

Overview of the updated antiemetic guidelines for chemotherapy-induced nausea and vomiting

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Nausea and vomiting associated with cancer chemotherapy are experienced by 70%–80% of patients receiving chemotherapy and can result in significant morbidity. Chemotherapy-induced nausea and vomiting (CINV) adversely affects patient quality of life, often leading to poor compliance with the treatment regimen and serious metabolic complications. Several classes of antiemetic drugs are available to prevent or treat CINV. Older agents include phenothiazines, antihistamines, and corticosteroids. Serotonin (5-HT₃) receptor antagonists became available in the 1990s for use in preventing CINV. Recently, the NK₁ receptor antagonist aprepitant was introduced for use in combination therapy regimens. Despite this introduction of new and more effective antiemetic agents, emesis remains a significant complication of chemotherapy. Updated antiemetic guidelines were published in 2007 by the National Comprehensive Cancer Network and in 2006 by the American Society of Clinical Oncology. Updates for clinicians who treat patients with CINV are now available and are reviewed here.

Chemotherapy-induced nausea and vomiting (CINV) is a distressing and common adverse event associated with cancer treatment. Seventy percent to eighty percent of patients undergoing chemotherapy experience emesis, with 10%–44% experiencing anticipatory emesis.^{1,2} CINV results in significant morbidity and negatively impacts patient quality of life.^{3–5} CINV may cause nonadherence to chemotherapy or dose reductions due to anticipatory nausea and vomiting.^{6–8}

Increased risk of CINV is associated with the following factors: age < 50 years, female gender, vomiting during previous chemotherapy, pregnancy-induced nausea/vomiting, history of motion sickness, and anxiety.^{9,10} CINV can result in weakness, weight loss, electrolyte imbalance, dehydration, or anorexia and is associated with a variety of complications, including fractures, esophageal tears, decline in behavioral and mental status, and

wound dehiscence.¹¹ Patients who are dehydrated, debilitated, or malnourished, as well as those who have an electrolyte imbalance or those who have recently undergone surgery or radiation therapy, are at greater risk of experiencing serious complications from CINV.¹¹

Despite the recent introduction of new and more effective antiemetic agents, emesis remains a significant complication of chemotherapy. Updated antiemetic guidelines were published in 2007 by the National Comprehensive Cancer Network (NCCN) and in 2006 by the American Society of

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Clinical Oncology (ASCO).

Pathophysiology of nausea and vomiting

The sensation of nausea and act of vomiting are protective reflexes that rid the intestine and stomach of toxic substances. The experience of nausea is subjective, and nausea may be considered a prodromal phase to the act of vomiting.¹² Vomiting consists of a pre-ejection phase, retching, and ejection and is accompanied by shivering and salivation. Vomiting is triggered when afferent impulses from the cerebral cortex, chemoreceptor trigger zone (CTZ), pharynx, and vagal afferent fibers of the gastrointestinal (GI) tract travel to the vomiting center, located in the medulla. Efferent impulses then travel from the vomiting center to the abdominal muscles, salivation center, cranial nerves, and respiratory center, causing vomiting.

It is thought that chemotherapeutic agents cause vomiting by activating neurotransmitter receptors located in the CTZ, GI tract, and vomiting center. Serotonin (5-hydroxytryptamine [5-HT₃]) and dopamine receptors are the primary neuroreceptors involved in the emetic response, particularly the 5-HT₃ receptor.^{1,12-14}

Types, causes, and risk categories of CINV

Five categories are used to classify CINV: acute, delayed, anticipatory, breakthrough, and refractory. Acute-onset CINV refers to nausea and/or vomiting occurring within 24 hours of drug administration.⁹ The incidence of acute emesis reflects several treatment-related factors, including the environment in which chemotherapy is administered, the efficacy of antiemetic therapy, and the dosage of the emetogenic agent. Patient-related factors include age and gender, history of motion sickness,

previous episodes of nausea and vomiting, and a history of alcoholism (which reduces the likelihood of acute emesis).^{1,15}

