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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Antiemesis, Version 2.2017

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>AGENT</th>
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<tbody>
<tr>
<td>High emetic risk (&gt;90% frequency of emesis)</td>
<td>AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>• Carboplatin AUC ≥4</td>
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<td></td>
<td>• Carmustine &gt;250 mg/m²</td>
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<td></td>
<td>• Cisplatin</td>
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<td>• Cyclophosphamide &gt;1,500 mg/m²</td>
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<td>• Dasarbazine</td>
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<td></td>
<td>• Doxorubicin ≥60 mg/m²</td>
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<td></td>
<td>• Epirubicin &gt;90 mg/m²</td>
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<td></td>
<td>• Ifosfamide ≥2 g/m² per dose</td>
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<td>• Mechlorethamine</td>
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<td></td>
<td>• Streptozocin</td>
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<tr>
<td>Moderate emetic risk (&gt;30%-90% frequency of emesis)</td>
<td>• Aldesleukin &gt;12-15 million IU/m²</td>
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<td>• Amifostine &gt;300 mg/m²</td>
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<td>• Arsenic trioxide</td>
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<td>• Carboplatin AUC &lt;4</td>
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<td>• Carmustine ≤250 mg/m²</td>
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<td>• Clofarabine</td>
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<td></td>
<td>• Cyclophosphamide ≤1500 mg/m²</td>
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<td>• Cytarabine &gt;200 mg/m²</td>
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<tr>
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<td>• Daunomycin³</td>
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<td>• Dinutuximab</td>
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<td></td>
<td>• Doxorubicin³ &lt;60 mg/m²</td>
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<td>• Epirubicin³ ≤90 mg/m²</td>
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<td>• Idarubicin</td>
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<td></td>
<td>• Ifosfamide³ &lt;2 g/m² per dose</td>
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<td></td>
<td>• Interferon alfa ≤10 million IU/m²</td>
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<td>• Irinotecan³</td>
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<td>• Methotrexate³ ≤250 mg/m²</td>
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<td>• Oxaliplatin³</td>
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<td>• Temozolomide</td>
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<td>• Trabectedin³</td>
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Low Emetic Risk (See AE-3)
Minimal Emetic Risk (See AE-3)
Oral Chemotherapy (See AE-4)

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,⁵-⁹ which is often referred to as chemotherapy-induced nausea and vomiting (CINV), and is commonly classified as acute, delayed, anticipatory, breakthrough, or refractory.⁵

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

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,⁵-⁹ which is often referred to as chemotherapy-induced nausea and vomiting (CINV), and is commonly classified as acute, delayed, anticipatory, breakthrough, or refractory.⁵

The incidence and severity of N/V in patients receiving chemotherapy, RT, or chemoradiation
HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION

**DAY 1:** Select option A, B, C, D, E, F (order does not imply preference)
**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
   • Dexamethasone 12 mg PO/IV once

B: • Fosaprepitant 150 mg IV once
   • 5-HT3 RA (choose one):
     ▶ Palonosetron 0.25 mg IV once
     ▶ Granisetron 10 mg SQ once
   • Dexamethasone 12 mg PO/IV once
   • Dolasetron 100 mg PO once

C: • Rolapitant 180 mg PO once
   • 5-HT3 RA (choose one):
     ▶ Palonosetron 0.25 mg IV once
     ▶ Granisetron 10 mg SQ once
   • Dexamethasone 12 mg PO/IV once

D: • Netupitant 300 mg/palonosetron 0.5 mg PO once
   • Dexamethasone 12 mg PO/IV once

E: • Olanzapine 10 mg PO once
   • Palonosetron 0.25 mg IV once
   • Dolasetron 20 mg IV once

F: • Aprepitant 125 mg PO once or fosaprepitant 150 mg IV once
   • 5-HT3 RA (choose one):
     ▶ Palonosetron 0.25 mg IV once
     ▶ Granisetron 10 mg SQ once
   • Dexamethasone 12 mg PO/IV once

See Breakthrough Treatment (AE-10)

**DAY 2, 3, 4:**

A: • Aprepitant 80 mg PO daily on days 2, 3
   • Dexamethasone 8 mg PO/IV daily on days 2, 3, 4

B: • Dexamethasone 8 mg PO/IV daily on day 2, then
dexamethasone 8 mg PO/IV twice daily on days
3, 4

C: • Dexamethasone 8 mg PO/IV twice daily on days
2, 3, 4

D: • Dexamethasone 8 mg PO daily on days 2, 3, 4

E: • Olanzapine 10 mg PO daily on days 2, 3, 4

F: • Aprepitant 80 mg PO daily on days 2, 3 (if
   • Dexamethasone 8 mg PO/IV daily on days 2, 3, 4
   • Olanzapine 10 mg PO daily on days 2, 3, 4

**Frequency of chemotherapy-induced emesis depends on 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. 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. The Grunberg classification is updated each...
year by the NCCN Antiemesis Panel with recently introduced drugs.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.
Footnotes for pages AE-5 and AE-6

1See Emetogenic Potential of Intravenous Antineoplastic Agents.
2Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
3See Principles of Managing Multidrug Emetogenic Chemotherapy Regimens (AE-A).
4With 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 Emetesis Control for the Cancer Patient (AE-1).
5See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
6GRanisetron 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.
7If 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).
8Dexamethasone 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.
9Raplopart is an extended half-life and should not be administered at less than 2-week intervals.
11Available as a combination product only.
16Consider 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 Emetics (AE-G).
17Some 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).
18As 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).
19When used in combination with an NK-1 antagonist, there is no preferred 5-HT3 RA. See Principles of Managing Multidrug Emetogenic Chemotherapy Regimens (AE-A).
21No further therapy required if palonosetron, granisetron extended-release injection, or granisetron transdermal patch given on day 1.

Prevention of Acute and Delayed Emetics

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 maximize anxiety and dyspepsia/relux-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, rolipitant). 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/relux-related symptoms, respectively.6 Adding an NK1 RA to a regimen with dexamethasone and one of the 5-HT3 antagonist options is recommended for select patients with...
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 METOTIC CHEMOTHERAPY REGIMENS

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.5
- 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.


#{4} 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...
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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.

References


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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