NCCN Guidelines® Insights
Antiemesis, Version 2.2017
Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis address all aspects of management for chemotherapy-induced nausea and vomiting. These NCCN Guidelines Insights focus on recent updates to the NCCN Guidelines for Antiemesis, specifically those regarding carboplatin, granisetron, and olanzapine.

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Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.**

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The full and most current version of these NCCN Guidelines are available at NCCN.org.

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Target Audience: This activity is designed to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with cancer.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Antiemesis
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Antiemesis

Disclosure of Relevant Financial Relationships

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EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[a]

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[b,c]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4	• Carmustine >250 mg/m² • Cisplatin • Cyclophosphamide >1,500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m²	• Epirubicin >90 mg/m² • Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis)[b,c]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC <4[d] • Carmustine[d] ≤250 mg/m²	• Clofarabine • Cyclophosphamide ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin[d] • Daunorubicin[d] • Dinutuximab • Doxorubicin[d] <60 mg/m² • Epirubicin[d] ≤90 mg/m² • Idarubicin	• Ifosfamide[d] <2 g/m² per dose • Interferon alfa ≥10 million IU/m² • Irinotecan[d] • Melphalan • Methotrexate[d] ≥250 mg/m² • Oxaliplatin[d] • Temozolomide • Trabectedin[d]

Adapted with permission from:
Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer 2010;19:S43-47.

Low Emetic Risk (See AE-3)

Minimal Emetic Risk (See AE-3)

Oral Chemotherapy (See AE-4)

[a]Potential drug interactions between antineoplastic agents/antiemetic therapies and various other drugs should always be considered.
[b]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
[c]Continuous infusion may make an agent less emetogenic.
[d]These agents may be highly emetogenic in certain patients.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Vomiting (emesis) and nausea induced by systemic or radiation therapy (RT) can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy or RT. Nausea and/or vomiting (N/V) can result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of performance status and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment.[1–4] Systemic therapy includes chemotherapy, targeted therapy, and immunotherapy, herein referred to as *chemotherapy*. Patients receiving whole-body RT, upper abdominal RT, or chemotherapy combined with RT can develop N/V,[5–7] which is often referred to as *chemotherapy-induced nausea and vomiting* (CINV), and is commonly classified as acute, delayed, anticipatory, breakthrough, or refractory.[8]

The incidence and severity of N/V in patients receiving chemotherapy, RT, or chemoradiation

HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[f,g,h,i,j]

DAY 1: Select option A, B, C, D, E, F (order does not imply preference) All are category 1, start before chemotherapy:[h]	**DAYS 2, 3, 4:**
A: • Aprepitant 125 mg PO once • 5-HT3 RA (choose one): ‣ Palonosetron 0.25 mg IV once ‣ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ‣ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ‣ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[l,m]	**A:[v]** • Aprepitant 80 mg PO daily on days 2, 3 • Dexamethasone 8 mg[l,m] PO/IV daily on days 2, 3, 4
B: • Fosaprepitant 150 mg IV once • 5-HT3 RA (choose one): ‣ Palonosetron 0.25 mg IV once ‣ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ‣ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ‣ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[l,m]	**B:[v]** • Dexamethasone 8 mg[l,m] PO/IV daily on day 2, then dexamethasone 8 mg[l,m] PO/IV twice daily on days 3, 4
C: • Rolapitant 180 mg PO once[n,o] • 5-HT3 RA (choose one): ‣ Palonosetron 0.25 mg IV once ‣ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24 h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ‣ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ‣ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[l,m]	**C:[v]** • Dexamethasone 8 mg[l,m] PO/IV twice daily on days 2, 3, 4
D: • Netupitant 300 mg/palonosetron 0.5 mg PO once[p,q] • Dexamethasone 12 mg PO/IV once[l,m]	**D:** • Dexamethasone 8 mg[l,m] PO daily on days 2, 3, 4
E: • Olanzapine 10 mg PO once[r,s] • Palonosetron 0.25 mg IV once • Dexamethasone 20 mg IV once[m]	**E:** • Olanzapine 10 mg PO daily on days 2, 3, 4[s]
F: • Aprepitant 125 mg PO once or fosaprepitant 150 mg IV once[t,u] • 5-HT3 RA (choose one): ‣ Palonosetron 0.25 mg IV once ‣ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24 h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ‣ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ‣ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[l,m] • Olanzapine 10 mg PO once[s]	**F:[v]** • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant on day 1) • Dexamethasone 8 mg[l,m] PO/IV daily on days 2, 3, 4 • Olanzapine 10 mg PO daily on days 2, 3, 4[s]