Nausea and/or vomiting that develops more than 24 hours after chemotherapy administration is known as delayed emesis. Typically occurring with administration of carboplatin, doxorubicin, or cyclophosphamide, delayed emesis is more common in those who experience acute emesis. Other predictive factors include the dose of the chemotherapeutic agent, patient gender and age, and protection against nausea and vomiting in previous cycles of chemotherapy.^{4,16} For cisplatin, which has been most extensively studied, delayed emesis reaches peak intensity 2–3 days subsequent to chemotherapy administration and can last up to a week.^{1,4,17}

If patients experience CINV, they may develop a conditioned response known as anticipatory nausea and/or vomiting during future chemotherapy cycles. This response refers to nausea or vomiting occurring prior to treatment with chemotherapy. Incidence rates for this type of nausea and vomiting range from 18% to 57%,¹ with nausea occurring more frequently. Predictive factors include previous CINV and patient age. Younger patients more frequently experience CINV; it is thought to be linked to the more aggressive chemotherapy used in this population as well as poorer emesis control with pharmacologic agents.^{1,18}

Vomiting that occurs after prophylactic use of antiemetic agents or requires “rescue” is called breakthrough emesis. Vomiting occurring in subsequent chemotherapy cycles when antiemetic prophylaxis and/or rescue has failed in earlier cycles is known as refractory emesis.¹

Several systems have been designed to classify agents by degree of emetogenicity, since the fre-

quency with which patients develop CINV is related to the inherent emetogenicity of the chemotherapeutic agents that comprise the treatment regimen (Table 1).^{1,17-19} In 1997, Hesketh and colleagues published a classification schema that divided agents into five levels according to the percentage of patients experiencing acute emesis without prophylactic antiemetic therapy in clinical trials: level 1 (< 10%), level 2 (10%–30%), level 3 (30%–60%), level 4 (60%–90%), and level 5 (> 90%).¹⁹ Combination regimens were classified according to an algorithm. The Hesketh system was updated by Grunberg and colleagues in 2005; they used four levels and also included a separate classification of oral antineoplastic agents.¹⁰ The categories correspond to classifications used in the current ASCO and NCCN guidelines.^{1,18} These classifications and the risk of emesis associated with various chemotherapeutic agents appear in Tables 1 and 2.^{1,17-19}

Hyperfractionated total-body irradiation (TBI) also has emetogenic potential, which is proportional to the dose per fraction and the volume of the abdomen exposed.²⁰ Nausea and vomiting occur when enterochromaffin cells in the GI mucosa release serotonin, which interacts with 5-HT₃ receptors in the CTZ and on vagal afferent neurons.²¹ The resulting nausea and vomiting can erode patient quality of life and cause distress; elderly patients (> 65 years of age) are particularly at risk for GI complications, including dehydration and malnutrition.²² The emetogenic potential of TBI—as well as optimal antiemetic regimens for controlling TBI-related nausea and vomiting—remains less well characterized than that associated with chemotherapy, because TBI is often used in combination with or after emetogenic chemotherapy.^{20,21}

