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NEW TRENDS IN CLINICAL ONCOLOGY

Chemotherapy-induced nausea and vomiting: pathophysiology and therapeutic principles

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Abstract Chemotherapy-induced nausea and vomiting (CINV) is a major determinant of quality of life in cancer patients. In addition, the perceptions that oncology professionals have about CINV quite often do not coincide with reality. Antineoplastic agents and their combinations can be categorised according to their emetogenic level, and this categorisation is helpful for classifying the severity of CINV and treating it. All CINV treatment guidelines emphasise the need to administer prophylaxis to patients who receive highly or moderately emetogenic chemotherapy. With the introduction of NK1 receptor antagonists, the control of acute and delayed CINV after highly or moderately emetogenic chemotherapy schedules has improved in the great majority of patients. NK1 receptor antagonists have been demonstrated to improve the control of CINV in all risk subgroups of patients.

Keywords Acute emesis · Antiemetics · Delayed emesis · Highly emetogenic chemotherapy · Risk factors · Moderately emetogenic chemotherapy

Introduction

Chemotherapy-induced nausea and vomiting (CINV) negatively affects patients' quality of life. Clinical studies have emphasised the importance of controlling nausea and vomiting from the first cycle of chemotherapy. Understanding of CINV pathophysiology as well as identification of risk factors for acute and delayed vomiting has allowed the development of new effective drugs and management strategies. Guidelines have been created to individualise

antiemetic therapy. The aim of this paper is to review the basis for CINV therapy and offer a critical review of treatment guidelines.

Pathophysiology of CINV

Several factors are involved in the aetiology of CINV including type of therapy, such as opioid therapy, metabolic abnormalities, gastrointestinal irritation, increased intracranial pressure caused by the tumour itself or by the presence of metastasis, and treatment with radiotherapy and/or chemotherapy [1]. In recent years, the increasing knowledge of the physiology of vomiting and the neurotransmitters involved has allowed the development of specific antiemetic drugs.

Neurophysiology of vomiting

The motor-reflex response of vomiting-the reflex act of ejecting the contents of the stomach through the mouth–usually follows on from the sensation of nausea [2]. Retching is a related symptom where there is no expulsion of stomach contents, although it still entails abdominal and respiratory rhythmical muscle contraction [3]. The central nervous system receives and processes the emetic stimuli. This system generates efferent signals that are sent to a number of organs and tissues in a process that finally results in vomiting [2]. The vomiting process does not depend on a unique area but involves a number of them. These areas are the chemoreceptor trigger zone and the vomiting centre in the brain, as well as the vagal afferent pathway and the enterochromaffin cells in the gastrointestinal tract.

The chemoreceptor trigger zone –also known as the *area postrema*– is located within the fourth ventricle in the brain. Opioids and dopaminergic agonists can bind local receptors and produce emesis as a result of a relatively permeable blood–brain barrier in this area [4]. Other inducers include gut-derived peptides and metabolites derived from chemotherapeutic agents [5–7].

Several neuronal areas within the medulla of the brain coordinate the vomiting reflex [8, 9]. The action of vomiting is controlled and integrated by the vomiting centre. This centre reacts to afferent stimuli from different parts of the body, such as the gastrointestinal tract, the brain cortex, the higher brain stem, and especially the chemoreceptor trigger zone and the labyrinth apparatus [10].

CINV depends on the stimuli of vagal afferent nerves. P-substance, cholecystokinin and, most importantly, 5-hydroxytryptamine (5-HT3), are segregated from the enterochromaffin cells in the gastrointestinal mucosa as a response to chemotherapy. These mediators bind to 5-HT3 and neurokinin-1 (NK1) receptors, which are located on the end of vagal afferent nerves.

Neurotransmitters and antiemetic drugs

A variety of receptors take part in the complex process of vomiting. Three main groups of neurotransmitter receptors are involved in the process, including dopamine, serotonin and P-substance receptors. Antiemetics that have a known effect on dopamine receptors belong to the phenothiazine, benzamide and butyrophenone groups [11]. Other drugs such as metoclopramide, a kind of benzamide, not only affect the dopamine receptor but also the serotonin receptor. 5-HT3 receptor antagonists are particularly relevant as these receptors, located in the gastrointestinal tract and the central nervous system, play an important role in the vomiting process through the vagal afferent pathway [11]. NK1 receptors (targets of P-substance) are another major determinant of CINV [12–14] and specific antagonists have been developed. Aprepitant was the first agent in this class of drugs [15, 16]. Antiemetics with other mechanisms of action are corticosteroids, benzodiazepines, cannabinoids and antihistamines [17].

