

REVIEW ARTICLE

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Antiemetic Prophylaxis for Chemotherapy-Induced Nausea and Vomiting

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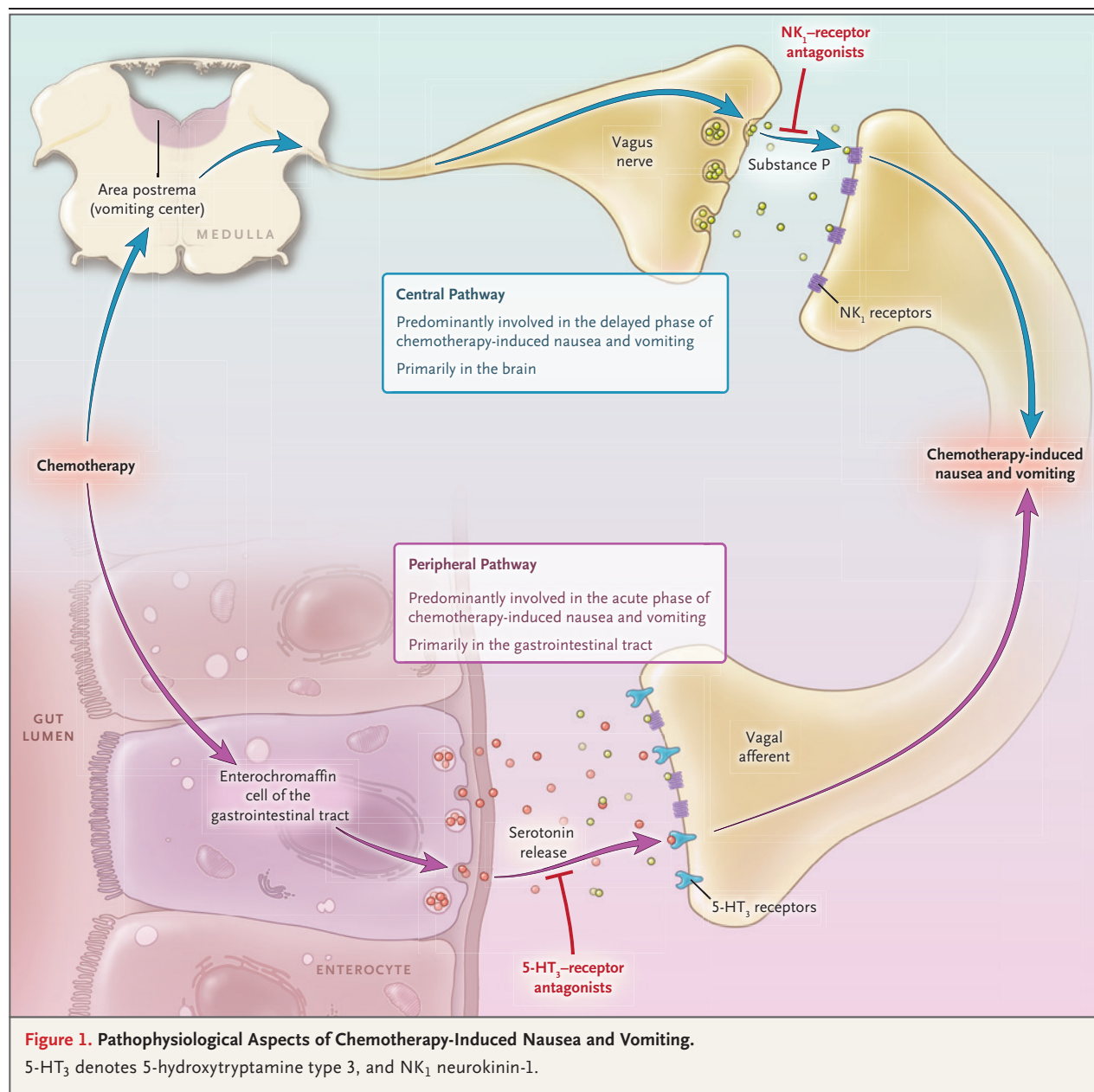
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CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CHEMOTHERAPY-induced emesis) is a common treatment-related side effect that has a detrimental effect on the quality of life of patients with cancer and may lead to dose reductions in or discontinuation of chemotherapy. The development of new antiemetic agents has dramatically changed the landscape of chemotherapy-induced emesis. In the 1970s, prolonged hospital stays for nausea after chemotherapy were common practice.¹ In 1979, a randomized trial involving patients with cancer showed that the overall incidence of chemotherapy-induced emesis was approximately 83%.² Two decades later, with newly available antiemetics, an observational study reported incidences of acute nausea and vomiting of 35% and 13%, respectively, among patients receiving highly and moderately emetogenic chemotherapy.³ Currently, adherence to antiemetic guidelines provides effective relief from chemotherapy-induced emesis,⁴⁻⁶ and patients rapidly return to normal daily activities after treatment.^{7,8} As a result, the quality of life of patients with cancer has improved, and better control of chemotherapy-induced emesis may help avoid reductions in and discontinuation of chemotherapy. These major advances have been recognized in a worldwide online survey conducted by the American Society of Clinical Oncology (ASCO) in 2014, in which antiemetics were voted by physicians, patients, and the public as one of the “Top 5 Advances in 50 Years of Modern Oncology.”⁹ In this review, we provide background information and the history of the major landmarks in prophylaxis for chemotherapy-induced emesis in adult patients, describe current clinical practices and challenges, and discuss potential approaches to addressing the remaining gaps in the understanding and prevention of chemotherapy-induced emesis.

THE BASIS OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Chemotherapy-induced emesis is classified into five categories, depending on when it starts in relation to the course of chemotherapy and on what the patients' previous responses to prophylaxis have been (Table 1).¹⁰⁻¹⁴ Advances during the past three decades have helped to elucidate some of the mechanisms by which chemotherapeutic agents induce nausea and vomiting. Several neurotransmitters, including dopamine, serotonin, and substance P, have been identified as important mediators of chemotherapy-induced emesis.¹⁵ The current understanding is that receptors for these neurotransmitters, and possibly other, yet-unrecognized receptors, are involved in the pathophysiological mechanisms of chemotherapy-induced emesis¹ (Fig. 1).

