NCCN Guidelines Version 2.2015 Panel Members

Antiemesis

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NCCN Guidelines Panel Disclosures

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**Clinical Trials:** NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html.

**NCCN Categories of Evidence and Consensus:** All recommendations are Category 2A unless otherwise specified. See NCCN Categories of Evidence and Consensus.

<table>
<thead>
<tr>
<th>NCCN Antiemesis Panel Members</th>
<th>Guidelines Updates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principles of Emesis Control for the Cancer Patient (AE-1)</td>
<td></td>
</tr>
</tbody>
</table>

**CHEMOTHERAPY-INDUCED EMESIS:**

- High Emetic Risk Intravenous Chemotherapy - Acute and Delayed Emesis Prevention (AE-2)
- Moderate Emetic Risk Intravenous Chemotherapy - Emesis Prevention (AE-3)
- Low and Minimal Emetic Risk Intravenous Chemotherapy - Emesis Prevention (AE-4)
- Oral Chemotherapy - Emesis Prevention (AE-5)
- Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-6)
- Emetogenic Potential of Intravenous Antineoplastic Agents (AE-7)
- Emetogenic Potential of Oral Antineoplastic Agents (AE-9)
- Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A)
- Principles for Managing Breakthrough Emesis (AE-B)

**RADIATION-INDUCED EMESIS:**

- Radiation-Induced Emesis Prevention/Treatment (AE-10)

**ANTICIPATORY EMESIS:**

- Anticipatory Emesis Prevention/Treatment (AE-11)
Updates in Version 2.2015 of the NCCN Guidelines for Antiemesis from Version 1.2015 include:

**AE-2**
- High emetic risk intravenous chemotherapy - acute and delayed emesis prevention:
  - Day 1 added:
    - ◊ Rolapitant 180 mg PO once (category 1).
    - ◊ If rolapitant given: Dexamethasone 20 mg PO/IV once
  - Day 2, 3, 4 added:
    - ◊ If rolapitant is given on day 1, dexamethasone 8 mg PO/IV twice daily days 2, 3, 4

**AE-3**
- Moderate emetic risk intravenous chemotherapy - emesis prevention:
  - Day 1 added:
    - ◊ Rolapitant 180 mg PO once (category 1).
  - Day 2 and 3 added:
    - ◊ Rolapitant used day 1: ± dexamethasone 8 mg PO/IV daily on days 2, 3
Updates in Version 1.2015 of the NCCN Guidelines for Antiemesis from Version 2.2014 include:

**AE-2**
- The information on this page has been reformatted for clarity and consistency.
- High emetic risk intravenous chemotherapy - acute and delayed emesis prevention:
  - Removed “Preferred” from palonosetron 0.25 mg IV day 1
  - Day 1, added the following netupitant-containing regimen:
    - Netupitant 300 mg/palonosetron 0.5 mg PO once
    - Dexamethasone 12 mg PO day 1
  - Changed lorazepam from every 4-6 h to every 6 h. (also applies to AE-3 and AE-6)
  - Added a new footnote, “If neither aprepitant nor fosaprepitant are given on day 1, then dexamethasone 20 mg PO/IV once on day 1, followed by 8 mg BID PO/IV on days 2, 3, 4.

**AE-3**
- Moderate emetic risk intravenous chemotherapy - emesis prevention:
  - Day 1, added the following netupitant-containing regimen:
    - Netupitant 300 mg/palonosetron 0.5 mg PO once
    - Dexamethasone 12 mg PO day 1
  - Changed olanzapine from days 2, 3, 4 to days 2, 3.
  - Modified footnote “m”: As per high emetic risk prevention, aprepitant or fosaprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients with additional risk factors or who have failed previous therapy with a steroid + 5HT3 antagonist alone (See AE-2).
  - Added a new footnote, “No further therapy required if palonosetron or granisetron patch given on day 1.”