TABLE 1

Emetic risk of antineoplastic agents

High emetic risk (> 90% frequency of emesis)*	Moderate emetic risk (30%–90% frequency of emesis)*	Low emetic risk (10%–30% frequency of emesis)*	Minimal emetic risk (< 10% frequency of emesis)*
AC combination defined as either doxorubicin or epirubicin with cyclophosphamide	Aldesleukin (> 12–15 million units/m ²) ¹	Amifostine (≤ 300 mg)	Alemtuzumab
Altretamine	Amifostine (> 300 mg/m ²)	Bexarotene	Asparaginase
Carmustine (> 250 mg/m ²)	Arsenic trioxide	Capecitabine	Bevacizumab
Cisplatin (≥ 50 mg/m ²)	Azacitidine	Cetuximab	Bleomycin
Cyclophosphamide (> 1,500 mg/m ²)	Busulfan (> 4 mg/d)	Cytarabine (low dose; 100–200 mg/m ²)	Bortezomib ¹
Dacarbazine	Carboplatin	Docetaxel	Busulfan
Mechlorethamine	Carmustine (≤ 250 mg/m ²)	Doxorubicin (liposomal)	Chlorambucil (oral)
Procarbazine (oral)	Cisplatin (< 50 mg/m ²)	Etoposide	Cladribine
Streptozocin	Cyclophosphamide (≤ 1,500 mg/m ²)	Fludarabine (oral)	Dasatinib ¹
	Cyclophosphamide (oral)	Fluorouracil	Decitabine ¹
	Cytarabine (> 1 g/m ²)	Gemcitabine	Denileukin diftitox
	Dactinomycin	Methotrexate (> 50 mg/m ² to < 250 mg/m ²)	Dexrazoxane
	Daunorubicin	Mitomycin	Erlotinib
	Doxorubicin	Mitoxantrone	Fludarabine
	Epirubicin	Paclitaxel	Gefitinib
	Etoposide (oral)	Paclitaxel (albumin-stabilized nanoparticle formulation) ¹	Gemtuzumab
	Idarubicin	Pemetrexed	Hydroxyurea (oral)
	Ifosfamide	Topotecan ¹	Interferon alfa
	Imatinib (oral) [†]		Lenalidomide ¹
	Irinotecan		Melphalan (oral; low-dose)
	Lomustine		Methotrexate (≤ 50 mg/m ²)
	Melphalan (> 50 mg/m ²)		Nelarabine ¹
	Methotrexate (250 to > 1,000 mg/m ²)		Pentostatin
	Oxaliplatin (> 75 mg/m ²)		Rituximab
	Temozolomide (oral)		Sorafenib ¹
	Vinorelbine (oral)		Sunitinib ¹
			Thalidomide ¹
			Thioguanine (oral)
			Trastuzumab ¹
			Valrubicin
			Vinblastine
			Vincristine
			Vinorelbine

*Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis

[†] Daily use of antiemetics is not recommended based on clinical experience

Adapted, with permission from the American Society of Clinical Oncology,¹⁹ with additional information.¹

Principles in the management of CINV

Updated antiemetic guidelines were published by the NCCN in 2007¹ and by ASCO in 2006.¹⁸ The updates were based in part on the 2004 Perugia International Antiemetic Consensus Conference of the Multinational Association of Supportive Care in Cancer.¹⁷ Representatives from nine cancer organizations (including ASCO and NCCN) participated, using a literature review and consensus statements to create organization-specific guidelines. The NCCN antiemetic guidelines

are based on clinical consensus, with recommendations reflecting uniform agreement based on lower-level evidence, such as clinical experience, unless specifically stated.^{1,17} The 2006 ASCO guidelines update guidelines previously published in 1999.^{18,23}

The NCCN Antiemesis Panel set forth several principles of effective antiemetic therapy¹:

- The goal of antiemetic therapy is to prevent nausea and vomiting throughout the entire period of emetic risk (the risk of emesis persists for up to 4 days for patients receiving highly or moderately emetogenic chemotherapy).

- Oral and intravenous (IV) formulations have equivalent efficacy.
- Use of the lowest maximally effective antiemetic dose is recommended prior to chemotherapy or radiation therapy.
- Toxicity of antiemetic agent(s) should be considered.
- Choice of antiemetic agent should be based on the emetogenic potential of the chemotherapy regimen, in addition to patient-specific risk factors.

Antiemetic agents

Agents used to treat CINV include 5-HT₃ receptor antagonists, NK₁ receptor antagonists, cortico-