Chemotherapeutic drugs can cause nausea and vomiting by activating neurotransmitter receptors that are present in the area postrema of the brain. Receptors are also found in the terminal ends of the vagal afferents near the enterochro-



maffin cells in the intestine¹⁵; afferent fibers transmit the stimuli to the brainstem, which processes the emetic reflex and sends efferent signals to organs and tissues to induce vomiting.¹⁵ Current knowledge suggests that the emetic response to chemotherapy can occur through a peripheral pathway and a central pathway.^{15,16} The peripheral pathway, which is activated within 24 hours after initiation of chemotherapy, is associated primarily with acute chemotherapy-induced emesis (occurring 0 to 24 hours after chemotherapy) (Table 1).¹⁰⁻¹⁴ Antineoplastic agents

induce enterochromaffin cells to release serotonin, which then activates the 5-hydroxytryptamine type 3 (5-HT₃) receptors in the vagal afferents that transmit the stimulus to the brain.¹⁵ The central pathway, located primarily in the brain, is activated after the first 24 hours after chemotherapy and is associated mainly with delayed chemotherapy-induced emesis (occurring 25 to 120 hours after chemotherapy) (Table 1),¹⁰⁻¹⁴ although it can also induce acute chemotherapy-induced emesis.¹⁵ Substance P is the principal neurotransmitter that activates neurokinin-1

Table 1. Classes of Chemotherapy-Induced Nausea and Vomiting.

Classification	Definition
Acute	Occurring within the first 24 hours after initiation of chemotherapy ¹⁰ ; generally peaks after 5 to 6 hours ¹¹
Delayed	Occurring from 24 hours to several days (days 2 to 5) after chemotherapy ¹²
Breakthrough	Occurring despite appropriate prophylactic treatment ¹³
Anticipatory	Occurring before a treatment as a conditioned response to the occurrence of chemotherapy-induced nausea and vomiting in previous cycles ¹⁴
Refractory	Recurring in subsequent cycles of therapy, excluding anticipatory chemotherapy-induced nausea and vomiting ¹³

Table 2. Levels of Emetogenic Potential of Chemotherapeutic Agents.

Level	Emetogenic Potential (% of Patients with Emesis)
1	Minimal (0 to <10%)
2	Low (10 to 30%)
3	Moderate (>30 to 90%)
4	High (>90%)

(NK₁) receptors in the central nervous system. A 5-HT₃-NK₁ receptor crosstalk has been suggested, by which the activation of one receptor by its ligand can potentiate the effects of the signaling pathway of the other receptor, but the exact mechanism is unknown.^{1,16} Most drugs used as prophylaxis for chemotherapy-induced emesis belong to the classes of dopamine, 5-HT₃, and NK₁ receptor antagonists. Several agents, such as cisplatin, carboplatin, cyclophosphamide, and doxorubicin, can induce both acute and delayed chemotherapy-induced emesis.¹¹ For example, cisplatin has biphasic activity, causing an initial emetic peak within the first 24 hours followed by a delayed emetic period that peaks 48 to 72 hours after administration.¹⁷

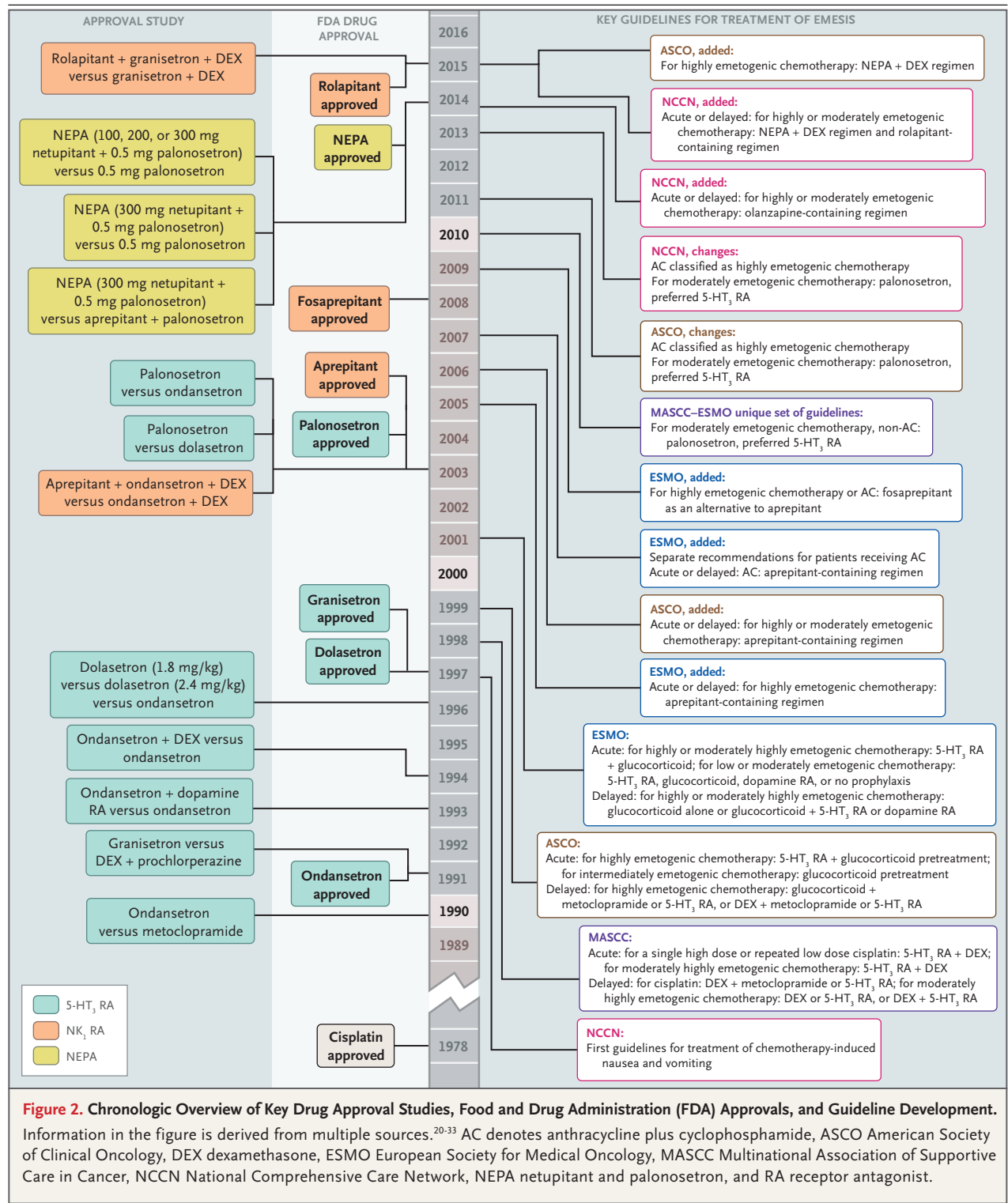
Chemotherapy-induced nausea and vomiting is also associated with operant conditioning, such that unrelated stimuli may induce the symptoms. Environmental cues (such as certain odors, the elevator to the clinic, or meeting the chemotherapy nurse in a grocery store) can elicit the nausea even years after treatment. The mechanism of this conditioning has not been well studied.