**AE-5**
- Oral chemotherapy - emesis prevention:
  - High to moderate emetic risk, clarified ondansetron 16-24 mg (total dose) PO daily.
  - Low to minimal emetic risk, clarified
    - Dolasetron 100 mg PO daily added “PRN”
    - Granisetron 1-2 mg (total dose) PO added “PRN”
    - Ondansetron 8-16 mg (total dose) PO daily added “PRN”

**AE-8**
- Emetogenic potential of Intravenous antineoplastic agents
  - Added the following agents to low emetic risk:
    - Belinostat
    - Blinatumomab
  - Added the following agents to minimal emetic risk:
    - Nivolumab
    - Obinutuzumab
    - Pembrolizumab
    - Ramucirumab
    - Siltuximab

**AE-9**
- Emetogenic potential of oral antineoplastic agents
  - Added the following agents to moderate to high emetic risk:
    - Ceritinib
    - Lenvatinib
    - Olaparib
    - Panobinostat
  - Added the following agents to minimal to low emetic risk:
    - Afatinib
    - Ibrutinib
    - Idelalisib
    - Palbociclib

**AE-11**
- Anticipatory emesis prevention treatment, modified the following recommendation
  - “Consider anxiolytic therapy:
    - For example, alprazolam 0.5-1 mg or lorazepam 0.5-2 mg PO \( \text{TID} \) beginning on the night before treatment and then repeated the next day 1-2 hours before chemotherapy begins

**AE-A**
- Principles of managing multiday emetogenic chemotherapy regimens:
  - Included “transdermal” as an optional route of administration for antiemetic regimens.
PRINCIPLES OF EMESIS CONTROL FOR THE CANCER PATIENT

- Prevention of nausea/vomiting is the goal.
  - The risk of nausea/vomiting for persons receiving chemotherapy of high and moderate emetic risk lasts for at least 3 days for high and 2 days for moderate after the last dose of chemotherapy. Patients need to be protected throughout the full period of risk.
- Oral and intravenous 5-HT3 antagonists have equivalent efficacy when used at the appropriate doses.
- Consider the toxicity of the specific antiemetic(s).
- Choice of antiemetic(s) used should be based on the emetic risk of the therapy, prior experience with antiemetics, and patient factors.
- There are other potential causes of emesis in cancer patients.
  These may include:
  - Partial or complete bowel obstruction
  - Vestibular dysfunction
  - Brain metastases
  - Electrolyte imbalance: hypercalcemia, hyperglycemia, or hyponatremia
  - Uremia
  - Concomitant drug treatments, including opiates
  - Gastroparesis: tumor or chemotherapy (eg, vincristine) induced or other causes (eg, diabetes)
  - Psychophysiologic:
    - Anxiety
    - Anticipatory nausea/vomiting
- For use of antiemetics for nausea/vomiting that are not related to radiation and/or chemotherapy, see NCCN Guidelines for Palliative Care.
- For multi-drug regimens, select antiemetic therapy based on the drug with the highest emetic risk. See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-7).
- Consider using an H2 blocker or proton pump inhibitor to prevent dyspepsia, which can mimic nausea.
- Lifestyle measures may help to alleviate nausea/vomiting, such as eating small frequent meals, choosing healthful foods, controlling the amount of food consumed, and eating food at room temperature. A dietary consult may also be useful. See NCI's “Eating Hints: Before, During, and After Cancer Treatment.” (http://www.cancer.gov/cancertopics/coping/eatinghints/page2#4)
### HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION<sup>a,b</sup>

**DAY 1:** Select option A, B, or C (order does not imply preference)

<table>
<thead>
<tr>
<th>A: Aprepitant- or rolapitant-containing regimen:&lt;sup&gt;d&lt;/sup&gt; select one agent from each of the following groups (category 1):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neurokinin-1 (NK1) antagonist:</td>
</tr>
<tr>
<td>‣ Aprepitant 125 mg PO once</td>
</tr>
<tr>
<td>‣ Fosaprepitant 150 mg IV once</td>
</tr>
<tr>
<td>‣ Rolapitant 180 mg PO once&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>• Serotonin (5-HT3) antagonist:&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>‣ Dolasetron 100 mg PO once</td>
</tr>
<tr>
<td>‣ Granisetron 2 mg PO once, or 1 mg PO BID, 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</td>
</tr>
<tr>
<td>‣ Palonosetron 0.25 mg IV once&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>• Steroid:&lt;sup&gt;i,j&lt;/sup&gt;</td>
</tr>
<tr>
<td>‣ If aprepitant/fosaprepitant given: Dexamethasone 12 mg PO/IV once</td>
</tr>
<tr>
<td>‣ If rolapitant given: Dexamethasone 20 mg PO/IV once</td>
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</tbody>
</table>