TABLE 2
Antiemetic recommendations by emetic-risk categories

Emetic-risk category	ASCO guidelines	NCCN guidelines
High (> 90%) risk	Three-drug combination of a 5-HT ₃ receptor antagonist, dexamethasone, and aprepitant recommended before chemotherapy	Before chemotherapy, a 5-HT ₃ receptor antagonist (ondansetron, granisetron, dolasetron, or palonosetron*), dexamethasone (12 mg), and aprepitant (125 mg) recommended, with or without lorazepam
	For patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant recommended for prevention of delayed emesis	For prevention of delayed emesis, dexamethasone (8 mg) on days 2–4 plus aprepitant (80 mg) on days 2 and 3 recommended, with or without lorazepam on days 2–4
Moderate (30%–90%) risk	For patients receiving an anthracycline and cyclophosphamide, the three-drug combination a 5-HT ₃ receptor antagonist, dexamethasone, and aprepitant recommended before chemotherapy; single-agent aprepitant recommended on days 2 and 3 for prevention of delayed emesis	For patients receiving an anthracycline and cyclophosphamide and selected patients receiving other chemotherapies of moderate emetic risk (eg, carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate), a 5-HT ₃ receptor antagonist (ondansetron, granisetron, dolasetron, or palonosetron*), dexamethasone (12 mg), and aprepitant (125 mg) recommended, with or without lorazepam, before chemotherapy; for other patients, aprepitant is not recommended
	For patients receiving other chemotherapies of moderate emetic risk, the two-drug combination of a 5-HT ₃ receptor antagonist and dexamethasone recommended before chemotherapy; single-agent dexamethasone or a 5-HT ₃ receptor antagonist suggested on days 2 and 3 for prevention of delayed emesis	For prevention of delayed emesis, dexamethasone (8 mg) or a 5-HT ₃ receptor antagonist on days 2–4 or, if used on day 1, aprepitant (80 mg) on days 2 and 3, with or without dexamethasone (8 mg) on days 2–4, recommended, with or without lorazepam on days 2–4
Low (10%–30%) risk	Dexamethasone (8 mg) suggested; no routine preventive use of antiemetics for delayed emesis suggested	Metoclopramide, with or without diphenhydramine; dexamethasone (12 mg); or prochlorperazine recommended, with or without lorazepam
Minimal (< 10%) risk	No antiemetic administered routinely before or after chemotherapy	No routine prophylaxis; consider using antiemetics listed under primary prophylaxis as treatment

* Order of listed antiemetics does not reflect preference

ASCO = American Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; 5-HT₃ = 5-hydroxytryptamine

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steroids, benzamide analogs, phenothiazine derivatives, butyrophenones, and benzodiazepines.^{1,13,17,18} The updated guidelines from ASCO and NCCN state that patients receiving chemotherapy should preferentially be treated with antiemetic

regimens with the highest therapeutic index. These agents include 5-HT₃ receptor antagonists, corticosteroids, and NK₁ receptor antagonists, which are effective, have a good safety profile when used appropriately, and can be administered safely in combination.

5-HT₃ receptor antagonists

This class of agents includes dolasetron (Anzemet), granisetron (Kytril), ondansetron (Zofran), and palonosetron (Aloxi; available for IV administration only; Table 3).¹⁸ Introduced in the 1990s, the 5-HT₃ receptor antagonists are the most widely used drugs for CINV. They work to suppress nausea and vomiting via

antagonism of 5-HT₃ receptors located in vagal afferents, the solitary tract nucleus of the vagus nerve, and the CTZ of the area postrema.

These agents differ in their 5-HT₃ receptor affinity, pharmacokinetic profile, and chemical structure.¹³ The 5-HT₃ receptor antagonists are well absorbed from the GI tract. Ondansetron is metabolized in the liver by CYP1A2, CYP2D6, and CYP3A4. Clearance is reduced in the elderly and in those with hepatic dysfunction.¹³ Granisetron is metabolized by the liver, a process involving the CYP3A subfamily, as well as the CYP1A1 enzyme.²⁴ Dolasetron, a prodrug, is converted by plasma carbonyl reductase to its

TABLE 3
5-HT₃ receptor antagonists: single dose administered before chemotherapy

Agent	Oral	Intravenous (IV)
Dolasetron	100 mg	100 mg or 1.8 mg/kg
Granisetron	2 mg	1 mg or 0.01 mg/kg*
Ondansetron	24 mg	8 mg or 0.15 mg/kg
Palonosetron	–	0.25 mg

* The FDA-approved IV dose of granisetron is 0.01 mg/kg.

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active metabolite, hydrodolasetron, which undergoes biotransformation via CYP2D6 and CYP3A4.¹³ Administered intravenously, palonosetron is metabolized primarily by CYP2D6.¹³

Of note, the CYP2D6 isoenzyme is involved in the metabolism of all the 5-HT₃ receptor antagonists except granisetron.²⁵ This may affect the delivery of therapeutic doses of the antiemetic, as suggested in a study investigating antiemetic response in relationship to the 2D6 genotype in 270 cancer patients receiving moderately or highly emetogenic chemotherapy.²⁶ In this study, patients received either 5 mg once daily of tropisetron (a 5-HT₃ receptor antagonist not currently available in the United States)²⁷ or 8 mg twice daily of ondansetron (route not specified) before chemotherapy.²⁶