Type of vomiting according to time of onset

CINV is commonly classified according to time of onset:

– Acute CINV include episodes occurring within a few minutes to several hours after chemotherapy administration, with a maximal intensity after 5–6 h, and which resolve within 24 h [12, 18].

– Delayed CINV is defined as those episodes occurring more than 24 h after chemotherapy. Peaks of intensity are generally 48–72 h after drug administration [12, 18].

– Anticipatory emesis is defined as those episodes that precede drug administration. Since it is a conditioned response, this type of emesis occurs after a previous negative vomiting experience with chemotherapy [13, 14].

Categorisation of antineoplastic drugs and schedules according to their emetogenicity

Clinical guidelines commonly used in medical oncology have been published by several organisations such as the National Comprehensive Cancer Network (NCCN) v1.2012 [19], the American Society of Clinical Oncology (ASCO) 2011 [20], the Multinational Association for Supportive Care in Cancer and European Society for Medical Oncology (MASCC-ESMO) 2010 [21] and Sociedad Española de Oncología Médica (SEOM) 2010 [22]. These guidelines gather information about the treatment of various tumours as well as the management of related symptoms, and are periodically updated.

According to the guidelines of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [23], there are four grades of severity of CINV as specified in Table 1.

Table 1 Grading of vomiting according to the National Cancer Institute Common Criteria for Adverse Events version 4.0

Grade	1	2	3	4	5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake, tube feeding, TPN or hospitalisation indicated		
Vomiting	1–2 episodes (separated by 5 min) in 24 h	3–5 episodes (separated by 5 min) in 24 h	Six or more than 6 episodes (separated by 5 min) in 24 h; tube feeding, TPN or hospitalisation indicated	Life-threatening consequences; urgent intervention indicated	Death

Table 2 Highly emetogenic drugs according to different guidelines

Drug	ASCO	MASCC-ESMO	NCCN	SEOM
Cisplatin	Yes	Yes	If >50 mg/m^2	Yes
Cyclophosphamide	If ≥1.5 g/m^2	If ≥1.5 g/m^2	If >1.5 g/m^2	If >1.5 g/m^2
Dacarbazine	Yes	Yes	Yes	Yes
Streptozotocin	Yes	Yes	Yes	Yes
Carmustine	Yes	Yes	If >250 mg/m^2	Yes
Mecloretamine	Yes	Yes	Yes	Yes

ASCO, American Society of Clinical Oncology; MASCC-ESMO, Multinational Association for Supportive Care in Cancer and European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica

Emetogenicity of antineoplastic agents

Most classifications of antineoplastic agents are related to their emetogenicity, but do not differentiate between the type of vomiting according to time of onset (i.e., acute or delayed), nor do they consider important treatment-related factors such as dose, rate and route of administration. Additionally, most classifications do not consider patient-related factors either. In the following classification, new antineoplastic drugs have also been included, as well as oral cytotoxic and biologic agents, since the use of oral drugs has been increasing in the last years (Tables 2 and 3).

According to their emetogenic potential, drugs may be classified into four categories, namely highly emetogenic drugs, in which at least 90% of patients experience CINV after treatment; moderately emetogenic drugs, in which 30–90% of patients experience CINV after treatment; low emetogenic drugs, in which 10–30% of patients experience CINV after treatment; and finally drugs with minimal emetogenicity, in which less than 10% of patients experience CINV after treatment [21].

Emetogenicity of antineoplastic schedules

Hesketh et al. [24] estimated the potential emetogenicity of chemotherapy schedules based on the individual potential emetogenicity of the agents that comprise that regimen when no prophylactic antiemetic drugs are administered. In this classification system, firstly the most emetogenic agent in the regimen is identified. Secondly, this agent is classified according to five different levels of emetogenicity: level 5 is for those agents that elicit vomiting in over 90% of patients, level 4 for a frequency of 90% to 60%, level 3 for a frequency of 60% to 30%, level 2 for a frequency of 30% to 10% and level 1 for agents that induce vomiting in

Table 3 Moderately emetogenic drugs according to different guidelines

Drug	ASCO	MASCC-ESMO	NCCN	SEOM
Oxaliplatin	Yes	Yes	Yes	Yes
Carboplatin	Yes	Yes	Yes	Yes
Cyclophosphamide	If <1.5 g/m^2	If <1.5 g/m^2	If ≤1.5 g/m^2	If ≤1.5 g/m^2
Ifosmamide	Yes	Yes	If <10 mg/m^2	Yes
Doxorubicin	Yes	Yes	If ≤60 mg/m^2	Yes
Epirubicin	Yes	Yes	If ≤90 mg/m^2	Yes
Irinotecan	Yes	Yes	Yes	Yes