The emetogenic potential of each chemotherapeutic agent is the main determinant of the likelihood of chemotherapy-induced emesis.

In 2004, a four-level classification of antineoplastic agents was established (Table 2), which included four categories that were based on the percentage of patients with acute emesis caused by single agents in the absence of antiemetic prophylaxis.¹⁸ Separate classifications have been established for intravenous and oral antineoplastic agents (oral agents are usually given daily and over longer periods). This classification has some limitations: categorical data on the intrinsic emetogenic risk are available for few agents, the classification underestimates the risk of delayed emesis and of acute and delayed nausea, and the classification does not address the emetogenic potential of combination regimens, which is usually determined by the most emetic agent in the combination (e.g., recently, the anthracycline and cyclophosphamide regimen has been classified as highly emetogenic^{6,11} or as a separate category¹⁹ in different international guidelines). Despite these limitations, this classification system represented an important advance, enabling antiemetic regimens to be tailored and refined.

FIFTY YEARS OF RESEARCH ON CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

A chronologic overview of key antiemetic registration studies, Food and Drug Administration (FDA) approvals, centralized European Medicines Agency (EMA) approvals, and guideline evolution is shown in Figure 2.²⁰⁻³³ Cancer treatment with chemotherapy began shortly after the Second World War, when highly emetogenic nitrogen mustard¹⁰ was used to treat patients with lymphoma.³⁴ The marked efficacy of this agent set the stage for the development of alkylating agents, such as chlorambucil and cyclophospha-



mide, and the discovery of glucocorticoids, methotrexate, and thiopurines, which were directed mainly against hematologic neoplasms.

In 1957, the fluoropyrimidine fluorouracil (also called 5-fluorouracil), the first compound that showed remarkable activity against solid tumors,

was identified.³⁴ During the 1960s, the concept of cure was introduced, which led to more aggressive and toxic chemotherapy dosing and schedule approaches, as well as to the use of drug combinations. As a result, effective antiemetics became an area of high, unmet need.

DOPAMINE-RECEPTOR ANTAGONISTS

Until the late 1970s, dopamine-receptor antagonists, such as metoclopramide, prochlorperazine, and haloperidol, formed the basis of antiemetic therapy.³⁵ FDA approval in 1978 of the highly emetogenic compound cisplatin¹⁸ dramatically increased the incidence of chemotherapy-induced emesis, especially acute emesis¹⁰, and the effectiveness of low-dose metoclopramide among patients treated with cisplatin was not better than that of placebo.³⁶ The increasing use of cisplatin also led to research that concentrated on the prevention of emesis associated with high-dose cisplatin-based therapy; most clinical trials focused on efficacy at reducing the number of emetic episodes (vomiting or retching) during the acute phase (0 to 24 hours after chemotherapy) as the primary end point. In the 1980s, metoclopramide at high doses proved to be effective at reducing the frequency of vomiting among patients treated with cisplatin.^{37,38} These results led to the implementation of high-dose metoclopramide combined with glucocorticoids, such as dexamethasone (recognized as an active antiemetic agent in 1981³⁹), as the clinical standard in the prevention of chemotherapy-induced emesis.^{1,35} Further appreciable benefits in the management of chemotherapy-induced emesis were not seen until serotonin (5-HT₃) receptor antagonists were introduced in the early 1990s — a landmark in the treatment of acute chemotherapy-induced emesis.

FIRST-GENERATION 5-HT₃-RECEPTOR ANTAGONISTS

In 1991, the first 5-HT₃-receptor antagonist, ondansetron, was approved by the FDA for the treatment of chemotherapy-induced emesis and was immediately incorporated into routine oncology practice. Ondansetron–dexamethasone was found to be superior to high-dose metoclopramide–dexamethasone for protection from chemotherapy-induced emesis in patients receiving highly emetogenic chemotherapy⁴⁰ and had a much better side-effect profile.⁴¹

In 1997, two additional 5-HT₃-receptor antagonists, granisetron and dolasetron, received FDA approval as prophylaxis for chemotherapy-induced emesis. A study comparing granisetron with ondansetron as single agents in patients receiving highly emetogenic chemotherapy showed that the two agents had similar efficacy for the prevention of chemotherapy-induced emesis.⁴² In a second study, ondansetron and granisetron, both in combination with dexamethasone, had similar efficacy for the control of acute and delayed chemotherapy-induced emesis in patients who were treated with highly emetogenic chemotherapy.⁴³ With regard to dolasetron, a single intravenous dose (1.8 or 2.4 mg per kilogram of body weight) had efficacy similar to that of a single intravenous dose (32 mg) of ondansetron in patients who were receiving highly emetogenic chemotherapy.²⁵ Findings from a meta-analysis indicated that ondansetron, granisetron, and dolasetron had similar clinical efficacy for the prevention of acute chemotherapy-induced emesis.⁴⁴ Of note, intravenous dolasetron and the 32-mg intravenous dose of ondansetron are no longer indicated for the prevention of chemotherapy-induced emesis, because of an associated dose-dependent increase in the corrected QT (QTc) interval. Other 5-HT₃-receptor antagonists, such as tropisetron, are also approved for use in many countries (but have not been approved by the FDA).⁴⁴