Genotyping for CYP2D6 found that extensive metabolizers had the highest intensity of vomiting or nausea and poor metabolizers had the least intensity of vomiting or nausea. Ultrafast metabolizers of CYP2D6 demonstrated the highest incidence and severity of emesis and nausea after chemotherapy when ondansetron or tropisetron was given as antiemetic treatment. Granisetron is not metabolized by the CYP2D6 pathway. Thus, drug metabolism may play a role in dosing antiemetic medication for the cancer patient.²⁶

To date, however, the first-generation 5-HT₃ receptor antagonists available in the United States (dolasetron, granisetron, ondansetron) appear to be equivalent in efficacy and toxicity when used in the recommended doses.²⁸

NK₁ receptor antagonists

Located in the GI tract and the brain-stem emetic center, NK₁ receptors are the binding sites of the tachykinin substance P, which has been demonstrated to produce emesis when administered to animals.

Aprepitant (Emend) is the first commercially available NK₁ receptor antagonist. It is metabolized primarily via CYP3A4, with a half-life of 9–13 hours. Dose adjustment of other substrates of CYP3A4, including dexamethasone and warfarin, may be needed when administering aprepitant. Concomitant administration with cisapride (Propulsid) may cause life-threatening prolongation of the QT interval.¹³

Corticosteroids

It is thought that corticosteroids such as dexamethasone and methylprednisolone work to suppress CINV by limiting peritumoral inflammation and prostaglandin production.¹³ Corticosteroids are among the most frequently used antiemetics and are often given in combination with 5-HT₃ receptor antagonists.^{1,17,18}

Benzamide analogs

Dopamine stimulates the medullary CTZ, producing nausea and vomiting. Metoclopramide appears to have an antiemetic effect due to its antagonism of central and peripheral dopamine receptors. At higher doses, metoclopramide acts as a 5-HT₃ receptor antagonist; however, its antiemetic efficacy is less than that observed with 5-HT₃ receptor antagonists. Side effects of benzamide analogs include sedation, acute dystonic reactions, and akathisia.²³

Butyrophenones

Butyrophenones such as haloperidol also have antiemetic activity mediated by antidopaminergic action; efficacy is less than that observed with metoclopramide.²⁹ Side effects of butyrophenones include sedation, dystonic reactions, akathisia, and postural hypotension.^{23,29}

Benzodiazepines

With limited antiemetic activity, benzodiazepines such as lorazepam are typically given as adjunctive

therapy for their antianxiety effects.^{23,30} Although not approved by the US Food and Drug Administration (FDA) for management of nausea and vomiting, olanzapine (Zyprexa), an antipsychotic agent of the thienobenzodiazepine class,³¹ has recently been shown to have antiemetic activity, most likely due to its ability to block dopaminergic, serotonergic, adrenergic, histaminic, and muscarinic neurotransmitter receptors.^{32,33}

Efficacy and safety of antiemetic agents in clinical trials

Antiemetic agents classified with the highest therapeutic index include 5-HT₃ receptor antagonists, corticosteroids, and NK₁ receptor antagonists. Dexamethasone is the preferred corticosteroid, and aprepitant is the only currently available NK₁ receptor antagonist.^{1,18} Clinical trials examining the efficacy and safety of 5-HT₃ receptor antagonists show consistent safety and efficacy profiles.^{6,21,34–41}

Granisetron and ondansetron

The comparative efficacy of granisetron and ondansetron has been extensively studied.^{21,36,40,42} In one multicenter, randomized, double-blind study, 1,054 patients were randomized to receive either 2 mg of oral granisetron or 32 mg of IV ondansetron prior to administration of platinum-based chemotherapy.³⁶ Total control of acute emesis was equivalent between the granisetron and ondansetron groups (54.7% and 58.3%, respectively). Common side effects included constipation, headache, and diarrhea.³⁶