ASCO, American Society of Clinical Oncology; MASCC-ESMO, Multinational Association for Supportive Care in Cancer and European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica

fewer than 10% of patients. Thirdly, the relative contribution of the remainder of the drugs included in the schedule is taken into account according to three rules: (i) agents in level 1 do not affect the emetogenicity of the schedule; (ii) one or more agents in level 2 increase the emetogenicity of the schedule by one level greater than the previous level established; (iii) agents in level 3 or 4 increase the emetogenicity of the schedule by one level per each drug added.

Risk factors for CINV

Several risk factors have been linked to the development of CINV. Some of them are related to the patient, whereas others are related to the cytostatic treatment administered. Risk factors related to the patient include a previous history of poor vomiting control, because delayed and anticipatory vomiting occur more frequently in these patients; alcohol intake, because chronic high level alcoholics are less prone to vomiting; age, because in older patients vomiting is easier to control; gender, because women have less control over nausea and vomiting; and motion sickness, because patients with a history of motion sickness are more prone to show CINV [11, 25]. Among risk factors associated with cytostatic treatment, not only the emetogenic potential of the drug, but also the dosage, the combination with other cytostatic(s), the combined administration of radiation therapy and the route of administration should be considered [26].

Two large studies have assessed the influence of risk factors for CINV in patients treated with high or medium emetogenic cytostatic agents who receive prophylaxis with aprepitant [27, 28]. Seventy-six percent of patients with four to six risk factors had CINV despite the administration of prophylaxis with 5-HT3 receptor antagonists and dexamethasone. On the other hand, in the absence of any of these factors, the risk of CINV was 20%.

One of these large studies is a retrospective pooled analysis of two randomised phase III trials that included patients treated with cisplatin [27]. This study included 1043 patients and its objectives were to confirm the importance of several previously reported adverse risk factors for CINV in patients receiving chemotherapy, to assess the impact of the NK1 receptor antagonist aprepitant and to assess the impact of age on antiemetic outcome. The primary endpoint was complete response (i.e., no vomiting and no use of rescue therapy). Patients were randomised to receive standard treatment with dexamethasone and 5-HT3 receptor antagonists or the same treatment plus aprepitant. The risk factors evaluated were female sex, cisplatin dose >80 mg/m^2, low alcohol intake and age <65 years. The analysis of results confirmed the relevance of these risk factors for CINV in patients receiving chemotherapy. Aprepitant improved complete response regardless of the presence of these risk factors and eliminated the increased risk of CINV associated with female gender.

The second study is a retrospective analysis of a phase III trial that included 866 patients. This trial assessed the role of several risk factors in patients receiving a moderately emetogenic schedule such as adriamycin-cyclophosphamide (AC)-based chemotherapy [28]. The risk factors analysed were age <55 years, history of motion sickness or morning sickness during pregnancy, and low consumption of alcohol. Patients were randomised to receive treatment with dexamethasone and ondansetron with or without aprepitant. Aprepitant markedly improved the control of vomiting in patients with one, two or three risk factors. However, this analysis did not support the use of risk factors for modifying the antiemetic strategy. Gender, age, alcohol intake and motion sickness have been identified as risk factors for acute vomiting.

Healthcare perception vs. reality regarding CINV

Several studies have examined the impact of CINV on quality of life and have compared patients' and healthcare professionals' perceptions of the problem. Healthcare professionals usually underestimate the intensity and impact of CINV on their patients.

In a study reported by Osoba et al. [29], 832 patients who received either moderately or highly emetogenic chemotherapy completed the European Organization for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) in the 7 days before starting chemotherapy, in the first week after treatment and on the first day of the second cycle. They also filled in a self-reported nausea and vomiting diary for 6 days after chemotherapy. Patients had been treated with 5-HT3 receptor antagonists and dexamethasone before chemotherapy and also on the first day of treatment. Responses were stratified into four groups according to the presence or absence of nausea and/or vomiting. Patients with nausea and vomiting showed statistically significant deterioration of physical performance, cognitive function, and social and global quality of life compared with the group of patients without nausea and vomiting. Patients with nausea, but no vomiting, suffered less deterioration than patients with nausea and vomiting.

