepitant arm because aprepitant increases dexamethasone plasma concentrations with an approximately twofold increase in the plasmatic level; because different dexamethasone doses could change the efficacy of the antiemetic regimen, a 40–50 % reduction of the oral dexamethasone dose was made in the aprepitant arm.

The primary endpoint was complete response (no emesis, no use of rescue antiemetics) over the 5-day study period. In both studies complete response was significantly superior with aprepitant (73 % vs. 52 %, 63 % vs. 43 %). The complete response on day 1 was also significantly superior with aprepitant (89 % vs. 78 %, 83 % vs. 68 %). Complete response from nausea was significantly superior with aprepitant only in the second study. In both the studies side effects were mild, with no difference between the two arms.

Another study used a similar design [10], but with prolonged ondansetron in the control arm on days 2–4, with the dose of 8 mg orally twice a day. The aprepitant arm was superior in this case also.

Concerning the type of 5-HT3 antagonist, at the present all the 5-HT3 antagonists available are to be considered with similar efficacy and tolerability in this setting of patients [11]. The single lowest tested fully effective dose, intravenous or oral, should be used before chemotherapy.

Based on these results, a combination of a 5-HT3 antagonist, dexamethasone, and aprepitant should be recommended to prevent acute nausea and vomiting induced by highly emetogenic chemotherapy.

Recently, fosaprepitant, a new NK1 receptor antagonist, has been approved. When administered intravenously, fosaprepitant is converted within 30 min into aprepitant. A phase III, randomized study [12] compared the standard combination of dexamethasone, ondansetron, and aprepitant (125 mg

orally, day 1; 80 mg orally, days 2–3) with dexamethasone, ondansetron, and fosaprepitant (150 mg intravenously, day 1). The study, in which 2,322 patients were enrolled, showed the noninferiority of the fosaprepitant arm.

Prevention of Delayed Emesis

The main risk factor for delayed nausea and vomiting is the presence of acute nausea and vomiting, so the incidence of delayed emesis is high in those patients who experienced acute emesis. Therefore, the guidelines recommend that all patients submitted to cisplatin-based chemotherapy receive the adequate prophylaxis for acute and delayed emesis.

Before the introduction of NK1 receptor antagonists, the recommended therapy was with dexamethasone (8 mg twice a day on days 23, and 4 mg twice a day on days 4–5) and oral metoclopramide (0.5 mg/kg four times a day on days 2–5) or a 5-HT3 receptor antagonist.

In the two previously mentioned phase III trials, complete response on days 2–5 was significantly superior with aprepitant plus dexamethasone than with dexamethasone alone (75 % vs. 56 % and 68 % vs. 47 %, respectively).

Therefore, the combination of aprepitant and dexamethasone should be recommended in patients submitted to cisplatin-based chemotherapy and receiving a combination of aprepitant, 5-HT3 receptor antagonist, and dexamethasone for the prevention of acute emesis. The recommended doses are aprepitant, 80 mg orally on days 2–3, and dexamethasone, 8 mg orally on days 2–4.

Unfortunately, in both studies, patients received two different combinations of drugs for acute emesis prevention, and the difference in acute emesis protection may influence the incidence of delayed emesis between the two arms.

Moreover, the combination of aprepitant and dexamethasone has been compared with dexamethasone alone and not with the standard delayed emesis prophylaxis, such as the combination of dexamethasone and metoclopramide.

In conclusion, the real impact of aprepitant in the prevention of delayed emesis is not well known: aprepitant is more efficacious than placebo, and, combined with dexamethasone, it is more efficacious than dexamethasone alone; the efficacy with respect to the combination of dexamethasone and metoclopramide or 5-HT3 antagonists remains to be evaluated. An ongoing randomized, double-blind trial of Italian Group for Antiemetic Research (IGAR) is evaluating this aspect: the patients submitted for the first time to cisplatin-based chemotherapy receive a combination of aprepitant, dexamethasone, and palonosetron on day 1; they are randomized to receive aprepitant on days 2–3 and dexamethasone on days 2–4 or dexamethasone and metoclopramide on days 2–4.