See Breakthrough Treatment (AE-10)

AE-5

are affected by numerous factors, including: (1) the specific therapeutic agents used; (2) dosage of the agents; (3) schedule and route of administration of the agents; (4) target of the RT, such as whole body or upper abdomen; and (5) individual patient variability, such as age, sex, prior chemotherapy, and history of alcohol use.[9,10] More than 90% of patients receiving highly emetogenic chemotherapy (HEC) will have episodes of vomiting. However, if patients receive prophylactic (preventive) antiemetic regimens before treatment with HEC, the incidence of vomiting decreases to approximately 30%.[9,11,12] Although vomiting can often be prevented or substantially decreased by using prophylactic antiemetic regimens, nausea is much harder to control.[13–18]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis are intended to provide an overview of the treatment principles for preventing chemotherapy-induced (or RT-induced) N/V, and to provide recommendations for antiemetic prophylaxis according to the emetogenic potential of antitumor therapies. These NCCN Guidelines are updated at least once a year by a multidisciplinary panel of experts; the first guidelines were published in 1997.[19] Major updates to the 2017 version, described in these NCCN Guidelines Insights, are as follows: (1) carboplatin is now categorized as HEC if administered at an area under the curve (AUC) of ≥4, and remains categorized as moderately emetogenic chemotherapy (MEC) if administered at an AUC of <4; (2) subcutaneous granisetron extended-release injection is a new formulation that is now recommended in antiemetic regimens for HEC and MEC; and (3) a new 4-drug antiemetic regimen containing olanzapine is now recommended (category 1) for HEC.

Emetogenicity of Chemotherapy

Frequency of chemotherapy-induced emesis depends on the emetogenic potential of the systemic agents used.[8] The Grunberg classification is updated each

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MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[f,g,h,i,j]

DAY 1: Select option G, H, I, J, K, L (order does not imply preference) All are category 1, start before chemotherapy:[h]	**DAYS 2, 3:**	
G: • 5-HT3 RA (choose one): ‣ Palonosetron 0.25 mg IV once (preferred) ‣ Granisetron 10 mg SQ once[k] (preferred), or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ‣ Ondansetron 16-24 mg PO once,or 8-16 mg IV once ‣ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[m]	**G:** • Dexamethasone 8 mg[m] PO/IV daily on days 2, 3 OR • 5-HT3 RA monotherapy[z]: ‣ Granisetron 1-2 mg (total dose) PO daily or 0.01 mg/kg (max 1 mg) IV daily on days 2 and 3 ‣ Ondansetron 8 mg PO twice daily or 16 mg PO daily or 8-16 mg IV daily on days 2, 3 ‣ Dolasetron 100 mg PO on days 2, 3	
H: • Aprepitant 125 mg PO once[w] • 5-HT3 RA (choose one)[x]: ‣ Palonosetron 0.25 mg IV once ‣ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ‣ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ‣ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[m]	**H:** • Aprepitant 80 mg PO daily on days 2, 3 • ± Dexamethasone 8 mg[m] PO/IV daily on days 2, 3	**See Breakthrough Treatment (AE-10)**
I: • Fosaprepitant 150 mg IV once[w] • 5-HT3 RA (choose one)[x]: ‣ Palonosetron 0.25 mg IV once ‣ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ‣ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ‣ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[m]	**I:** • ± Dexamethasone 8 mg[m] PO/IV daily on days 2, 3	
J: • Rolapitant 180 mg PO once[n,w,y] • 5-HT3 RA (choose one)[x]: ‣ Palonosetron 0.25 mg IV once ‣ Granisetron 10 mg SQ once[k], or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first dose of chemotherapy. ‣ Ondansetron 16-24 mg PO once, or 8-16 mg IV once ‣ Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once[m]	**J:** • ± Dexamethasone 8 mg[m] PO/IV daily on days 2, 3	
K: • Netupitant 300 mg/palonosetron 0.5 mg PO once[p,q] • Dexamethasone 12 mg PO/IV once[m]	**K:** • ± Dexamethasone 8 mg[m] PO/IV on days 2, 3	
L: • Olanzapine 10 mg PO once[r,s] • Palonosetron 0.25 mg IV once • Dexamethasone 20 mg IV once[m]	**L:** • Olanzapine 10 mg PO daily on days 2, 3[s]	