Another study assessed the ability of physicians and nurses to estimate the incidence of CINV [30]. The study included 24 physicians or nurses and 298 patients who received moderately or highly emetogenic chemotherapy along with 5-HT3 receptor antagonists and dexamethasone as antiemetics. The study concluded that, although healthcare professionals correctly predicted the incidence of acute CINV, they underestimated the incidence of delayed nausea and vomiting with both types of chemotherapy, highlighting the importance of improving the recognition and management of these events.

A similar study was performed after the introduction of aprepitant [31]. Twenty-nine physicians and nurses, and 95 patients were included. Patients were treated with highly

or moderately emetogenic chemotherapy. Although all patients received 5-HT3 receptor antagonists and dexamethasone, only those receiving highly emetogenic chemotherapy with cisplatin also received aprepitant. The results of the study showed that physicians and nurses accurately predicted the incidence of both acute and delayed CINV in patients treated with highly emetogenic chemotherapy with cisplatin that received 5-HT3 receptor antagonists, dexamethasone and aprepitant. However, they underestimated the incidence of acute nausea and acute or delayed emesis in patients treated with highly emetogenic chemotherapy without cisplatin or moderately emetogenic chemotherapy. It was also concluded that aprepitant helps to improve the control of CINV in schedules with cisplatin.

Antiemetic prophylaxis for patients treated with highly emetogenic chemotherapy

Over 90% of patients receiving highly emetogenic chemotherapy experience nausea or vomiting in the absence of prophylaxis. Cisplatin, high-dose cyclophosphamide, carmustine, dacarbazine, mechlorethamine and streptozotocin are chemotherapy agents with a high degree of emetogenicity. Even when prophylaxis is administered, 30% of patients experience nausea and vomiting after receiving highly emetogenic chemotherapy [24, 32]. To date, the main clinical antiemetic guidelines, such as NCCN v1.2012 [19], MASCC-ESMO 2010 [21], ASCO 2011 [20] and SEOM 2010 [22], recommend the administration of antiemetic prophylaxis to patients receiving highly emetogenic chemotherapy, with the aim of controlling both acute and delayed CINV. Therapy should combine corticosteroids, 5-HT3 receptor antagonists and NK1 receptor antagonist.

Antiemetic prophylaxis with corticosteroids

The antiemetic action of corticosteroids, unlike that of other antiemetic drugs, has not been studied through well controlled, randomised studies. Dexamethasone, methylprednisolone and prednisone are all effective against mild to moderately emetogenic chemotherapy [33, 34], but not against highly emetogenic chemotherapy such as high-dose cisplatin [35]. However, more recently, a meta-analysis published in 2000 that includes 32 studies and 5613 patients showed that dexamethasone is clearly effective in protecting against CINV in both acute and delayed phases in patients treated with highly or moderately emetogenic chemotherapy. Dexamethasone was superior to placebo or to no treatment for complete protection from acute vomiting (hazard ratio [HR]: 2.22; 95% confidence interval [CI]: 1.89–2.60) and for the complete protection from delayed vomiting (HR: 2.04; 95% CI: 1.63–2.56), with a good toxicity profile [36].

Antiemetic prophylaxis with 5-HT3 receptor antagonists

First-generation 5-HT3 receptor antagonists (i.e., granisetron, ondansetron, dolasetron and tropisetron) effectively control acute CINV when combined with corticosteroids. A recent meta-analysis published in 2010 reviewed 16 studies and 7808 patients and concluded that first-generation 5-HT3 receptor antagonists are all effective and equivalent to each other in the prophylaxis of acute and delayed CINV following the use of highly emetogenic chemotherapy. The main adverse effects observed were gastrointestinal (i.e., constipation, abdominal pain, diarrhoea) and central nervous system (i.e., headache, dizziness) [37].

Palonosetron is a second-generation 5-HT3 receptor antagonist with a long half-life of about 40 h and strong binding affinity for the serotonin receptor [38, 39]. In a pivotal phase III trial evaluating the efficacy and safety profile of palonosetron in preventing acute and delayed CINV following highly emetogenic chemotherapy (PALO-99-05 study) [40], 570 patients were randomised either to a single intravenous dose of palonosetron (0.25 or 0.75 mg) or to ondansetron (32 mg). Additionally, patients were stratified based on the pre-treatment administration of dexamethasone at the investigator's discretion. The phase III trial concluded that 0.25 mg of palonosetron significantly reduced acute, delayed and overall CINV periods.