In 1997, the first National Comprehensive Cancer Network (NCCN) antiemetic guidelines were published.⁴⁵ Guidelines from the Multinational Association of Supportive Care in Cancer (MASCC) followed in 1998.⁴⁶ These guidelines recommended the use of 5-HT₃-receptor antagonists for the prevention of acute and delayed emesis associated with both highly and moderately emetogenic chemotherapy. No preference was given to any of the available 5-HT₃-receptor antagonists. One year later, ASCO published its first guidelines for antiemetic therapy.⁴⁷ In 2001, the European Society for Medical Oncology (ESMO) published its first antiemetic guidelines.⁴⁸

THE SECOND-GENERATION 5-HT₃-RECEPTOR ANTAGONIST PALONSETRON

In 2003, the treatment landscape was radically altered by the FDA approval of two new com-

pounds: palonosetron and aprepitant.⁴⁹ Palonosetron is a 5-HT₃-receptor antagonist that has a prolonged half-life, receptor binding affinity higher than that of other antiemetic agents, and positive cooperativity when binding to the 5-HT₃ receptor; this binding triggers 5-HT₃-receptor internalization, leading to the inhibition of the 5-HT₃-NK₁ receptor and of 5-HT₃-NK₁ receptor crosstalk.^{1,50} Because of these characteristics, palonosetron has increased efficacy in preventing both acute and delayed chemotherapy-induced emesis and is referred to as a second-generation 5HT₃-receptor antagonist. Two large phase 3 trials involving patients treated with moderately emetogenic chemotherapy showed higher rates of prevention of chemotherapy-induced emesis with palonosetron than with ondansetron or dolasetron.^{27,28} Palonosetron was also found to be superior to granisetron (when each agent was combined with dexamethasone) for the prevention of chemotherapy-induced emesis in patients treated with highly or moderately emetogenic chemotherapy.⁵¹ A study involving patients receiving doxorubicin plus cyclophosphamide showed that treatment with palonosetron–dexamethasone on day 1 allowed the discontinuation of dexamethasone treatment on the days after chemotherapy, without significantly affecting antiemetic control or patient function during a 5-day postchemotherapy period.⁵²

NK₁-RECEPTOR ANTAGONISTS

Antagonists targeting NK₁ receptors for substance P were recognized as promising therapeutic agents for chemotherapy-induced emesis in the 1990s, but aprepitant, the first NK₁-receptor antagonist to be approved, did not reach the market until 2003. When combined with dexamethasone and a 5-HT₃-receptor antagonist, aprepitant was found to be effective at preventing chemotherapy-induced emesis in patients receiving highly emetogenic chemotherapy.⁴⁹ Two trials that involved patients receiving highly emetogenic drugs showed significantly higher efficacy in the control of chemotherapy-induced emesis with the addition of oral aprepitant to ondansetron–dexamethasone than with ondansetron–dexamethasone alone.^{20,26} In 2008, fosaprepitant, a prodrug and intravenous form of aprepitant, was approved by the FDA on the ba-

sis of a phase 3 noninferiority trial.⁵³ Patients receiving highly emetogenic drugs were administered ondansetron–dexamethasone plus either aprepitant at the approved 3-day oral schedule or a single intravenous dose of fosaprepitant. The trial showed similar efficacy with aprepitant and fosaprepitant.

Between 2013 and 2015, phase 2 and phase 3 trials of two new NK₁-receptor antagonists, netupitant (administered as an oral fixed-dose combination of netupitant [300 mg] and palonosetron [0.50 mg] [NEPA]) and rolapitant, were completed and led to a substantial improvement in prophylaxis for chemotherapy-induced emesis, especially during the delayed phase (25 to 120 hours after chemotherapy).⁵⁴ Netupitant has a half-life of 90 hours and high binding affinity, and like aprepitant, netupitant can also inhibit CYP3A4. A reduced dose of dexamethasone (CYP3A4 substrate) should be administered with aprepitant and NEPA. NEPA–dexamethasone was found to be superior to palonosetron–dexamethasone for the prevention of chemotherapy-induced emesis in patients receiving highly emetogenic drugs²⁹ or the combination of doxorubicin plus cyclophosphamide,³² and the clinical efficacy was maintained over multiple chemotherapy cycles.^{32,33,55} The FDA and the EMA approved NEPA for the prevention of chemotherapy-induced emesis in October 2014 and May 2015, respectively.

In September 2015, the FDA approved rolapitant for the prevention of delayed chemotherapy-induced emesis.⁵⁶ In three phase 3 trials, the rates of chemotherapy-induced emesis after prophylaxis with rolapitant combined with granisetron–dexamethasone were significantly lower than those associated with granisetron–dexamethasone alone in patients receiving moderately or highly emetogenic chemotherapy.^{30,31} Rolapitant has a half-life of approximately 180 hours and is metabolized primarily by CYP3A4. It is a moderate inhibitor of CYP2D6 and an inhibitor of breast-cancer resistance protein and P-glycoprotein, and its concomitant use with substrates of these enzymes that have a narrow therapeutic index should be avoided.

OLANZAPINE

In 2014, olanzapine, an atypical antipsychotic agent that is indicated for the treatment of schizophrenia and bipolar disorder, was incor-

porated into the NCCN antiemetic guidelines. Phase 2 studies showed that olanzapine, in combination with a 5-HT₃-receptor antagonist and dexamethasone, is effective at controlling both acute and delayed chemotherapy-induced emesis in patients who are being treated with highly or moderately emetogenic drugs.⁵⁷ In a phase 3 trial, olanzapine was compared with aprepitant (both in combination with palonosetron–dexamethasone) in patients receiving cisplatin or doxorubicin plus cyclophosphamide.⁵⁸ The efficacy of olanzapine was similar to that of aprepitant for the control of chemotherapy-induced emesis in the acute phase (0 to 24 hours), the delayed phase (25 to 120 hours), and overall (0 to 120 hours). Notably, olanzapine was more effective for nausea control during the delayed phase. Olanzapine was also shown to be effective in the control of breakthrough chemotherapy-induced emesis in patients receiving moderately or highly emetogenic drugs.⁵⁹