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year by the NCCN Antiemesis Panel with recently introduced drugs.[14,20] The NCCN Guidelines outline treatment using 4 categories of emetogenic potential for intravenous agents:

- High emetic risk: >90% of patients experience acute emesis
- Moderate emetic risk: >30% to 90% of patients experience acute emesis
- Low emetic risk: 10% to 30% of patients experience acute emesis
- Minimal emetic risk: <10% of patients experience acute emesis

The NCCN panel also categorized the emetogenic potential of oral antineoplastic agents as (1) high to moderate emetic risk (>30% frequency of emesis) or (2) low to minimal emetic risk (<30% frequency of emesis).[14]

For the 2017 update, the panel revised the emetogenic classification for carboplatin. When dosed at an AUC of ≥4, it is now categorized as HEC, whereas at an AUC of <4 it remains categorized as MEC (see AE-2; page 885). Data suggest that carboplatin, although less emetogenic than cisplatin, is perhaps on the higher end of emetogenic potential within the MEC classification.[21–24] Several trials and a subset analysis have shown benefit in terms of complete response (CR) in the overall and delayed phases with the addition of a neurokinin-1 (NK1) receptor antagonist (RA) to the 2-drug regimen of a 5-HT3 antagonist and dexamethasone for the prevention of CINV associated with carboplatin-based regimens, thereby affirming the higher emetogenic potential of carboplatin.[21–24] All of the commercially available NK1 RAs have an FDA-approved indication for MEC chemotherapy, but previous versions of the NCCN Guidelines have supported the addition of an NK1 RA only for select patients receiving MEC with additional CINV risk factors or in those for whom previous therapy with a steroid and 5-HT3 antagonist alone failed. The panel did not want a "carboplatin subset" within the MEC classi-