In another phase III trial, palonosetron plus dexamethasone combination was compared with granisetron plus dexamethasone for the prevention of CINV in 1114 patients treated with highly emetogenic chemotherapy [41]. It was concluded that palonosetron administered with dexamethasone before highly emetogenic chemotherapy is as effective as granisetron in the prevention of the acute phase of CINV, but has a greater activity in the delayed phase, with a comparable safety profile.

Antiemetic prophylaxis with NK1 receptor antagonists

NK1 receptor antagonists include the potent and selective oral nonpeptide antagonist of the NK1 receptor aprepitant and the intravenous pro-drug fosaprepitant. Aprepitant was registered after two phase III, multicentre, randomised clinical trials [15, 16]. In both studies, patients treated with high-dose cisplatin chemotherapy were randomised to receive a standard therapy with intravenous ondansetron plus oral dexamethasone or the same standard treatment plus aprepitant. Compared with the standard treatment, the addition of aprepitant was generally well tolerated and provided consistently superior protection against CINV in both the acute and delayed phases.

Fosaprepitant is a more recently introduced drug and allows the administration of a single intravenous dose. In a recent phase III, randomised, double-blind study, a single dose of intravenous fosaprepitant given with ondansetron and dexamethasone was demonstrated to be non-inferior to

Table 4 Prevention of CINV in patients treated with highly emetogenic chemotherapy

	ASCO	MASCC-ESMO	NCCN	SEOM	Differences
Acute emesis	5-HT3 RAs+dexamethasone +aprepitant	5-HT3 RAs+dexamethasone +aprepitant	5-HT3 RAs+dexamethasone +aprepitant[a]	5-HT3 RAs+dexamethasone +aprepitant	SEOM specifically recommends palonosetron, while NCCN, MASC-ESMO and ASCO recommend 5-HT3 RAs
Delayed emesis	Dexamethasone+aprepitant	Dexamethasone+aprepitant	Dexamethasone+aprepitant*	Dexamethasone+aprepitant	No differences

[a]As alternative to aprepitant, 150 mg of fosaprepitant as single dose, or 115 mg of fosaprepitant on day 1 plus 80 mg of aprepitant on days 2 and 3, are also recommended

5-HT3 RAs, 5-hydroxytryptamine 3 receptor antagonists; ASCO, American Society of Clinical Oncology; MASCC-ESMO, Multinational Association for Supportive Care in Cancer and European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica

the three-day regimen of oral aprepitant during delayed and overall risk phase [42].

Recommendations of clinical guidelines for the prevention of CINV in patients treated with highly emetogenic chemotherapy

Table 4 shows a comparison of the recommendations issued by different organisations for the prevention of CINV in patients treated with highly emetogenic chemotherapy.

NCCN guideline

Compared with other guidelines, one of the main innovations of this guideline is the withdrawal of the recommendation for intravenous dolasetron, since the US Food and Drug Administration found it to be associated with an increased frequency of cardiac arrhythmias [19, 43]. However, this guideline continues to recommend the use of the oral formulation of this antiemetic. It also proposes the use of a transdermal patch of granisetron.

Due to the long half-life of palonosetron (>40 h), the guideline recommends its use for delayed CINV in moderately emetogenic therapies, but not in highly emetogenic therapies, as the NCCN does not acknowledge any distinction among 5-HT3 receptor antagonists. The recommended steroid chosen by NCCN is intravenous or oral dexamethasone. Lastly, regarding NK1 receptor antagonists, this guideline recommends oral aprepitant as well as single-dose intravenous fosaprepitant.

The recommended dosing is summarised as follows:

– On day 1, an oral 5-HT3 receptor antagonist (100 mg of dolasetron, 2 mg of granisetron, 16–24 mg of ondansetron) or 0.25 mg of intravenous palonosetron plus oral or intravenous dexamethasone (12 mg) plus oral aprepitant (125 mg) or a single dose of intravenous fosaprepitant (150 mg).

– On days 2–4, oral or intravenous dexamethasone (8 mg) plus oral aprepitant (80 mg/day). Aprepitant administration is not necessary if fosaprepitant (150 mg) is given on day 1.

This guideline also recommends palonosetron as an alternative in a chemotherapy regimen of 3–5 days. Aprepitant is also recommended on days 4–5 as an alternative when chemotherapy is highly emetogenic. In terms of CINV occurring between cycles of chemotherapy, there is no evidence for one treatment being more effective than another.