In a double-blind, randomized, stratified, parallel-group study, the efficacy and safety of a single IV infusion of granisetron (0.01 mg/kg or 0.04 mg/kg) and 3 doses of ondansetron (0.15 mg/kg) were compared in 987 chemotherapy-naïve

patients who received cisplatin in doses ≥ 60 mg/m². Results of the study indicated comparable efficacy between 0.01 and 0.04 mg/kg of granisetron and demonstrated that a single dose of granisetron (0.01 mg/kg) was as effective as 3 doses of ondansetron (0.15 mg/kg) in the prevention of cisplatin-induced nausea and vomiting.⁴²

In a double-blind, parallel-group study involving 1,085 patients, the antiemetic efficacy of oral granisetron was compared with that of IV ondansetron in patients receiving moderately emetogenic chemotherapy.⁴⁰ Single-dose oral granisetron (2 mg) resulted in equivalent levels of total control of emesis compared with 32 mg of IV ondansetron. During the first 24 hours after chemotherapy, total control was achieved by 59% of granisetron-treated patients and by 58% of ondansetron-treated patients. At 48 hours, 46.7% of granisetron-treated patients and 43.8% of ondansetron-treated patients achieved total control. Both agents were well tolerated, with headache, asthenia, and constipation being the most common side effects.⁴⁰

Oral granisetron (2 mg once daily) and ondansetron (8 mg three times daily) were also studied in patients receiving hyperfractionated TBI.²¹ In this double-blind study, significantly more patients receiving oral granisetron (33.3%) or ondansetron (26.7%) had no emetic episodes over 4 days compared with the historic control group (0%; $P < 0.01$). The historic control group comprised 90 patients who received the same TBI but no 5-HT₃ receptor antagonist.²¹

Dolasetron and ondansetron

A double-blind, randomized comparison of the antiemetic efficacy of IV dolasetron and IV ondansetron in the prevention of acute cisplatin-induced emesis

demonstrated that a single dose of dolasetron (1.8 mg/kg or 2.4 mg/kg) had comparable safety and efficacy to a single 32-mg dose of ondansetron.⁴³ These results support the use of 1.8 mg/kg as the appropriate dose of dolasetron for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy.⁴³ The safety and antiemetic efficacy of oral dolasetron have also been demonstrated in patients receiving moderately emetogenic chemotherapy.⁴⁴

Palonosetron

Palonosetron, with its longer half-life, higher 5-HT₃ receptor binding affinity, and IV route of administration, is the newest 5-HT₃ receptor antagonist.⁴⁵ In non-inferiority registration trials, the primary endpoint of noninferiority compared with first-generation 5-HT₃ receptor antagonists was met for acute emesis following chemotherapy of moderate^{18,46,47} and high emetogenic risk.⁴⁸ The trials resulted in an FDA-approved indication for palonosetron for the treatment of delayed emesis for patients receiving moderately emetogenic chemotherapy.⁴⁵

A retrospective chart review was performed to evaluate the relative efficacy of ondansetron, granisetron, dolasetron, and palonosetron given with dexamethasone in controlling acute nausea and vomiting caused by platinum-based chemotherapy.³⁷ A total of 181 patients were evaluated; dolasetron, granisetron, ondansetron, and palonosetron achieved complete control of nausea and vomiting in 89.8%, 95.5%, 92.3%, and 88.1% of cycles, respectively. The authors concluded that the four agents had comparable efficacy rates.³⁷

Aprepitant

Aprepitant significantly improves the control of acute CINV when add-

ed to a 5-HT₃ receptor antagonist and dexamethasone for patients receiving highly emetogenic chemotherapy.^{49,50} Aprepitant alone does not appear to control acute emesis as well as the 5-HT₃ receptor antagonists, nor does it in combination with dexamethasone alone, compared with 5-HT₃ receptor antagonists and dexamethasone.^{49,50} Aprepitant does improve the control of delayed CINV for patients receiving highly emetogenic chemotherapy when compared with placebo and in combination with dexamethasone when compared with dexamethasone alone.^{49,51} The efficacy of aprepitant appears to be maintained over repeated cycles of cisplatin chemotherapy. All of the initial published studies on aprepitant have been conducted with cisplatin chemotherapy.⁵⁰

Data from a 2005 study of patients receiving moderately emetogenic chemotherapy suggested that the addition of aprepitant to ondansetron and dexamethasone improved the complete response in the 24 hours post chemotherapy; however, there was no difference in complete response from day 2 to day 5 post chemotherapy when aprepitant alone was compared with ondansetron alone.⁵² Aprepitant did not improve nausea in the study.