Footnotes for pages AE-5 and AE-6

[f]See Emetogenic Potential of Intravenous Antineoplastic Agents.
[g]Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[h]See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[i]With or without lorazepam 0.5–2 mg PO or IV or sublingual every 6 hours as needed days 1–4. With or without H2 blocker or proton pump inhibitor. See Principles of Emesis Control for the Cancer Patient (AE-1).
[j]See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[k]Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the intravenous formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals.
[l]If NK1 antagonists are not given on day 1, then recommend dexamethasone 20 mg PO/IV once on day 1, followed by 8 mg twice daily PO/IV on days 2, 3, 4 (category 2B).
[m]Dexamethasone doses and schedules shown are largely based on the doses and schedules used in the clinical trial(s) for each regimen. Dexamethasone doses may be individualized; lower doses, frequency, or even elimination of dexamethasone on subsequent days may be acceptable based on patient characteristics (category 2B). See Discussion.
[n]Rolapitant has an extended half-life and should not be administered at less than 2-week intervals.
[o]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;16:1079-1089.
[p]Available as a combination product only.
[q]Hesketh PJ, Rossi G, Rizzi 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;25:1340-1346.
[r]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;9:188-195.
[s]Consider 5 mg dose for elderly or over-sedated patients. Hashimoto H, Yanai T, Nagashima K, et al. A double-blind randomized phase II study of 10 versus 5 mg olanzapine for emesis induced by highly emetogenic chemotherapy with cisplatin [abstract]. J Clin Oncol 2016;34: Abstr 10111). See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[t]Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med 2016; 375:134-142.
[u]Consider escalating to this option (F) when emesis occurred during a previous cycle of chemotherapy using an olanzapine regimen (E) or an NK1 antagonist-containing regimen (A, B, C, or D). See Principles for Managing Breakthrough Emesis (AE-C).
[v]Some NCCN Member Institutions use a 5-HT3 RA (unless palonosetron, granisetron extended-release injection, or granisetron transdermal patch given on day 1) on days 2, 3, and 4 in addition to steroid and NK1 antagonist therapy (category 2B).
[w]As per high emetic risk prevention, an NK1 antagonist should be added (to dexamethasone and a 5-HT3 RA regimen) for select patients with additional risk factors or previous treatment failure with a steroid + 5HT3 RA alone (See AE-5).
[x]When used in combination with an NK-1 antagonist, there is no preferred 5-HT3 RA. See Prinicples of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A)
[y]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;9:1071-1079.
[z]No further therapy required if palonsetron, granisetron extended-release injection, or granisetron transdermal patch given on day 1.

fication; therefore, high-dose carboplatin (AUC ≥4) was escalated to the HEC classification, where 3- or 4-drug regimens are recommended (category 1) for all patients.

Prevention of Acute and Delayed Emesis

The NCCN Guidelines recommend several different antiemetic regimen options for patients receiving HEC. Recommended antiemetic regimens may include 5-HT3 antagonists, dexamethasone, NK1 RAs, and olanzapine (see AE-5 and AE-7; pages 886 and 888). Lorazepam and a histamine (H2) blocker or a proton pump inhibitor may also be added to all of these regimens to manage anxiety and dyspepsia/reflux-related symptoms, respectively.[7,25,26] Regimens for day 1 of therapy (all are category 1) include those containing dexamethasone, a 5-HT3 antagonist option (ie, dolasetron, granisetron, ondansetron, palonosetron), and an NK1 RA option (ie, aprepitant, fosaprepitant, rolapitant). Other antiemetic regimens (category 1) for HEC on day 1 include (1) oral netupitant combined with oral palonosetron (NEPA) in a single capsule plus dexamethasone; (2) olanzapine, palonosetron, and dexamethasone; or (3) olanzapine, aprepitant or fosaprepitant, palonosetron, and dexamethasone; this 4-drug regimen was added for the 2017 update (see "Olanzapine," page 891). Note that the regimens and doses are often modified on days 2 to 4 after chemotherapy.

The NCCN Guidelines recommend several antiemetic regimens for intravenous MEC, including (1) dexamethasone and one of the 5-HT3 antagonist options with or without one of the NK1 RA options; (2) NEPA in a single tablet plus dexamethasone; or (3) olanzapine, palonosetron, and dexamethasone. If needed, lorazepam and either an H2 blocker or a proton pump inhibitor may be added to these regimens to manage anxiety and dyspepsia/reflux-related symptoms, respectively.[9] Adding an NK1 RA to a regimen with dexamethasone and one of the 5-HT3 antagonist options is recommended for select patients with