ADDITIONAL AGENTS

Agents with other mechanisms of action, including gabapentin⁶⁰ and the synthetic cannabinoids dronabinol⁶¹ and nabilone,⁶² have also been evaluated as prophylaxis for chemotherapy-induced emesis. Initial studies suggested a role for gabapentin in the control of chemotherapy-induced emesis, especially during the delayed phase.⁶⁰ However, in a recent phase 3 trial, gabapentin provided no additional benefit over placebo in patients receiving highly emetogenic agents (ClinicalTrials.gov number, NCT00880191). Dronabinol was found to have efficacy similar to that of ondansetron for the prevention of chemotherapy-induced emesis in 61 patients receiving moderately or highly emetogenic agents,⁶¹ and nabilone was superior to prochlorperazine in patients receiving any type of chemotherapy.⁶² These agents may have a role in the treatment of selected patients who do not have an adequate response to 5-HT₃-receptor antagonists and NK₁-receptor antagonists or in the prevention of anticipatory chemotherapy-induced emesis.⁶²

As a result of the increases in the number of studies and consequent knowledge, international guidelines have been updated or revised almost every year since 2004 (Fig. 2).^{6,11,19–33} Other advances in the management of chemotherapy-induced emesis include the identification of patient-related characteristics that may increase

the risk of chemotherapy-induced emesis, including age (<55 years); female sex; a history of nausea or vomiting, anxiety, fatigue, or motion sickness; impaired quality of life; and no history of alcohol use.^{54,63–65} Independent factors that can lead to prolonged nausea or vomiting after treatment have also been described, including metabolic abnormalities, gastrointestinal irritation, increased intracranial pressure, and treatment with radiotherapy.⁶⁶ Nevertheless, there is no consensus in this area, and these risk factors are not used to suggest the appropriate antiemetic combination in the guidelines.

WHERE ARE WE? CLINICAL REALITY TODAY

ANTIEMETIC GUIDELINES

The guidelines on antiemetic therapy that have been developed by the various cancer societies^{6,11,19} show broad agreement on key principles, including that prophylaxis should be the primary goal of antiemetic therapy and should be implemented for groups of patients who have a 10% or greater risk of chemotherapy-induced emesis; that the duration of prophylaxis should cover the entire risk period; that oral and intravenous administration routes have the same efficacy; and that the most effective antiemetic treatment is determined on the basis of chemotherapy emetogenicity, a patient's history of chemotherapy-induced emesis, and additional patient-related factors.⁶⁴

Table 3 summarizes the current international recommendations regarding antiemetic therapy.^{6,11,19} The NCCN guidelines on antiemetic therapy have been developed on the basis of evidence and the consensus of clinicians regarding their views of an acceptable treatment approach. The MASCC–ESMO and ASCO guidelines for antiemetic therapy are evidence-based. Overall, there is consistency among international guidelines, with only minor differences (Table 3).^{6,11,19} All guidelines recommend the use of 5-HT₃-receptor and NK₁-receptor antagonists with dexamethasone for patients receiving highly emetogenic agents and anthracycline-based chemotherapy regimens (palonosetron is preferred in the MASCC–ESMO guidelines for patients receiving treatment with anthracycline and cyclophosphamide if the NK₁-receptor antagonist is unavailable); for patients receiving moderately

Table 3. Antiemetic Treatment Recommendations for Emetogenic Intravenous Chemotherapy.*

Emetogenic Risk Level	Antiemetic Therapy	
	Acute Phase	Delayed Phase
MASCC–ESMO guidelines¹⁹		
High	5-HT ₃ –receptor antagonist, dexamethasone, and either aprepitant or fosaprepitant	Dexamethasone and aprepitant†
AC	5-HT ₃ –receptor antagonist, dexamethasone, and either aprepitant or fosaprepitant	Aprepitant‡
Moderate (associated with agents other than AC)	Palonosetron and dexamethasone	Dexamethasone
Low	Dexamethasone, 5-HT ₃ –receptor antagonist, or dopamine-receptor antagonist	—
ASCO guidelines⁶		
High (including AC)	5-HT ₃ –receptor antagonist, dexamethasone, and aprepitant	Dexamethasone and aprepitant
	NEPA and dexamethasone	Dexamethasone
Moderate	Either palonosetron and dexamethasone or 5-HT ₃ –receptor antagonist, dexamethasone, and aprepitant	5-HT ₃ –receptor antagonist, dexamethasone, or aprepitant
Low	Dexamethasone	—
NCCN guidelines¹¹		
High (including AC)	5-HT ₃ –receptor antagonist and dexamethasone, plus one of the following agents: aprepitant, fosaprepitant, or rolapitant§	Aprepitant plus dexamethasone¶
	NEPA and dexamethasone§	Dexamethasone
	Olanzapine, palonosetron, and dexamethasone§	Olanzapine
Moderate	5-HT ₃ –receptor antagonist and dexamethasone, with or without aprepitant, fosaprepitant, or rolapitant§	5-HT ₃ –receptor antagonist, dexamethasone, or aprepitant with or without dexamethasone**
	NEPA and dexamethasone§	Dexamethasone may be used
	Olanzapine, palonosetron, and dexamethasone§	Olanzapine
Low	Dexamethasone§, metoclopramide§, prochlorperazine§, or 5-HT ₃ –receptor antagonist§ (ondansetron, granisetron, or dolasetron)	—

* AC denotes anthracycline plus cyclophosphamide, ASCO American Society of Clinical Oncology, ESMO European Society for Medical Oncology, 5-HT₃ 5-hydroxytryptamine type 3, MASCC Multinational Association of Supportive Care in Cancer, NCCN National Comprehensive Cancer Network, and NEPA netupitant plus palonosetron.

† Use dexamethasone alone, if fosaprepitant was used on day 1.

‡ Do not use any drug if fosaprepitant was used on day 1.

§ This regimen can be administered with or without lorazepam and with or without an H₂ blocker or proton pump inhibitor.

¶ If aprepitant was used on day 1, continue treatment with aprepitant on days 2 and 3; if fosaprepitant was used on day 1, no additional aprepitant is needed.

|| No additional therapy is required if a palonosetron or granisetron patch is given on day 1.