Moreover, the better aprepitant schedule is not perfectly clarified: pilot studies showed no differences between 1 day versus 3 days of aprepitant therapy, and further trials are necessary to validate the use of single-day aprepitant.

Nausea and Vomiting Induced by Moderately Emetogenic Chemotherapy

Prevention of Acute Emesis

For the prevention of acute emesis induced by moderately emetogenic chemotherapy, not including a combination of anthracycline and cyclophosphamide, a combination of dexamethasone and palonosetron should be used.

This suggestion is based on three studies evaluating the efficacy of palonosetron in this situation.

In the first two trials, two different doses of palonosetron (0.25 and 0.75 mg intravenously) were compared with dolasetron, 100 mg intravenously [13], and ondansetron, 32 mg intravenously [14], in patients chemotherapy-naïve or pretreated, receiving moderately emetogenic chemotherapy. Palonosetron was superior in both trials. Unfortunately, in these trials the 5-HT3 receptor antagonist was not combined with dexamethasone, as recommended by guidelines.

Moreover, in both studies only 5 % of patients received dexamethasone combined with 5-HT3 antagonist in the acute phase and no one in the delayed phase, and this may be a confounding factor.

In the third trial [15] palonosetron, 0.75 mg intravenously, was compared with granisetron, both combined with dexamethasone, 16 mg, in patients receiving high emetogenic cisplatin-based or anthracycline-cyclophosphamide-based chemotherapy. The acute emesis control was similar in both arms, while palonosetron showed superior efficacy for delayed emesis control. In this study, patients with a different emetogenic risk were randomized, and dexamethasone was used at different doses with respect to those recommended by guidelines. In conclusion, the real efficacy of palonosetron, when combined with dexamethasone, as recommended by guidelines, has not been definitely clarified.

The combination of anthracycline and cyclophosphamide represents a particular situation, with high risk of nausea and vomiting, especially in young women.

A double-blind study [16], randomizing 866 patients receiving anthracycline and cyclophosphamide, evaluated the efficacy of aprepitant combined with a 5-HT3 antagonist and dexamethasone. The patients received on day 1 aprepitant, 125 mg orally, plus dexamethasone, 12 mg intravenously, plus ondansetron, 8 mg before and 8 mg after chemotherapy, or dexamethasone, 20 mg intravenously, plus ondansetron, 8 mg before and 8 mg after chemotherapy. On days 2–3, the patients received aprepitant, 80 mg orally, once a day or ondansetron, 8 mg, twice a day.

The complete response over the 5-day study period was significantly superior with aprepitant (51 % vs. 42 %); the complete response was also significantly superior with aprepitant on day 1 (76 % vs. 69 %) and on days 2–5 (55 % vs. 49 %). Complete response from nausea was not significantly different. In both the studies side effects were mild, with no difference between the two arms.

Therefore, to prevent acute nausea and vomiting in women receiving a combination of anthracycline and

cyclophosphamide, a three-drug regimen, including a single dose of 5-HT3 antagonist, dexamethasone, and aprepitant given before chemotherapy, is recommended. If aprepitant is not available for anthracycline-cyclophosphamide-based chemotherapy, palonosetron should be used in combination with dexamethasone, based on the results of the study reported above.

Prevention of Delayed Emesis

The guidelines recommend the prophylaxis of delayed emesis induced by moderately emetogenic chemotherapy.

The incidence of delayed emesis depends on the incidence of acute emesis: in fact, it is low (12 % delayed vomiting and 14 % delayed nausea) if the patients did not have acute emesis; instead, it is high (55 % delayed vomiting and 75 % delayed nausea) if the patients had acute emesis. The patients submitted to moderately emetogenic chemotherapy, without the combination of anthracycline and cyclophosphamide, receiving palonosetron plus dexamethasone for the prevention of acute emesis, should receive dexamethasone orally on days after chemotherapy.