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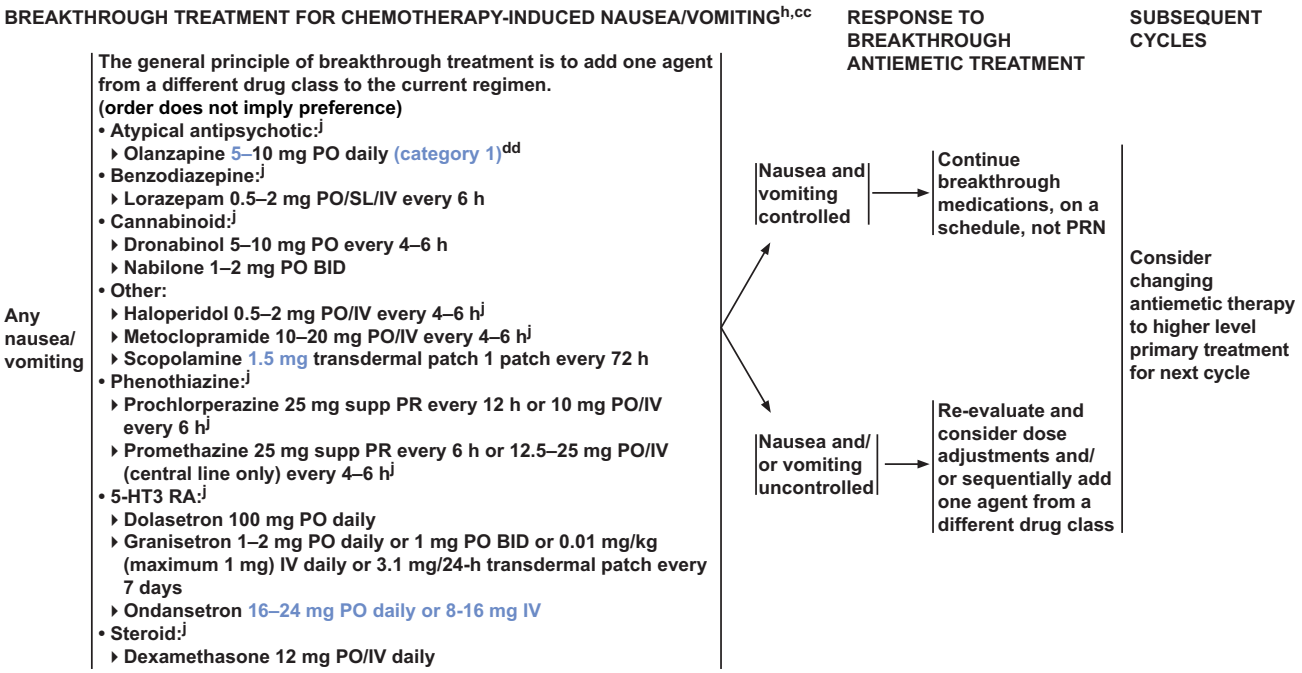

[h]See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[j]See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[cc]See Principles of Managing Breakthrough Emesis (AE-C).
[dd]When not used as part of the acute and delayed emesis prevention regimen. Navari RM, Nagy 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;21:1655-1663.

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additional risk factors or failure of previous therapy with a 2-drug regimen of dexamethasone and a 5-HT3 antagonist. Any one of the 5-HT3 antagonists can be used in the first regimen for day 1; however, palonosetron and subcutaneous granisetron extended-release injection are preferred options when an NK1 RA is not included.[27,28] The NCCN Guidelines recommend the use of 5-HT3 antagonists as one of several options to prevent delayed emesis for MEC.

Granisetron

All of the 5-HT3 antagonists (dolasetron, granisetron, ondansetron, palonosetron) have been shown to be effective in controlling acute N/V associated with cancer chemotherapy when used in multidrug antiemetic regimens.[29–45] For the 2017 update, the NCCN panel added recommendations for a new formulation of granisetron—subcutaneous granisetron extended-release injection—in antiemetic regimens for HEC and MEC based on published data and recent FDA approval (see AE-5, AE-6, AE-7, and AE-A 2; pages 886–888 and 890). It is important to note that subcutaneous granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the intravenous formulation (see AE-A 2; page 890). Subcutaneous granisetron has an extended half-life and should not be administered at <1-week intervals. To date, subcutaneous granisetron has only been studied with single-day chemotherapy regimens. Efficacy and safety with multiday chemotherapy regimens are currently unknown.