** Use this regimen if aprepitant was given on day 1.

emetogenic agents, 5-HT₃–receptor antagonists (palonosetron is preferred in the MASCC–ESMO, ASCO, and NCCN guidelines) and dexamethasone are recommended. For chemotherapy with a low emetic risk, guidelines suggest a single antiemetic drug, such as dexamethasone or a 5-HT₃–receptor antagonist.

REFRACTORY AND ANTICIPATORY CHEMOTHERAPY-INDUCED EMESIS

In patients with refractory chemotherapy-induced emesis, patient adherence to the recommended antiemetic regimen should be reevaluated, and a change in regimens should be considered. Frequently, changes involve the addition of an agent

from a different drug class, adjustment of the dose of the 5-HT₃-receptor antagonist, or a switch to a different agent within the same class. The olanzapine-containing regimen is recommended for patients receiving highly emetogenic agents who have refractory chemotherapy-induced emesis.⁶ For patients in whom high-level anxiety is the main trigger for chemotherapy-induced emesis, the addition of lorazepam or alprazolam is recommended.^{6,11,59}

Because many patients have had previous negative experiences involving chemotherapy-induced emesis, the recommendations for the treatment of anticipatory chemotherapy-induced emesis are based on providing patients with adequate information, as well as on the use of the most appropriate antiemetic regimen. Administration of anxiolytic agents, beginning on the night before chemotherapy, should be considered for patients who have excessive anxiety.^{6,11,19}

SAFETY PROFILE OF ANTIEMETIC AGENTS

Adverse events associated with the antiemetic agents included in the guidelines are few. Headache and constipation are the most common adverse events among patients receiving 5-HT₃-receptor antagonists.⁶⁷ The potential for QTc prolongation has been identified as a safety concern associated with the first-generation 5-HT₃-receptor antagonists.⁶⁷ Asthenia, fatigue, and hiccups have been associated with the use of NK₁-receptor antagonists.²⁰ The most common adverse events associated with olanzapine are somnolence, postural hypotension, and constipation.^{58,59}

ADHERENCE TO ANTIEMETIC GUIDELINES

Aapro et al.⁴ found that adherence to antiemetic guidelines significantly increased the control of chemotherapy-induced emesis over a 5-day period in patients receiving highly or moderately emetogenic drugs. Although further study is needed to assess adherence to guidelines, there is evidence that guidelines are not uniformly followed. A single-center study in Switzerland showed that only 61% of patients were treated in accordance with MASCC-ESMO guidelines, and prophylaxis for delayed chemotherapy-induced emesis was not adhered to in 89% of patients.⁶⁸ Similar results have been reported in other European studies.⁶⁹ Several factors may influence suboptimal adherence to guidelines among physicians. An observational study showed that health care profes-

sionals accurately predict the incidence of acute chemotherapy-induced emesis but markedly underestimate the incidence of delayed chemotherapy-induced emesis.³ The administration of chemotherapy in an outpatient setting may contribute to this underestimation, because patients who have delayed chemotherapy-induced emesis at home are likely to underreport it.⁶⁹ Patients may find it more relevant to report treatment benefits than adverse events,⁷⁰ may forget the severity of chemotherapy-induced emesis, or may fear chemotherapy adjustments or discontinuation as a result of the development of chemotherapy-induced emesis.⁷¹ Patient-centered strategies should be used to ensure accurate self-reporting of chemotherapy-induced emesis. In this regard, oncology nurses can play an important role; they have more contact with patients than do physicians and are able to evaluate the risk of chemotherapy-induced emesis, assess the efficacy of antiemetic treatment, educate patients and caregivers, and elicit patient feedback.

A lack of continued education of health care professionals may also contribute to low levels of guideline awareness⁶⁸; however, the simple dissemination of educational materials may not be a sufficient solution.⁷² A study involving 103 Italian cancer centers showed that combining the dissemination of guidelines with an “audit-and-feedback” strategy and an educational outreach visit significantly increased the use of guideline-recommended prophylactic treatment.⁷² Alternatively, the implementation of guidelines at the hospital level may help to clarify for the staff the antiemetic agents that are available to patients.⁷¹ In a U.S. hospital, the implementation of a program that included an educational session, risk-assessment tools, and computerized standard order sets based on guidelines regarding antiemetic therapy was found to efficiently increase adherence.⁵

Finally, a lack of availability of or reimbursement for antiemetic drugs, as well as the direct and indirect costs (e.g., administration time, product storage, and the need for education) associated with treatment for chemotherapy-induced emesis,^{7,8} may be limiting factors in many countries. Reports have shown that pharmacist interventions can help reduce the costs of antiemetics by 16% in outpatient clinics.⁷³ In Canada, a pharmacist-driven multifaceted program for the implementation of guidelines on

antiemetic therapy efficiently promoted the use of antiemetic agents in a clinically appropriate manner.⁷⁴

In conclusion, multiple approaches need to be implemented to increase adherence to guidelines. These strategies should involve not only a multidisciplinary team of oncology professionals, including physicians, pharmacists, and nurses, but also active engagement of patients in the diagnostic and decision-making process.

LOOKING FORWARD

The administration of a 5-HT₃-receptor antagonist typically reduces or prevents emesis in 50% of patients. This percentage increases to 70% when the agent is given in combination with dexamethasone, and it increases further, to approximately 84%, when an NK₁-receptor antagonist is added.^{54,69} Nevertheless, the ultimate goal is to prevent all nausea and vomiting associated with cancer treatment.

Although physicians have often treated nausea and vomiting as a unified symptom,^{75,76} nausea has a higher incidence, is more difficult to control, and has a greater effect on a patient's quality of life.⁷⁶ Even though clinicians may be aware of these challenges, recognizing and treating

nausea is complicated because it can be measured only subjectively by patients. Studies associate nausea with retching or vomiting, but patients may also refer to dysgeusia and other symptoms as nausea. More comprehensive nausea-specific questionnaires might contribute to the ability of physicians to treat nausea effectively.