This recommendation has been based especially on a large trial of the IGAR that demonstrated oral dexamethasone superior with respect to placebo with 10 % difference in complete response [17]. The recommended dose is 4 mg orally twice a day on days 2–4.

For the women submitted to the combination of anthracycline and cyclophosphamide, receiving aprepitant plus 5-HT3 antagonist plus dexamethasone for the prevention of acute emesis, aprepitant is recommended to prevent delayed emesis. The dose of aprepitant is 80 mg orally once a day on days 2–3.

Unfortunately, in the previously evaluated study [16], the patients received a different antiemetic combination on day 1, and the different acute emesis protection may influence the incidence of delayed emesis in the two arms.

Moreover, aprepitant was compared with ondansetron to prevent delayed emesis and not with the standard therapy, represented by dexamethasone. So it is unknown if dexamethasone

is as effective as aprepitant or if the combination of dexamethasone and aprepitant could be more effective than aprepitant alone to prevent delayed emesis. An ongoing randomized, double-blind trial of IGAR is evaluating this aspect: the patients submitted for the first time to anthracycline-cyclophosphamide chemotherapy receive a combination of aprepitant, dexamethasone, and palonosetron on day 1; they are randomized to receive aprepitant on days 2–3 or dexamethasone on days 2–4.

Recently, two randomized phase III, noninferiority trials evaluated the possibility of reducing the duration of dexamethasone therapy in delayed emesis, using palonosetron as 5-HT3 antagonist, to minimize the possible side effects related to corticosteroids.

In the first study [18], 300 female chemotherapy-naive patients with breast cancer were enrolled. The patients were submitted to anthracycline-cyclophosphamide chemotherapy, and they received a combination of palonosetron, 0.25 mg intravenously, and dexamethasone, 8 mg, on day 1; then, they were randomized to receive placebo or dexamethasone, 4 mg orally twice a day on days 2–3.

During the overall period of study of 5 days, the complete response was similar in both arms: 53.6 % versus 53.7 %, respectively; similar noninferiority results were achieved in the acute phase (69.5 % vs. 68.5 %) and in the delayed phase (62.3 % vs. 65.8 %).

In the second study [19], 322 patients receiving moderately emetogenic chemotherapy for the first time were enrolled. The chemotherapy included anthracycline-cyclophosphamide combination, oxaliplatin, carboplatin, or irinotecan-based therapy. The patients received palonosetron, 0.25 mg intravenously, and dexamethasone, 8 mg intravenously, on day 1; then, they were randomized to receive no additional therapy or dexamethasone, 8 mg orally, on days 2–3.

During the overall period of study of 5 days, the complete response was similar in both arms: 67.5 % versus 71.1 %, respectively; similar noninferiority results were also achieved in the acute phase (88.6 % vs. 84.3 %) and in the delayed phase (68.7 % vs. 77.7 %). Therefore, both the studies seem

to demonstrate a lack of efficacy against delayed emesis of dexamethasone when used in patients receiving palonosetron. On the other hand, the studies are noninferiority studies with a sample size calculated considering equivalent of the drug if the complete response was inferior to 15 %. We think that further larger studies should be conducted to clarify the problem.

Nausea and Vomiting Induced by Low or Minimally Emetogenic Chemotherapy

Only a few trials have been carried out in patients submitted to low and minimal emetogenic chemotherapy, so there is very little evidence. Moreover, the number of agents with low and minimal emetogenic risk was increased with the addition of several target therapies, and there is the possibility of an over- or undertreatment by antiemetics.

Nevertheless, the guidelines recommend that the patients submitted to chemotherapy with low emetogenic risk should receive a single antiemetic agent, such as dexamethasone, or a 5-HT3 antagonist or a dopamine-receptor antagonist to prevent acute emesis.