MASCC-ESMO guideline

This guideline emphasises the use of intravenous fosaprepitant (115 mg), which is equivalent to oral aprepitant (125 mg), and can be used as a parenteral alternative to oral aprepitant on day 1 of a 3-day regimen [21]. Like the NCCN guideline, the MASCC-ESMO guideline considers that AC schedule is a highly emetogenic treatment.

The main difference with regard to the NCCN guideline in the dosage procedure for AC schedule is that on days 2–3 the only drug used is aprepitant, and not dexamethasone. Also, this guideline maintains the use of intravenous dolasetron. In the next update of this guideline, the recommendation for intravenous dolasetron will be likely discontinued due to the increased frequency of cardiac arrhythmias observed after its administration [43].

The recommended doses established in the MASCC-ESMO guideline are:

– Fosaprepitant, 115 mg intravenous.

– Aprepitant, 125 mg oral.

– Dexamethasone, 12 mg oral or intravenous, or 20 mg if aprepitant is not administered.

– Palonosetron, 0.25 mg intravenous or 0.50 mg oral.

For an appropriate prevention of the delayed phase, optimal antiemetic prophylaxis with dexamethasone and aprepitant is recommended. For the acute phase, the use of aprepitant plus 5-HT3 receptor antagonists and dexamethasone is advised.

ASCO guideline

This guideline sorts drugs according to therapeutic index [20]. Thus, high therapeutic index includes the combination of 5-HT3 receptor antagonist, corticoids and NK1 receptor antagonist. Unlike the rest of the guidelines, this one does not mention the use of fosaprepitant.

The dosage recommended by this guideline is the same as in the other guidelines:

– Acute CINV: 5-HT3 receptor antagonist, dexamethasone and aprepitant.

– Delayed CINV: Dexamethasone and aprepitant.

In the special situation of high-dose chemotherapy administered in paediatric oncology, this guideline suggests the use of 5-HT3 receptor antagonist and dexamethasone.

SEOM guideline

This is the only guideline [22] that specifically recommends palonosetron as 5-HT3 antagonist of the serotonin pathway and does not include fosaprepitant. Treatment schedules are otherwise similar to those in previous guidelines.

Additional comments on highly emetogenic therapy

Contrary to what might be expected with the combination of 5-HT3 receptor antagonists and corticosteroids, CINV remains a major concern for patients. An article published by Hofman et al. in 2004 [44] concluded that CINV was still the second greatest concern for cancer patients. CINV occurs not only as a consequence of the different therapies defined by the different guidelines as being highly emetogenic, but also following those considered to be moderately emetogenic, where the incidence of CINV may reach up to 58% of patients [45]. This lack of protection against CINV may be partly due to the fact that, although serotonin plays a role in CINV during the acute phase, P-substance becomes important during the delayed phase and therefore requires the addition of NK1 receptor antagonists as an antiemetic regimen to protect against CINV when 5-HT3 receptor antagonist protection is not complete, even for moderately emetogenic chemotherapy treatments.

As a result, several international guidelines consider the combination of two moderately emetogenic chemotherapy agents as highly emetogenic chemotherapy and therefore to be treated with triple antiemetic therapies. This would lead to the addition of NK1 receptors antagonists to the antiemetic regimen together with 5-HT3 and corticosteroids. In this way, the study reported by Warr et al. showed almost the same incidence of CINV with the combination AC scheme as with highly emetogenic chemotherapy, when a dual therapy was used as prophylaxis [45]. Therefore, from this study onwards, the AC scheme started to be considered as highly emetogenic by several international guidelines.

There are several reasons for the lack of control of delayed CINV. One of them is the role played by the hospital staff in the monitoring and control of CINV during chemotherapy administration, and the difficulty for such monitoring once the patient leaves the hospital. This fact may explain the difference between perception and reality of symptoms experienced by healthcare professionals and patients regarding the incidence of delayed CINV.

After the first data from previous studies that showed discrepancy between perception vs. reality, another study by Majem et al. [31] confirmed not only that this discrepancy increased in highly and moderately emetogenic regimens, where only a double antiemetic prophylaxis therapy was used, but also decreased or disappeared in the group treated with highly emetogenic chemotherapy based on cisplatin, where the NK1 receptor antagonists were used as part of the antiemetic therapy. In fact, one of the most relevant conclusions that can be drawn from this study is that the control of CINV was higher in patients treated with highly emetogenic chemotherapy regimens based on cisplatin in whom a triple therapy was given, than in patients treated with highly emetogenic chemotherapy not based on cisplatin or moderately emetogenic chemotherapy regimens.