A phase III trial assessed subcutaneous granisetron extended-release injection versus intravenous palonosetron in a 2-drug regimen with dexamethasone for patients receiving HEC or MEC.[28] A limitation of this study was that the emetogenicity of the chemotherapy regimens was reclassified after the study. For example, anthracycline

PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS[1]

Serotonin receptor antagonists (5-HT3 RA):

- **A 5-HT3 RA should be administered prior to the first (and subsequent) doses of moderately or highly emetogenic chemotherapy. The frequency or need for repeated administration of the 5-HT3 RA depends on the agent chosen and its mode of administration (parenteral/oral/transdermal).**
- **Palonosetron:**
  - **A single intravenous palonosetron dose of 0.25 mg may be sufficient prior to the start of a 3-day chemotherapy regimen instead of multiple daily doses of another oral or intravenous 5-HT3 RA.**
  - **Repeat dosing of palonosetron 0.25 mg IV is likely to be safe, based on available evidence.**
  - **In terms of efficacy, limited data are available for multi-day dosing.[6]**
- **Granisetron extended-release injection:**
  - **Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the intravenous formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals**
  - **A single subcutaneous dose of 10 mg was found to be non-inferior to a single intravenous dose of palonosetron 0.25 mg for the prevention of acute and delayed CINV following MEC or HEC when both are used in combination with dexamethasone.[7]**
  - **A single subcutaneous dose of 10 mg was found to be superior to a single intravenous dose of ondansetron for the prevention of delayed CINV following HEC when both are used in combination with fosaprepitant and dexamethasone.[8]**
- **When palonosetron or granisetron extended-release injection is used as part of an antiemetic regimen that does NOT contain an NK1 antagonist, palonosetron or granisetron extended-release injection are the preferred 5-HT3 RA.[7,9]**

NK1 antagonists:

- **NK1 antagonists may be used for multi-day chemotherapy regimens likely to be moderately or highly emetogenic and associated with significant risk for delayed nausea and emesis.**
- **For single-day chemotherapy regimens, category 1 evidence is available for aprepitant, fosaprepitant, netupitant, or rolapitant administered in combination with a 5-HT3 RA and steroid (see AE-5 and AE-6).**
- **If the oral aprepitant regimen is chosen, limited data exist to support administration of aprepitant on days 4 and 5 after multiday chemotherapy.**
- **Data from a small phase III randomized study support the use of aprepitant (125 mg day 3, 80 mg days 4–7) with 5-HT3 RA (days 1–5) and dexamethasone (20 mg days 1, 2) in patients with germline cancers treated with a 5-day cisplatin-based chemotherapy.[10]**
- **Studies investigating repeat dosing of fosaprepitant, netupitant, and rolapitant are not available.**
- **Fosaprepitant, aprepitant, and netupitant inhibit the metabolism of dexamethasone and may cause higher dexamethasone concentrations. Rolapitant does not inhibit dexamethasone metabolism.**
- **Rolapitant has an extended half-life and should not be administered at less than 2-week intervals.**

[1]The panel acknowledges that evidence is lacking to support every clinical scenario. Decisions should be individualized for each chemotherapy regimen and each patient. An extensive knowledge of the available clinical data, pharmacology, pharmacodynamics, and pharmacokinetics of the antiemetics and the chemotherapy and experience with patients (regarding tolerability and efficacy) are all paramount to successfully implementing these guidelines into clinical practice.

[6]Giralt SA, Mangan KF, Maziarz RT, et al. Three palonosetron regimens to prevent CINV in myeloma patients receiving multiple-day high-dose melphalan and hematopoietic stem cell transplantation. Ann Oncol 2011;22:939-946.

[7]Raftopoulos H, Cooper W, O'Boyle E, et al. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial. Supportive Care Cancer 2015 Mar; 23(3):723-732.