**Start before chemotherapy:<sup>c</sup>**

<table>
<thead>
<tr>
<th>A:&lt;sup&gt;k&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If aprepitant PO given day 1, aprepitant 80 mg PO daily on days 2, 3</td>
</tr>
<tr>
<td>• If fosaprepitant IV given on day 1, no further aprepitant is needed on days 2, 3</td>
</tr>
</tbody>
</table>

AND

<table>
<thead>
<tr>
<th>B: Cetirizine-containing regimen:&lt;sup&gt;d,k&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Netupitant 300 mg/palonosetron 0.5 mg PO once</td>
</tr>
<tr>
<td>• Dexamethasone 12 mg PO/IV once</td>
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</table>

<table>
<thead>
<tr>
<th>B:</th>
</tr>
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<tbody>
<tr>
<td>• Dexamethasone 8 mg PO/IV daily on days 2, 3, 4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>C: Olanzapine-containing regimen:&lt;sup&gt;d,l&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Olanzapine 10 mg PO once</td>
</tr>
<tr>
<td>• Palonosetron 0.25 mg IV once</td>
</tr>
<tr>
<td>• Dexamethasone 20 mg IV once</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Olanzapine 10 mg PO daily on days 2, 3, 4</td>
</tr>
</tbody>
</table>

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<sup>a</sup>See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-7).

<sup>b</sup>Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.

<sup>c</sup>See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).

<sup>d</sup>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).


<sup>f</sup>Serotonin (5-HT3) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.

<sup>g</sup>The FDA recommends a maximum of 16 mg for a single dose of IV ondansetron.

<sup>h</sup>Data with palonosetron are based on randomized studies in combination with steroids only.

<sup>i</sup>Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.

<sup>j</sup>If neither aprepitant nor fosaprepitant are given on day 1, then dexamethasone 20 mg PO/IV once on day 1, followed by 8 mg BID PO/IV on days 2, 3, 4.


<sup>m</sup>Some NCCN Member Institutions use a 5-HT3 antagonist (unless palonosetron or granisetron patch given on day 1) on days 2, 3, 4 in addition to steroid ± aprepitant.

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**Note:** All recommendations are category 2A unless otherwise indicated.

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

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<sup>See Breakthrough Treatment (AE-6)</sup>
## MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION\(^a,b\)

### DAY 1: Select option A, B, or C (order does not imply preference)

**Start before chemotherapy:**\(^c\)

<table>
<thead>
<tr>
<th>Option</th>
<th>Treatment Details</th>
</tr>
</thead>
</table>
| A:     | Serotonin (5-HT3) antagonist + steroid (category 1) ± NK-1 antagonist\(^d\)  
   • Serotonin (5-HT3) antagonist (Select one):\(^f\)  
      ▶ Dolasetron 100 mg PO once  
      ▶ Granisetron 2 mg PO once, or 1 mg PO BID, 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\(^g\)  
      ▶ Palonosetron 0.25 mg IV once\(^h\) (preferred)  
   AND  
   • Steroid:\(^i\)  
      ▶ Dexamethasone 12 mg PO/IV once  
WITH/WITHOUT  
   • Neurokinin-1 (NK1) antagonist:\(^n\)  
      ▶ Aprepitant 125 mg PO once  
      ▶ Fosaprepitant 150 mg IV once  
      ▶ Rolapitant 180 mg PO once (category 1)\(^o\) |
| B:     | Netupitant-containing regimen:\(^d,p\)  
   ▶ Netupitant 300 mg/palonosetron 0.5 mg PO once  
   ▶ Dexamethasone 12 mg PO/IV once |
| C:     | Olanzapine-containing regimen:\(^d,l\)  
   ▶ Olanzapine 10 mg PO once  
   ▶ Palonosetron 0.25 mg IV once  
   ▶ Dexamethasone 20 mg IV once |

### DAYS 2 and 3:

<table>
<thead>
<tr>
<th>Option</th>
<th>Treatment Details</th>
</tr>
</thead>
</table>
| A:     | Serotonin (5-HT3) antagonist monotherapy\(^d\) (Select one):\(^f\)  
   ▶ Dolasetron 100 mg PO daily on days 2, 3  
   ▶ Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV daily on days 2, 3  
   ▶ Ondansetron 8 mg PO/IV daily or 8-16 mg IV daily on days 2, 3\(^g\)  
   OR  
   • Steroid monotherapy:\(^i\)  
      ▶ Dexamethasone 8 mg PO/IV daily on days 2, 3  
   OR  
   • NK1 antagonist ± steroid:\(^i,j,n\)  
      ▶ Aprepitant used day 1: Aprepitant 80 mg PO daily on days 2, 3 ± dexamethasone 8 mg PO/IV daily on days 2, 3  
      ▶ Fosaprepitant used day 1: ± dexamethasone 8 mg PO or IV daily on days 2, 3  
      ▶ Rolapitant used day 1: ± dexamethasone 8 mg PO/IV daily on days 2, 3 |
| B:     | ± Dexamethasone 8 mg PO/IV daily on days 2, 3 |
| C:     | Olanzapine 10 mg PO daily days 2, 3 |