Rapoport et al. published a study that compared the efficacy of a dual therapy based on 5-HT3 receptor antagonists and dexamethasone with a triple therapy adding novel NK1 receptor antagonists as prophylactic treatment of CINV [46]. The results confirmed those previously obtained by Warr et al. [45] for the more effective control of CINV with triple therapy antiemetic prophylaxis in comparison with a dual therapy regimen in patients treated with moderately emetogenic chemotherapy (AC or non-AC schedules).

Recommendations of clinical guidelines for the prevention of CINV in patients treated with moderately emetogenic chemotherapy

Moderately emetogenic chemotherapy is primarily composed of anthracyclines, cyclophosphamide, carboplatin, oxaliplatin and irinotecan. Although the traditional Hesketh classification was based on the emetogenic power of each of them separately [24], the new treatment guidelines take into account that their combination may change their categorisation. Thus, the NCCN guideline classifies AC therapy (C dosage <1500 mg/m^2) as moderately emetogenic if drugs are administered sequentially as single agents, but when given concomitantly this schedule is classified as highly emetogenic [19]. Another aspect to consider is that emetogenic potential is calculated using the percentage of patients in which the agents produce CINV when there is no administration of antiemetic prophylaxis. Reclassification might be needed considering that patients always receive antiemetic treatment.

Table 5 shows a comparison of the recommendations issued by different organisations on this subject.

Table 5 Prevention of CINV in patients treated with moderately emetogenic chemotherapy

		ASCO	MASCC-ESMO	NCCN	SEOM
Acute emesis	AC scheme	5-HT3 RAs[a]+dexamethasone +aprepitant	5-HT3 RAs+dexamethasone +aprepitant	5-HT3 RAs+dexamethasone +aprepitant	5-HT3 RAs+ dexamethasone +aprepitant if needed
	Non-AC scheme	5-HT3 RAs[a]+dexamethasone	Palonosetron+dexamethasone	5-HT3 RAs+dexamethasone +aprepitant if needed	
Delayed emesis	AC scheme	Aprepitant	Aprepitant	Dexamethasone+aprepitant	Dexamethasone+aprepitant if needed
	Non-AC scheme	5-HT3 RAs[a] or dexamethasone	Dexamethasone	Dexamethasone or 5-HT3 or aprepitant if used in acute phase	

[a]Palonosetron is not recommended as a standard

5-HT3 RAs, 5-hydroxytryptamine 3 receptor antagonists; AC, anthracycline and cyclophosphamide; ASCO, American Society of Clinical Oncology; MASCC-ESMO, Multinational Association for Supportive Care in Cancer and European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica

ASCO guideline

ASCO guideline recommendations established therapeutic strategies based on whether or not an AC scheme is administered [20]. For the AC combination, the guideline recommends the use of triple therapy with 5-HT3 receptor antagonists, dexamethasone and aprepitant in acute CINV, while for delayed CINV it proposes the use of aprepitant as a single drug. For other chemotherapy regimens, it recommends dual therapy with dexamethasone and 5-HT3 receptor antagonists in acute CINV and maintenance treatment with dexamethasone or 5-HT3 receptor antagonists in delayed CINV. Despite being a relatively new guideline, it does not consider that there may be other combinations of chemotherapeutic agents that may be more emetogenic than the AC scheme, and considers the emetogenicity of drug combinations to be dependent on the agent of greatest emetic risk.

Regarding treatment with 5-HT3 receptor antagonists, the ASCO guideline does not recommend palonosetron as a standard over the other 5-HT3 receptor antagonists, even though the results of various studies comparing palonosetron vs. ondansetron showed a better control of CINV with palonosetron in both acute and delayed phase CINV [40].

MASCC-ESMO guideline

The MASCC-ESMO guideline [21], as well as the ASCO guideline [20], also makes a distinction between AC and non-AC schemes. The former recommends the use of triple therapy for acute CINV (level of evidence IA) and the control of delayed CINV treatment with aprepitant, similar to ASCO, but with a level of evidence IIB. For non-AC regimes, MASCC-ESMO guide recommends a dual therapy with palonosetron and dexamethasone (level of evidence IIB) in acute CINV and dexamethasone as a single agent in delayed CINV, also with a level of evidence IIB. For this guideline, palonosetron is considered superior to other 5-HT3 receptor antagonists, although evidence for this recommendation comes from non-inferiority studies.