Pharmacologic management by emetogenic potential

Current guidelines recommend that prechemotherapy management of CINV be based on the emetogenic potential of the chemotherapy agent(s) selected. For patients receiving regimens with high emetogenic potential, the combination of a 5-HT₃ receptor antagonist, aprepitant, and dexamethasone is recommended prior to chemotherapy; lorazepam may also be used. Aprepitant and dexamethasone are recommended post chemotherapy for the prevention of delayed emesis.

For those patients receiving moderately emetogenic chemotherapy,

the combination of a 5-HT₃ receptor antagonist and dexamethasone should be used prior to chemotherapy, with or without lorazepam. Patients receiving the combination of an anthracycline and cyclophosphamide, and select patients receiving certain other agents of moderate emetic risk, such as cisplatin (< 50 mg/m²) or doxorubicin, should also receive aprepitant. Postchemotherapy, a 5-HT₃ receptor antagonist and/or dexamethasone is recommended for the prevention of delayed emesis.

For regimens with low emetogenic potential, dexamethasone is recommended with or without lorazepam. For regimens with minimal emetogenic risk, no prophylaxis is suggested.^{1,18}

Pre- and postchemotherapy recommendations by emetogenic potential are summarized in Table 2.^{1,18}

Drug regimens for special categories of nausea and vomiting

Anticipatory nausea and vomiting relates to a previous experience of chemotherapy-associated nausea and vomiting, patient anxiety, and the inherent emetogenicity of the chemotherapy regimen.⁵³ The most effective prevention is to use an antiemetic regimen prior to chemotherapy.^{1,18,23} Both the ASCO and NCCN guidelines suggest the use of nonpharmacologic methods (eg, relaxation, systematic desensitization, hypnosis, guided imagery, music therapy, acupuncture, or acupressure)⁵⁴⁻⁵⁶ for controlling anticipatory nausea and vomiting.^{1,18,23}

For breakthrough or refractory nausea and emesis, the ASCO guidelines recommend the following steps:

- evaluate the emetic risk and evaluate antiemetic, chemotherapy, disease, and medication factors;
- ensure that the recommended antiemetic regimen is being used;

- consider adding lorazepam or alprazolam; and

- consider substituting high-dose IV metoclopramide for the 5-HT₃ receptor antagonist or adding a dopamine antagonist.^{18,23}

The NCCN guidelines suggest adding an agent from a different class, such as metoclopramide or a dopamine antagonist; dosing around the clock rather than as needed; and effectively treating dyspepsia, which can be mistaken for chemotherapy-induced nausea.¹ Additional antiemetics, including butyrophenones (eg, haloperidol), cannabinoids, corticosteroids, and agents such as lorazepam, may be required.¹

For prevention of radiation-induced nausea and vomiting in patients receiving TBI, a 5-HT₃ receptor antagonist (the NCCN guidelines specify granisetron or ondansetron), with or without dexamethasone, is recommended.^{1,18,23}

Conclusion

Nausea and vomiting associated with cancer chemotherapy can result in significant morbidity, adversely affect a patient's quality of life, and lead to poor compliance with the treatment regimen.^{7,8,11} CINV can also lead to metabolic disturbances, decline of performance and mental status, nutrient depletion, esophageal tears, and withdrawal from potentially beneficial/curative cancer treatment regimens.¹¹ Treatment of CINV remains a challenging aspect of managing chemotherapy.

Updated guidelines from ASCO and NCCN recommend that all patients receiving chemotherapy should be treated preferentially with antiemetic regimens containing agents with the highest therapeutic index from three classes: 5-HT₃ receptor antagonists, corticosteroids, and NK₁ receptor antagonists. These agents are effective, have few significant adverse effects,

and can be administered safely in combination.¹⁸ For the treatment of nausea and vomiting associated with initial and repeated courses of emetogenic cancer therapy, agents from these three classes should be used in accordance with the recommended doses (Table 3) both before and after chemotherapy. Oral agents are equally effective and safe as equivalent doses of IV agents.

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