The patients submitted to chemotherapy with minimal emetogenic risk should not routinely receive antiemetic prophylaxis before chemotherapy, if they do not have a history of nausea and vomiting.

No antiemetic prophylaxis should be administered for the prevention of delayed emesis induced by chemotherapy with low and minimal emetogenic risk.

Chemotherapy-Induced Anticipatory Nausea and Vomiting

Anticipatory emesis occurs before chemotherapy, usually in patients who experienced nausea and vomiting in previous chemotherapy courses. Several other factors may be associated with anticipatory nausea and vomiting: the number of

Table 17.3 ESMO and MASCC guidelines for prevention of radiotherapy-induced emesis

Emetogenic potential	Radiotherapy	Recommendations
High (>90 %)	Total body irradiation; total nodal irradiation	Dex + 5-HT3 antagonist
Moderate (60–90 %)	Upper abdomen, half body or upper body irradiation	5-HT3 antagonist + optional dex
Low (30–60 %)	Cranium, craniospinal, head and neck, lower thorax region, pelvis	5-HT3 antagonist (prophylaxis or rescue)
Minimal (<30 %)	Extremities, breast	Dopamine-receptor antagonist or 5-HT3 antagonist (rescue)

Abbreviation: *Dex* dexamethasone

chemotherapy cycles, age, sex, and anxiety. In fact, young patients, females, with a history of anxiety have a higher incidence of anticipatory emesis.

The guidelines recommend the best control of acute and delayed emesis as the best way to prevent anticipatory nausea and vomiting. Antiemetic agents usually given in the prevention of acute and delayed nausea and vomiting are often ineffective in treating anticipatory emesis. Behavioral techniques could be effective in reducing anticipatory symptoms, including progressive relaxation technique, desensitization, and hypnosis. Benzodiazepines may help to reduce the incidence of anticipatory emesis, but their efficacy decreases during the treatment.

Radiotherapy-Induced Nausea and Vomiting

Radiotherapy also is often associated with nausea and vomiting. Incidence and severity of radiotherapy-induced emesis depend on several factors, similar to chemotherapy-induced emesis. Some factors are patient-related (age, gender, state of

health, previous history of emesis), and others are treatment-related (irradiated site, single and total dose, fractionation, irradiate volume, radiotherapy techniques). Concurrent or recent chemotherapy is also an important factor. Overall cumulative incidence of emesis is estimated to be around 50–80 % of patients undergoing radiotherapy.

This may be a major problem, considering that fractionated radiotherapy involves a period of 6–8 weeks and prolonged nausea and vomiting may significantly decrease patients' quality of life.

Only a few randomized studies, and often with a small number of patients, evaluated the problem of radiotherapy-induced emesis, so only a little evidence is available. It is very important to investigate the role of individual risk factors, the incidence of delayed nausea and vomiting, the potential role of NK1 receptor antagonists, and the optimal duration of antiemetic prophylaxis [20].

Nevertheless, the guidelines proposed new recommendations, considering four levels of risk (high, moderate, low, and minimal), based on the irradiation area as the most important risk factor (Table 17.3). In the case of chemoradiotherapy, the antiemetic regimen is determined by the chemotherapy antiemetic recommendations of the corresponding risk level, unless the radiotherapy-related risk is higher.

Special Topics

Nausea and Vomiting Induced by Multiple-Day Cisplatin Therapy

Only a few studies evaluated antiemetic therapies in these patients. About 55–83 % of complete protection from vomiting has been achieved with a combination of dexamethasone and 5-HT3 antagonist administered all days of chemotherapy.

The guidelines recommend a combination of dexamethasone and 5-HT3 antagonist to prevent acute emesis and

dexamethasone to prevent delayed emesis, but the optimal dose of dexamethasone and 5-HT3 antagonist is unknown, as well as the optimal duration of antiemetic therapy [21].