New anticancer agents, particularly agents targeted against specific molecules, are continuously being developed and used in a variety of doses, schedules, and combinations. Antiemetic agents may be needed for patients who are treated with some of these agents. A total of 32 newly approved anticancer drugs, the majority of which represent targeted therapy and immunotherapy compounds, have recently been assessed for their emetogenic potential.⁷⁷ Despite the current lack of clinical trials on the prevention and treatment of nausea and vomiting caused by these new agents, the classification of their emetogenicity will help clinicians in the decision-making and guideline-development process.⁷⁷

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REFERENCES

1. Rojas C, Raje M, Tsukamoto T, Slusher BS. Molecular mechanisms of 5-HT₃ and NK₁ receptor antagonists in prevention of emesis. *Eur J Pharmacol* 2014;722:26-37.
2. Morran C, Smith DC, Anderson DA, McArdle CS. Incidence of nausea and vomiting with cytotoxic chemotherapy: a prospective randomised trial of antiemetics. *Br Med J* 1979;1:1323-4.
3. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer* 2004;100:2261-8.
4. Aapro M, Molassiotis A, Dicato M, et al. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Ann Oncol* 2012;23:1986-92.
5. Affronti ML, Schneider SM, Herndon JE II, Schlundt S, Friedman HS. Adherence to antiemetic guidelines in patients with malignant glioma: a quality improvement project to translate evidence into practice. *Support Care Cancer* 2014;22:1897-905.
6. Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology focused guideline update. *J Clin Oncol* 2016;34:381-6.
7. Haiderali A, Menditto L, Good M, Teitelbaum A, Wegner J. Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a U.S. population. *Support Care Cancer* 2011;19:843-51.
8. Viale PH, Grande C, Moore S. Efficacy and cost: avoiding undertreatment of chemotherapy-induced nausea and vomiting. *Clin J Oncol Nurs* 2012(4);16:E133-41.
9. American Society of Clinical Oncology. ASCO 50th anniversary poll names the top 5 advances from the past 50 years. September 17, 2014 (<http://www.asco.org/press-center/asco-50th-anniversary-poll-names-top-5-advances-past-50-years>).
10. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;15:103-9.
11. NCCN Clinical Practice Guidelines in Oncology. Antiemesis, version 2. Fort Washington, PA: Harborside Press, 2015.
12. Morrow GR, Hickok JT, Burish TG, Rosenthal SN. Frequency and clinical implications of delayed nausea and delayed emesis. *Am J Clin Oncol* 1996;19:199-203.
13. Navari RM. Treatment of breakthrough and refractory chemotherapy-induced nausea and vomiting. *Biomed Res Int* 2015;2015:595894.
14. Morrow GR, Roscoe JA, Hynes HE, Flynn PJ, Pierce HI, Burish T. Progress in reducing anticipatory nausea and vomiting: a study of community practice. *Support Care Cancer* 1998;6:46-50.
15. Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med* 2008;358:2482-94.
16. Janelins MC, Tejani MA, Kamen C, Peoples AR, Mustian KM, Morrow GR. Current pharmacotherapy for chemotherapy-induced nausea and vomiting in cancer patients. *Expert Opin Pharmacother* 2013;14:757-66.
17. Kris MG, Gralla RJ, Clark RA, et al. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. *J Clin Oncol* 1985;3:1379-84.
18. Roila F, Hesketh PJ, Herrstedt J. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol* 2006;17:20-8.

19. MASCC antiemetic guidelines. Hillerød, Denmark: Multinational Association of Supportive Care in Cancer, 2013 (<http://www.mascc.org/antiemetic-guidelines>).
20. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin — the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003;21:4112-9.
21. De Mulder PH, Seynaeve C, Vermorken JB, et al. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting: a multicenter, randomized, double-blind, crossover study. *Ann Intern Med* 1990;113:834-40.
22. Warr D, Willan A, Fine S, et al. Superiority of granisetron to dexamethasone plus prochlorperazine in the prevention of chemotherapy-induced emesis. *J Natl Cancer Inst* 1991;83:1169-73.
23. Herrstedt J, Sigsgaard T, Boesgaard M, Jensen TP, Dombernowsky P. Ondansetron plus metopimazine compared with ondansetron alone in patients receiving moderately emetogenic chemotherapy. *N Engl J Med* 1993;328:1076-80.
24. Hesketh PJ, Harvey WH, Harker WG, et al. A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. *J Clin Oncol* 1994;12:596-600.
25. Hesketh P, Navari RM, Grote T, et al. Double-blind, randomized comparison of the antiemetic efficacy of intravenous dolasetron mesylate and intravenous ondansetron in the prevention of acute cisplatin-induced emesis in patients with cancer. *J Clin Oncol* 1996;14:2242-9.
26. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003;97:3090-8.
27. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT₃ receptor antagonist: results of a phase III, single-dose trial versus dolasetron. *Cancer* 2003;98:2473-82.
28. Gralla R, Lichinitser M, Van Der Veet S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol* 2003;14:1570-7.
29. Hesketh PJ, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. *Ann Oncol* 2014;25:1340-6.
30. Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. *Lancet Oncol* 2015;16:1079-89.
31. Schwartzberg LS, Modiano MR, Rapoport BL, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. *Lancet Oncol* 2015;16:1071-8.
32. Aapro M, Rugo H, Rossi G, et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol* 2014;25:1328-33.
33. Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann Oncol* 2014;25:1333-9.
34. DeVita VT Jr, Chu E. A history of cancer chemotherapy. *Cancer Res* 2008;68:8643-53.
35. Gralla RJ. Metoclopramide: a review of antiemetic trials. *Drugs* 1983;25:Suppl 1: 63-73.
36. Frytak S, Moertel CG, Eagan RT, O'Fallon JR. A double-blind comparison of metoclopramide and prochlorperazine as antiemetics for platinum therapy. *Proc Am Soc Clin Oncol* 1981;22:421.
37. Gralla RJ, Itri LM, Pisko SE, et al. Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *N Engl J Med* 1981;305:905-9.
38. Gralla RJ, Tyson LB, Clark RA, Bordin LA, Kelsen DP, Kalman LB. Antiemetic trials with high dose metoclopramide: Superiority over THC, and preservation of efficacy in subsequent chemotherapy courses. *Proc Am Soc Clin Oncol* 1982;1: 58.
39. Aapro MS, Alberts DS. High-dose dexamethasone for prevention of cisplatin-induced vomiting. *Cancer Chemother Pharmacol* 1981;7:11-4.
40. Roila F, Tonato M, Ballatori E, Del Favero A. Prevention of cisplatin-induced emesis. *Lancet* 1992;340:972.
41. Joss RA, Bacchi M, Buser K, et al. Ondansetron plus dexamethasone is superior to ondansetron alone in the prevention of emesis in chemotherapy-naïve and previously treated patients. *Ann Oncol* 1994;5: 253-8.
42. Navari RM, Gandara D, Hesketh P, et al. Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin-induced emesis. *J Clin Oncol* 1995;13:1242-8.
43. Italian Group for Antiemetic Research. Ondansetron versus granisetron, both combined with dexamethasone, in the prevention of cisplatin-induced emesis. *Ann Oncol* 1995;6:805-10.
44. Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT₃-receptor antagonists for acute chemotherapy-induced emesis. *Support Care Cancer* 2007;15:1023-33.
45. NCCN antiemesis practice guidelines. Oncology (Williston Park) 1997;11(11A): 57-89.
46. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. *Ann Oncol* 1998;9:811-9.
47. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *J Clin Oncol* 1999;17:2971-94.
48. European Society for Medical Oncology. ESMO recommendations for prophylaxis of chemotherapy-induced nausea and vomiting (NV). *Ann Oncol* 2001;12:1059-60.
49. Navari RM. Pathogenesis-based treatment of chemotherapy-induced nausea and vomiting — two new agents. *J Support Oncol* 2003;1:89-103.
50. Rojas C, Stathis M, Thomas AG, et al. Palonosetron exhibits unique molecular interactions with the 5-HT₃ receptor. *Anesth Analg* 2008;107:469-78.
51. Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. *Lancet Oncol* 2009;10:115-24.
52. Aapro M, Fabi A, Nolè F, et al. Double-blind, randomised, controlled study of the efficacy and tolerability of palonosetron plus dexamethasone for 1 day with or without dexamethasone on days 2 and 3 in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy. *Ann Oncol* 2010;21:1083-8.
53. Grunberg S, Chua D, Maru A, et al. Single-dose fosaprepitant for the preven-