[8]Schnadig ID, Agajanian R, Dakhil C, et al. APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy. Future Oncol 2016;12:1469-1481.

[9]Saito M 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 Feb;10(2):115-24.

[10]Albany C, Brames MJ, Fausel C, et al. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study. J Clin Oncol 2012;30:3998-4003.

AE-A (2 OF 2)

plus cyclophosphamide is now classified as HEC by the NCCN panel, whereas it was classified as MEC for the study. Two doses of subcutaneous granisetron were assessed: 5 and 10 mg. Data showed that subcutaneous granisetron was not inferior to intravenous palonosetron for preventing acute and delayed CINV after either HEC or MEC. For patients receiving HEC, acute CRs (98% CI difference vs palonosetron) for the 5- and 10-mg dose of subcutaneous granisetron were 77.7% (−12.1, 6.1) and 81.3% (−8.2, 9.3), respectively, compared with 80.7% for those receiving palonosetron at 0.25 mg. For patients receiving MEC, acute CRs (98% CI difference) for 5 or 10 mg of subcutaneous granisetron were 74.8% (−9.8, 9.3) and 76.9% (−7.5, 11.4), respectively, compared with 75.0% for palonosetron. The FDA approved the use of a 10-mg dose of subcutaneous granisetron extended-release injection when used for the prevention of acute and delayed CINV associated with MEC. Based on this trial and FDA approval, the NCCN panel now recommends subcutaneous granisetron extended-release injection as a preferred 5-HT3 antagonist option for MEC when used with dexamethasone in antiemetic regimens that do not contain an NK1 RA (see AE-6 and AE-7; pages 887 and 888). The panel also recommends intravenous palonosetron as a preferred 5-HT3 antagonist option for MEC. Although 2-drug regimens can be used for MEC, the panel recommends 3- or 4-drug regimens for HEC (see AE-5 and AE-7; pages 886 and 888).

A phase III trial (MAGIC) assessed a single dose of subcutaneous granisetron extended-release injection compared with a single dose of intravenous ondansetron in a 3-drug regimen with dexamethasone and fosaprepitant for patients receiving cisplatin or anthracycline plus cyclophosphamide (both are classified as HEC by the NCCN panel).[46] No 5-HT3 antagonists were administered on days 2 to 5. When administered subcutaneously, granisetron extended-release injection is effective for ≥5 days. The subcutaneous granisetron regimen improved the CR rate (no emesis

or rescue medication) for delayed-phase CINV (24–120 hours) compared with the ondansetron regimen (*P*=.014). More patients receiving the subcutaneous granisetron regimen had delayed-phase CR (291/450; 64.7%) versus those receiving ondansetron (256/452; 56.6%); the absolute treatment difference was 8.0% (95% CI, 1.7–14.4; *P*=.014). Based on this trial, the FDA approved the use of a 10-mg dose of subcutaneous granisetron extended-release injection when used for the prevention of acute and delayed CINV associated with anthracycline plus cyclophosphamide chemotherapy (classified as HEC). The NCCN panel added a new recommendation in the 2017 update for a 10-mg dose of subcutaneous granisetron extended-release injection on day 1 only for patients receiving HEC when used in the antiemetic regimens recommended in the NCCN Guidelines based on the MAGIC trial and FDA approval (see AE-5, AE-6, AE-7, and AE-A; pages 886–888 and 890).[28,46]