These recommendations took into account the results reported by Rapoport et al., in which 848 patients received moderately emetogenic chemotherapy (AC and non-AC regimens) and were treated with an aprepitant triple-therapy regimen (aprepitant, ondansetron and dexamethasone) or a control regimen (ondansetron and dexamethasone) [46]. Although the aprepitant regimen provided superior efficacy in the treatment of CINV for both endpoints (number of patients without vomiting and complete response), the MASCC-ESMO guideline indicated that the high heterogeneity of chemotherapy regimens in the non-AC group and the type of post hoc analysis were factors that excluded its recommendation as a standard in this group.

NCCN guideline

The more recent recommendations come from the NCCN v.1.2012 [19]. This guideline recommends the use of triple antiemetic therapy in the AC scheme, which is considered highly emetogenic, with a combination of 5-HT3 receptor antagonists, NK1 antagonists and dexamethasone. In the correctly classified moderately emetogenic regimens for acute CINV, the combination of 5-HT3 receptor antagonists, corticosteroids (methylprednisolone or dexamethasone) and aprepitant in selected patients or when appropriate is recommended. Therefore, the inclusion of aprepitant would be considered in patients with risk factors or who have vomited in the previous cycle, as secondary prophylaxis. For delayed CINV, the guideline proposes single-agent therapy with either corticosteroid, 5-HT3 receptor antagonist, or aprepitant if used in the acute phase.

SEOM guideline

The SEOM guideline, updated in 2010 [22], is the only one that does not make any distinction between AC schemes and other schemes. Where appropriate, the recommended treatment for moderately emetogenic chemotherapy is the combination of 5-HT3 receptor antagonists and dexametha-

sone in acute CINV, and dexamethasone as a single agent for preventing delayed CINV. If the patient presents CINV, the guideline suggests several options for the subsequent cycles such as changing the 5-HT3 receptor antagonist, considering the use of palonosetron, the use of aprepitant as secondary prophylaxis or adding dopaminergic inhibitors to the treatment.

Conclusions

Effective management of CINV is still a challenge in the treatment of patients with cancer. Aggressive combination chemotherapy regimens may yield better therapeutic results in some patients, but often at the expense of an increased toxicity. This toxicity can raise the incidence of metabolic disorders, anorexia and malaise, and may even lead the patient to abandon potentially useful and curative antineoplastic treatments.

CINV remains one of the most undesirable consequences of chemotherapy for the quality of life of cancer patients. Moreover, healthcare professionals usually underestimate the incidence and severity of CINV. The management of CINV relies primarily on prevention rather than treatment, so choosing the most appropriate antiemetic regimen should be based on the emetogenic potential of the scheme to be administered, also taking into account individual risk factors of the patient [47, 48].

All guidelines on the treatment of CINV show a strong consensus in their recommendations to treat patients receiving highly emetogenic chemotherapy. Most guidelines consider the AC scheme of treatment as highly emetogenic and make no major distinctions between 5-HT3 receptor antagonists (although palonosetron may acquire a new position as further studies are being carried out). The NCCN is the only guideline so far that has withdrawn the recommendation of intravenous dolanosetron, but in the next revision it is possible that the rest of the guidelines will follow suit, due to the cardiac effects it produces.

Also, individual chemotherapies that are classified at present as moderately emetogenic can climb a step higher when combined with other cytostatic therapies. In this context, AC combinations, classically considered as being of moderate risk, are now managed as high risk. For AC scheme, all guidelines presented in this document, except SEOM, recommend triple therapy with aprepitant in acute vomiting. Additionally, with the exception of SEOM and MASCC, all guidelines recommend the use of aprepitant as a single agent for the control of delayed emesis. For non-AC schemes, dual therapy is recommended as the standard of treatment, in combination for acute CINV and as a single agent for delayed CINV.

Over 50% of patients who receive therapy prophylaxis with 5-HT3 receptor antagonist still require rescue medication, even if they receive moderately emetogenic chemotherapy. The use of NK1 receptor antagonists as part of an antiemetic scheme has led to more effective control of CINV, not only during the delayed phase, but globally, in highly and moderately emetogenic chemotherapy schemes. Aprepitant is useful in controlling CINV in highly and moderately emetogenic schemes, especially those based on cisplatin and AC-based chemotherapy. Also, aprepitant helps to control CINV regardless of the risk factors in the high- and low-risk subgroups. There may be a very low risk group where they are not useful, but this group is not well defined.

Conflict of interest The authors declare that they do not have any conflict of interest that may inappropriately influence this work.

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