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\(^a\)See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-7).  
\(^b\)Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.  
\(^c\)See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).  
\(^d\)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).  
\(^e\)Serotonin (5-HT3) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.  
\(^f\)Data with granisetron are based on randomized studies in combination with steroids only.  
\(^g\)Data with palonosetron are based on randomized studies in combination with steroids only.  
\(^h\)Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.  
\(^i\)If neither aprepitant nor fosaprepitant are given on day 1, dexamethasone 20 mg PO/IV once on day 1, followed by 8 mg PO/IV on days 2, 3, 4.  
\(^j\)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).  
\(^k\)Serotonin (5-HT3) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.  
\(^l\)The FDA recommends a maximum of 16 mg for a single dose of IV ondansetron.  
\(^m\)Data with palonosetron are based on randomized studies in combination with steroids only.  
\(^n\)Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.
LOW AND MINIMAL EMETIC RISK INTRAVENOUS CHEMOTHERAPY - EMESIS PREVENTION

- **Low**
  - Start before chemotherapy (order does not imply preference)\(^b,c,d\)
  - Repeat daily for multiday doses of chemotherapy
    - Dexamethasone 12 mg PO/IV daily\(^i\)
    - or
    - Metoclopramide 10-40 mg PO/IV and then either every 4 or every 6 h PRN\(^s\)
    - or
    - Prochlorperazine 10 mg PO/IV and then every 6 h PRN (maximum 40 mg/day)\(^s\)
    - or
    - Serotonin (5-HT3) antagonist\(^f\) (select one):
      - Dolasetron 100 mg PO daily
      - Granisetron 1-2 mg (total dose) PO daily
      - Ondansetron 8-16 mg PO daily

- **Minimal**
  - No routine prophylaxis

\(^b\)Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
\(^c\)See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
\(^d\)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).
\(^f\)Serotonin (5-HT3) antagonist may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.
\(^s\)Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.
\(^i\)See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-8).
\(^s\)Monitor for dystonic reactions; use diphenhydramine 25-50 mg PO or IV either every 4 or every 6 h for dystonic reactions. If allergic to diphenhydramine, use benztropine at 1-2 mg IV or IM x 1 dose, followed by oral dose of 1-2 mg daily or BID if needed to control the reaction.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ORAL CHEMOTHERAPY - EMESIS PREVENTION

High to moderate emetic risk
- Start before chemotherapy and continue daily (order does not imply preference)
  - Metoclopramide 10-40 mg PO and then every 4 or every 6 h PRN
  - Prochlorperazine 10 mg PO and then every 6 h PRN (maximum 40 mg/day)
  - Haloperidol 1-2 mg PO every 4 or every 6 h PRN
  - Serotonin (5-HT3) antagonist (Choose one):
    ◊ Dolasetron 100 mg PO daily
    ◊ Granisetron 1-2 mg (total dose) PO daily
    ◊ Ondansetron 16-24 mg (total dose) PO daily

Low to minimal emetic risk
- PRN recommended
- Nausea/vomiting
- Start before chemotherapy and continue daily (order does not imply preference)
  - Metoclopramide 10-40 mg PO and then every 4 or every 6 h PRN
  - Prochlorperazine 10 mg PO and then every 6 h PRN (maximum 40 mg/day)
  - Haloperidol 1-2 mg PO every 4 or every 6 h PRN
  - Serotonin (5-HT3) antagonist (Choose one):
    ◊ Dolasetron 100 mg PO daily PRN
    ◊ Granisetron 1-2 mg (total dose) PO daily PRN
    ◊ Ondansetron 8-16 mg (total dose) PO daily PRN

Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-6)

Note: All recommendations are category 2A unless otherwise indicated.
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Supplemental information:
- Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
- See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
- 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).
- Serotonin (5-HT3) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.