Olanzapine

Olanzapine is an atypical antipsychotic agent that is also useful as an antiemetic agent; it is an antagonist of multiple receptors involved in CINV, including acetylcholine-muscarine, dopamine, histamine, and serotonin receptors.[47] For the 2017 update, the NCCN panel added a new 4-drug regimen for HEC based on trial data: oral olanzapine (10 mg given once before HEC, then daily for 3 days), aprepitant or fosaprepitant, a 5-HT3 antagonist, and dexamethasone (see AE-5 and AE-7; pages 886 and 888). A phase III randomized trial assessed adding olanzapine or placebo to an antiemetic regimen of aprepitant or fosaprepitant, a 5-HT3 antagonist, and dexamethasone for patients receiving single-day HEC.[48] Data showed that the 4-drug regimen with olanzapine increased the CR rate (no emesis, no rescue) compared with placebo during 3 time periods (<24 hours after chemotherapy, 25–120 hours, and overall 120-hour period): 86% versus 65% (*P*<.001), 67% versus 52% (*P*=.007), and 64% versus 41% (*P*<.001), respectively. More patients receiving the 4-drug regimen with olanzapine had no chemotherapy-induced nausea compared with placebo during the 3 time periods: 74% versus 45% (*P*=.002); 42% versus 25% (*P*=.002); and 37% versus 22% (*P*=.002), respectively. Based on results of this trial, the panel recommends (category 1) this 4-drug regimen with olanzapine as a first-line option. The panel also recommends that clinicians consider switching to the 4-drug regimen after the first cycle of HEC if patients have significant emesis using other antiemetic regimens such as (1) NK1 RA–containing regimens; or (2) the olanzapine, dexamethasone, and palonosetron regimen (see AE-10; page 889). For the 2017 update, the NCCN panel revised the recommendation for olanzapine for breakthrough emesis to category 1 (from category 2A) given the magnitude of superiority shown over another rescue agent in a double-blind, randomized, prospective trial.[49]

Common side effects with olanzapine included fatigue, drowsiness, and sleep disturbances. Olanzapine should be used with caution in elderly patients (see boxed warning/label indication regarding death in patients with dementia-related psychosis, and additional warnings and precautions [eg, type II diabetes and hyperglycemia]).[50] A preliminary study suggests that a 5-mg dose of olanzapine may be considered in elderly or oversedated patients.[51] To avoid excessive dopamine blockade, clinicians should be cautious when using olanzapine concurrently with metoclopramide, phenothiazines, or haloperidol. Other drug–drug interactions may be important when including olanzapine in the antiemetic regimen. Rarely olanzapine is associated with a serious skin reaction (drug reaction with eosinophilia and systemic symptoms [DRESS]) (see prescribing information), but other symptoms include a fever with a rash and swollen lymph glands, or swelling in the face; patients with these symptoms should seek medical care as soon as possible. Thoughtful patient selection is key in order to take all of these concerns into account when considering olanzapine. Note that olanzapine-containing regimens are not approved by the FDA for CINV.

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Posttest Questions

1. Which of the following is/are true about subcutaneous granisetron extended-release injection?
    1. It is a new formulation of granisetron that is not interchangeable with the intravenous formulation.
    2. It is a preferred serotonin (5-HT3) antagonist option for MEC when used with dexamethasone in antiemetic regimens that do not contain a NK1 RA.
    3. It is only used in antiemetic regimens for MEC.
    4. The 5-mg dose is the preferred dose.

    a. 1
    b. 1 and 2
    c. 1, 2, and 3
    d. 1, 2, 3, and 4
    e. 2 and 4

2. True or False: Carboplatin dosed at an AUC of ≥4 is categorized as HEC in the NCCN Guidelines for Antiemesis.

3. Which of the following is/are true about olanzapine?
    1. When not used as part of prophylactic regimen, olanzapine can be added to the current regimens for patients with breakthrough emesis.
    2. A 5-mg dose of olanzapine may be considered in elderly or oversedated patients.
    3. A 4-drug regimen of oral olanzapine; aprepitant or fosaprepitant; a 5-HT3 antagonist; and dexamethasone is one of several recommended options for patients receiving HEC.
    4. A 4-drug regimen of oral olanzapine; aprepitant or fosaprepitant; a 5-HT3 antagonist; and dexamethasone is one of several recommended options for patients receiving MEC.

    a. 1
    b. 1 and 2
    c. 1, 2, and 3
    d. 1, 2, 3, and 4
    e. 2 and 4