- tion of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol — EASE. *J Clin Oncol* 2011;29:1495-501.
54. Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. *Ann Oncol* 2015;26:1081-90.
55. Navari RM. Profile of netupitant/palonosetron (NEPA) fixed dose combination and its potential in the treatment of chemotherapy-induced nausea and vomiting (CINV). *Drug Des Devel Ther* 2015;9:155-61.
56. Varubi (rolapitant) prescribing information. Waltham, MA: Tesaro, 2015 (http://varubirx.com/downloads/VARUBI_rolapitant_Full_Prescribing_Information_September_2015.pdf).
57. Navari RM. Olanzapine for the prevention and treatment of chronic nausea and chemotherapy-induced nausea and vomiting. *Eur J Pharmacol* 2014;722:180-6.
58. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. *J Support Oncol* 2011;9:188-95.
59. Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. *Support Care Cancer* 2013;21:1655-63.
60. Cruz FM, de Iracema Gomes Cubero D, Taranto P, et al. Gabapentin for the prevention of chemotherapy-induced nausea and vomiting: a pilot study. *Support Care Cancer* 2012;20:601-6.
61. Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin* 2007;23:533-43.
62. Ware MA, Daeninck P, Maida V. A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting. *Ther Clin Risk Manag* 2008;4:99-107.
63. Molassiotis A, Aapro M, Dicato M, et al. Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: results from a European prospective observational study. *J Pain Symptom Manage* 2014;47(5):839-848.e4.
64. Kris MG, Urba SG, Schwartzberg LS. Clinical roundtable monograph: treatment of chemotherapy-induced nausea and vomiting: a post-MASCC 2010 discussion. *Clin Adv Hematol Oncol* 2011;9:Suppl: 1-15.
65. Dranitsaris G, Bouganim N, Milano C, et al. Prospective validation of a prediction tool for identifying patients at high risk for chemotherapy-induced nausea and vomiting. *J Support Oncol* 2013;11: 14-21.
66. Bayo J, Fonseca PJ, Hernando S, et al. Chemotherapy-induced nausea and vomiting: pathophysiology and therapeutic principles. *Clin Transl Oncol* 2012;14:413-22.
67. Schwartzberg L, Barbour SY, Morrow GR, Ballinari G, Thorn MD, Cox D. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). *Support Care Cancer* 2014;22: 469-77.
68. Burmeister H, Aebi S, Studer C, Fey MF, Gautschi O. Adherence to ESMO clinical recommendations for prophylaxis of chemotherapy-induced nausea and vomiting. *Support Care Cancer* 2012;20:141-7.
69. Jordan K, Gralla R, Jahn F, Molassiotis A. International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): content and implementation in daily routine practice. *Eur J Pharmacol* 2014;722:197-202.
70. Di Maio M, Gallo C, Leighl NB, et al. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. *J Clin Oncol* 2015;33:910-5.
71. Vidall C, Dielenseger P, Farrell C, et al. Evidence-based management of chemotherapy-induced nausea and vomiting: a position statement from a European cancer nursing forum. *Ecancermedicalscience* 2011;5:211.
72. Roila F. Transferring scientific evidence to oncological practice: a trial on the impact of three different implementation strategies on antiemetic prescriptions. *Support Care Cancer* 2004;12:446-53.
73. Iihara H, Ishihara M, Matsuura K, et al. Pharmacists contribute to the improved efficiency of medical practices in the outpatient cancer chemotherapy clinic. *J Eval Clin Pract* 2012;18:753-60.
74. Dranitsaris G, Leung P, Warr D. Implementing evidence based antiemetic guidelines in the oncology setting: results of a 4-month prospective intervention study. *Support Care Cancer* 2001;9:611-8.
75. Navari RM. Treatment of chemotherapy-induced nausea. *Community Oncol* 2012;9:20-6.
76. Foubert J, Vaessen G. Nausea: the neglected symptom? *Eur J Oncol Nurs* 2005; 9:21-32.
77. Jordan K, Jahn F, Jahn P, Feyer P, Müller-Tidow C, Hesketh P. Proposed emetic risk classification of 32 recently approved anticancer agents. Presented at the MASCC/ISOO Annual Meeting on Supportive Care in Cancer, Copenhagen, April 14–17, 1985 (poster).

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