AE-5
**NCCN Guidelines Version 2.2015**

**Antiemesis**

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**BREAKTHROUGH TREATMENT FOR CHEMOTHERAPY-INDUCED NAUSEA/VOMITING**

<table>
<thead>
<tr>
<th>Any nausea/vomiting</th>
<th>The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen. (order does not imply preference)</th>
</tr>
</thead>
</table>
|                     | • Atypical antipsychotic:  
|                     |   ▶ Olanzapine 10 mg PO daily for 3 days\(^w\)  
|                     |   ▶ Benzodiazepine:  
|                     |     ▶ Lorazepam 0.5-2 mg PO/SL/IV every 6 h  
|                     |   ▶ Cannabinoid:  
|                     |     ▶ Dronabinol 5-10 mg PO every 3-6 h  
|                     |     ▶ Nabilone 1-2 mg PO BID  
|                     |   ▶ Other:  
|                     |     ▶ Haloperidol 0.5-2 mg PO/IV every 4-6 h\(^s\)  
|                     |     ▶ Metoclopramide 10-40 mg PO/IV every 4-6 h\(^s\)  
|                     |     ▶ Scopolamine transdermal patch 1 patch every 72 h  
|                     |   ▶ Phenothiazine:  
|                     |     ▶ Prochlorperazine 25 mg supp pr every 12 h or 10 mg PO/IV every 6 h\(^s\)  
|                     |     ▶ Promethazine 25 mg supp pr every 6 h or 12.5-25 mg PO/IV (central line only) every 4-6 h\(^s\)  
|                     |   ▶ Serotonin 5-HT3 antagonists:\(^f\)  
|                     |     ▶ Dolasetron 100 mg PO daily  
|                     |     ▶ Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV daily  
|                     |     ▶ Ondansetron 16 mg PO/IV daily  
|                     |   ▶ Steroid:  
|                     |     ▶ Dexamethasone 12 mg PO/IV daily |

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**RESPONSE TO BREAKTHROUGH ANTIEMETIC TREATMENT**

- Nausea and vomiting controlled: Continue breakthrough medications, on a schedule, not PRN
- Nausea and/or vomiting uncontrolled: Re-evaluate and consider dose adjustments and/or switching to a different therapy

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**SUBSEQUENT CYCLES**

- Consider changing antiemetic therapy to higher level primary treatment for next cycle

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\(^c\)See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).

\(^f\)Serotonin (5-HT3) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.

\(^s\)Monitor for dystonic reactions; use diphenhydramine 25-50 mg PO or IV either every 4 or every 6 h for dystonic reactions. If allergic to diphenhydramine use benztpine at 1-2 mg IV or IM x 1 dose, followed by oral dose of 1-2 mg daily or BID if needed to control the reaction.


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### EMETOCENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS

<table>
<thead>
<tr>
<th>High emetic risk ( &gt;90% frequency of emesis)</th>
<th>Moderate emetic risk (30%-90% frequency of emesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide</td>
<td>• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide</td>
</tr>
<tr>
<td>• Carmustine &gt;250 mg/m²</td>
<td>• Carmustine &gt;250 mg/m²</td>
</tr>
<tr>
<td>• Cisplatin</td>
<td>• Cisplatin</td>
</tr>
<tr>
<td>• Cyclophosphamide &gt;1,500 mg/m²</td>
<td>• Cyclophosphamide ≤1500 mg/m²</td>
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<tr>
<td>• Dacarbazine</td>
<td>• Dacarbazine</td>
</tr>
<tr>
<td>• Doxorubicin ≥60 mg/m²</td>
<td>• Doxorubicin ≥60 mg/m²</td>
</tr>
<tr>
<td>• Epirubicin &gt;90 mg/m²</td>
<td>• Epirubicin &gt;90 mg/m²</td>
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<tr>
<td>• Ifosfamide ≥2 g/m² per dose</td>
<td>• Ifosfamide ≥2 g/m² per dose</td>
</tr>
<tr>
<td>• Mechlorethamine</td>
<td>• Mechlorethamine</td>
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<tr>
<td>• Streptozocin</td>
<td>• Streptozocin</td>
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<tr>
<td>• Carmustine ≤250 mg/m²</td>
<td>• Carmustine ≤250 mg/m²</td>
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<tr>
<td>• Cyclophosphamide ≤1500 mg/m²</td>
<td>• Dactinomycinaa</td>
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<td>• Dactinomycinaa</td>
<td>• Daunorubicinaa</td>
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<tr>
<td>• Doxorubicinaa ≤60 mg/m²</td>
<td>• Doxorubicinaa ≤60 mg/m²</td>
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<tr>
<td>• Epirubicinaa ≤90 mg/m²</td>
<td>• Epirubicinaa ≤90 mg/m²</td>
</tr>
<tr>
<td>• Idarubicin</td>
<td>• Idarubicin</td>
</tr>
</tbody>
</table>