Patients have more severe nausea and vomiting on days 4 and 5, both in studies evaluating dexamethasone, 20 mg, on each day of cisplatin therapy or only on days 1 and 2, and it is unclear if this could reflect delayed emesis from days 1 and 2. The use of dexamethasone for 5 consecutive days, followed by three additional doses on days 6–8 (for delayed emesis prevention), may be an overtreatment, especially if repeated every 3 weeks for three or four courses, with side effects such as insomnia, agitation, weight gain, epigastric discomfort, and risk of femur osteonecrosis.

The possible role of NK1 antagonists is still undefined, because no large randomized clinical trial compared the addiction of NK1 antagonists to dexamethasone and 5-HT3 antagonist in this type of patient.

Recently, a small, double-blind, crossover study, presented at the 2011 ASCO meeting, was carried out in 68 patients with germ cell cancer, submitted to 5-day cisplatin chemotherapy [22]. The patients were randomized to receive aprepitant, 125 mg on day 3 and 80 mg on days 4–7, plus dexamethasone, 4 mg orally twice a day on days 6–8, or placebo plus dexamethasone, 8 mg twice a day on days 6–7 and 4 mg twice a day on day 8. A 5-HT3 receptor antagonist on days 1–5 plus dexamethasone, 20 mg on days 1 and 2, were utilized in both arms. A complete response was achieved in 47 % of patients in aprepitant arm versus 19 % in the placebo arm.

Further larger studies are necessary to confirm these interesting results and to clarify the better combination of antiemetic drugs in these patients.

Nausea and Vomiting in Children

This aspect of chemotherapeutic treatment for children is often underevaluated. It has been estimated that about 70 %

of children receiving chemotherapy experienced nausea and vomiting. Published studies present many problems, such as a low number of patients and nonoptimal design, so it is impossible to give a specific recommendation for many aspects of antiemetic therapy. Moreover, it is inappropriate to assume that the adult therapy can be directly applied to children, because efficacy and side effects of antiemetics may be different.

Nevertheless, the guidelines [23] recommend a combination of a 5-HT3 receptor plus dexamethasone to prevent acute nausea and vomiting in children receiving high or moderate emetogenic chemotherapy. The optimal dose and schedule are not well known, such as the optimal therapy for delayed emesis or for anticipatory emesis and the possible role of NK1 antagonists.

High-Dose Chemotherapy

In this case there are very few data on the effective use of antiemetics for patients treated with high-dose chemotherapy with stem cell support. The combination of a 5-HT3 receptor antagonist with dexamethasone represents the current standard of care, but complete protection is reached in a minority of patients. One of the major problems is that in these patients nausea and vomiting depend on several factors, including prophylactic antibiotics, narcotic analgesics, the administration of several highly emetogenic antineoplastic agents over consecutive days, and the use of total body irradiation [21]. All these factors make the research more difficult; nevertheless, randomized trials evaluating new antiemetic drugs are necessary to optimize the prophylaxis.

Summary

Major improvements have been achieved in the last 20 years in chemotherapy-induced emesis, especially in the control of vomiting. However, chemotherapy-induced nausea is still

hard to control, and it is one of the most important challenges in the following years. Future trials should be oriented to develop new antinausea drugs and to incorporate new agents into current antiemetic regimens.

Despite the increasing use of new antineoplastic agents (e.g., monoclonal antibodies or tyrosine kinase inhibitors) with minimal emetogenic potential and despite several antiemetic agents being available, nausea and vomiting are still disabling side effects. Therefore, the diffusion and the right utilization of the guidelines is a major objective.

Future improvement in antiemetic therapy will require well-designed clinical trials to define several unresolved questions: the best prophylaxis of delayed emesis induced by multiple days of cisplatin, control of nausea and vomiting induced by high-dose chemotherapy, chemoradiation therapy-induced emesis, and emesis in children.

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