Adapted with permission from:

*Potential drug interactions between antineoplastic agents / antiemetic therapies and various other drugs should always be considered.

YProportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.

ZContinuous infusion may make an agent less emetogenic.

These agents may be highly emetogenic in certain patients.
### EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>AGENT</th>
</tr>
</thead>
</table>
| Low emetic risk (10%-30% frequency of emesis) | • Ado-trastuzumab emtansine  
• Amifostine ≤300 mg/m²  
• Aldesleukin ≤12 million IU/m²  
• Belinostat  
• Blinatumomab  
• Brentuximab vedotin  
• Cabazitaxel  
• Carfilzomib  
• Cytarabine (low dose) 100-200 mg/m²  
• Docetaxel  
• Doxorubicin (liposomal) |
|                             | • Eribulin  
• Etoposide  
• 5-FU  
• Floxuridine  
• Gemcitabine  
• Interferon alfa >5 <10 million international units/m²  
• Ixabepolone  
• Methotrexate >50 mg/m² <250 mg/m²  
• Mitomycin |
|                             | • Mitoxantrone  
• Omacetaxine  
• Paclitaxel  
• Paclitaxel-albumin  
• Pemetrexed  
• Pentostatin  
• Pralatrexate  
• Romidepsin  
• Thiopeta  
• Topotecan  
• Ziv-aflibercept |
| Minimal emetic risk (<10% frequency of emesis) | • Alemtuzumab  
• Asparaginase  
• Bevacizumab  
• Bleomycin  
• Bortezomib  
• Cetuximab  
• Cladribine (2-chlorodeoxyadenosine)  
• Cytarabine <100 mg/m²  
• Decitabine  
• Denileukin difftiix  
• Dexrazoxane |
|                             | • Fludarabine  
• Interferon alpha ≤5 million IU/m²  
• Ipilimumab  
• Methotrexate ≤50 mg/m²  
• Nalarabine  
• Nivolumab  
• Obinutuzumab  
• Ofatumumab  
• Panitumumab  
• Pegasparagase  
• Peginterferon  
• Pembrolizumab |
|                             | • Pertuzumab  
• Ramucirumab  
• Rituximab  
• Siltuximab  
• Temsirolimus  
• Trastuzumab  
• Valrubicin  
• Vinblastine  
• Vincristine  
• Vincristine (liposomal)  
• Vinorelbine |

Adapted with permission from:

*Potential drug interactions between antineoplastic agents / antiemetic therapies and various other drugs should always be considered.

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

**Note:** All recommendations are category 2A unless otherwise indicated.

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

**High Emetic Risk (See AE-7)**

**Moderate Emetic Risk (See AE-7)**

**Oral Chemotherapy (See AE-9)**
# NCCN Guidelines Version 2.2015
## Antiemesis

### EMETOGENIC POTENTIAL OF ORAL ANTI NEOPLASTIC AGENTS

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>AGENT</th>
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<tbody>
<tr>
<td><strong>Moderate to high</strong></td>
<td>• Alretamine</td>
</tr>
<tr>
<td></td>
<td>• Busulfan (≥ 24 mg/day)</td>
</tr>
<tr>
<td></td>
<td>• Ceritinib</td>
</tr>
<tr>
<td></td>
<td>• Crizotinib</td>
</tr>
<tr>
<td></td>
<td>• Cyclophosphamide (≥ 100 mg/m²/day)</td>
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<tr>
<td></td>
<td>• Estramustine</td>
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<td></td>
<td>• Etoposide</td>
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<td></td>
<td>• Lenvatinib</td>
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<td></td>
<td>• Lomustine (single day)</td>
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<td></td>
<td>• Mitotane</td>
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<td></td>
<td>• Olaparib</td>
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<td>• Panobinostat</td>
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<tr>
<td></td>
<td>• Procarbazine</td>
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<tr>
<td></td>
<td>• Temozolomide (&gt; 75 mg/m²/day)</td>
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<tr>
<td></td>
<td>• Vismodegib</td>
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<tr>
<td><strong>Minimal to low</strong></td>
<td>• Afinatin</td>
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<td>• Axitinin</td>
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<td>• Bexarotene</td>
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<td></td>
<td>• Bosutinib</td>
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<td></td>
<td>• Busulfan (&lt; 4 mg/day)</td>
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<td></td>
<td>• Cabozantinib</td>
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<td></td>
<td>• Capecitabine</td>
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<td></td>
<td>• Chlorambucil</td>
</tr>
<tr>
<td></td>
<td>• Cyclophosphamide (&lt;100 mg/m²/day)</td>
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<td></td>
<td>• Dasatinib</td>
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<tr>
<td></td>
<td>• Dabrafenib</td>
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<td>• Erlotinib</td>
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<td>• Everolimus</td>
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<td>• Fludarabine</td>
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<td>• Gefitinib</td>
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<td>• Hydroxyurea</td>
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<td></td>
<td>• Ibrutinib</td>
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<td>• Idelalisib</td>
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<td></td>
<td>• Imatinib</td>
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<td></td>
<td>• Lapatinib</td>
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<td>• Lenalidomide</td>
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<td>• Melphalan</td>
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<td>• Mercaptopurine</td>
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<td></td>
<td>• Methotrexate</td>
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<td>• Nilotinib</td>
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<td>• Palbociclib</td>
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<td>• Pazopanib</td>
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<td>• Pomalidomide</td>
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<td>• Ponatinib</td>
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<td>• Regorafenib</td>
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<td>• Ruxolitinib</td>
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<td></td>
<td>• Sorafenib</td>
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<tr>
<td></td>
<td>• Sunitinib</td>
</tr>
<tr>
<td></td>
<td>• Temozolomide (≤ 75 mg/m²/day)</td>
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<tr>
<td></td>
<td>• Thalidomide</td>
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<tr>
<td></td>
<td>• Thioguanine</td>
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<tr>
<td></td>
<td>• Topotecan</td>
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<td>• Trametinib</td>
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<td>• Tretinoin</td>
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<td></td>
<td>• Vandetanib</td>
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<tr>
<td></td>
<td>• Vemurafenib</td>
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<td>• Vorinost</td>
</tr>
</tbody>
</table>

Adapted with permission from:

**High Emetic Risk (See AE-7)**

**Moderate Emetic Risk (See AE-7)**

**Low Emetic Risk (See AE-8)**

**Minimal Emetic Risk (See AE-8)**

*Potential drug interactions between antineoplastic agents / antiemetic therapies and various other drugs should always be considered.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
RADIATION-INDUCED EMESIS PREVENTION/TREATMENT

<table>
<thead>
<tr>
<th>EMETOGENIC POTENTIAL</th>
<th>TYPE OF RADIATION THERAPY</th>
<th>BREAKTHROUGH TREATMENT</th>
</tr>
</thead>
</table>
| Radiation therapy (RT) - upper abdomenlocalized sites | Start pretreatment for each day of RT treatment (order does not imply preference): †
- Granisetron 2 mg PO daily
- Ondansetron 8 mg PO BID
- ± Dexamethasone 4 mg PO daily | See Breakthrough Treatment (AE-6) |
| Total body irradiation (TBI) | Start pretreatment for each day of RT treatment (order does not imply preference): †
- Granisetron 2 mg PO daily
- Ondansetron 8 mg PO BID-TID
- ± Dexamethasone 4 mg PO daily |
| Chemotherapy and RT (including TBI) | See emesis prevention for chemotherapy-induced nausea/vomiting (High AE-2, Moderate AE-3, Low AE-4, and Oral AE-5) |

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

† Serotonin (5-HT3) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.
### ANTICIPATORY EMESIS PREVENTION/TREATMENT

**Prevention is key:**
- Use optimal antiemetic therapy during every cycle of treatment

**Behavioral therapy:**
- Relaxation/systematic desensitization
- Hypnosis/guided imagery
- Music therapy

**Acupuncture/acupressure**

**Consider anxiolytic therapy:**
- For example, alprazolam 0.5-1 mg or lorazepam 0.5-2 mg PO beginning on the night before treatment and then repeated the next day 1-2 hours before chemotherapy begins

See Primary and Breakthrough Treatments for Chemotherapy-Induced Nausea/Vomiting (Antiemesis TOC)
PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS

Summary:

- Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea/vomiting based on the emetogenic potential of the individual chemotherapy agents administered on any given day and their sequence. It is therefore difficult to recommend a specific antiemetic regimen for each day, especially since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy.
- After chemotherapy administration concludes, the period of risk for delayed emesis also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen.
- Practical issues also need to be considered when designing the antiemetic regimen, taking into account the administration setting (e.g., inpatient versus outpatient), preferred route of administration (IV, oral, or transdermal), duration of action of the serotonin antagonist and appropriate associated dosing intervals, tolerability of daily antiemetics (e.g., corticosteroids), and adherence/compliance issues.

General Principles:

- Corticosteroids:
  - Dexamethasone should be administered once daily (either orally or intravenously) for moderately or highly emetogenic chemotherapy and for 2 to 3 days after chemotherapy for regimens that are likely to cause significant delayed emesis.
  - Dexamethasone dose may be modified or omitted when the chemotherapy regimen already includes a corticosteroid.
  - Side effects associated with prolonged dexamethasone administration should be carefully considered.

- Serotonin Antagonists:
  - A serotonin antagonist 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 serotonin antagonist depends on the agent chosen and its mode of administration (IV, oral or 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 serotonin antagonist.
    - Repeat dosing of palonosetron 0.25 mg IV is likely to be safe, based on available evidence.
    - In terms of efficacy, the need for repeat dosing with palonosetron, either daily or less frequently, in the setting of multiday chemotherapy is not yet known.

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.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS

- NK1 Antagonists:
  - Aprepitant or fosaprepitant may be used for multiday chemotherapy regimens likely to be highly emetogenic and associated with significant risk for delayed nausea and emesis.
  - Category 1 evidence is available for single-day chemotherapy regimens only with aprepitant administered orally (as a 3-day regimen) in combination with a serotonin antagonist and corticosteroid (as noted on AE-2 and AE-3). Alternatively, for highly emetogenic regimens, fosaprepitant 150 mg IV with recommended dexamethasone dosing may be given on day 1 with no need for oral aprepitant on days 2 and 3.
  - If the oral aprepitant regimen is chosen, phase II data exists to support administration of aprepitant on days 4 and 5 after multiday chemotherapy. It is not yet known if dosing aprepitant after day 3 improves control of nausea or emesis in this clinical setting.
  - If the intravenous fosaprepitant regimen is chosen, pharmacokinetic data suggest that the single 150 mg intravenous dose provides antiemetic coverage for a similar period (up to 72 hours post chemotherapy). Studies investigating repeat dosing of intravenous fosaprepitant are not yet available.
  - 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 antagonist (days 1-5) and dexamethasone (20 mg days 1, 2) in patients with germ line cancers treated with a 5-day cisplatin-based chemotherapy. Reference: 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.

1The 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.
PRINCIPLES FOR MANAGING BREAKTHROUGH EMESIS

• Breakthrough emesis presents a difficult situation, as correction of refractory ongoing nausea/vomiting is often challenging to reverse. It is generally far easier to prevent nausea/vomiting than it is to treat it.
• The general principle of breakthrough treatment is to give an additional agent from a different drug class. No one drug class has been shown to be superior for the management of breakthrough emesis, and the choice of agent should be based on assessment of the current prevention strategies used. Some patients may require several agents utilizing differing mechanisms of action.
• One should strongly consider routine, around-the-clock administration rather than PRN dosing.
• The PO route is not likely to be feasible due to ongoing vomiting; therefore, rectal or IV therapy is often required.
• Multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary. Dopamine antagonists (eg, metoclopramide, haloperidol), corticosteroids, and agents such as lorazepam may be required.
• Ensure adequate hydration or fluid repletion, simultaneously checking and correcting any possible electrolyte abnormalities.
• Prior to administering the next cycle of chemotherapy the patient should be reassessed, with attention given to various possible non-chemotherapy-related reasons for breakthrough emesis with the current cycle:
  › Brain metastases
  › Electrolyte abnormalities
  › Tumor infiltration of the bowel or other gastrointestinal abnormality
  › Other comorbidities
• Prior to the next cycle of chemotherapy, reassess both the day 1 and post-chemotherapy antiemetic regimen, which did not protect the patient during the present cycle, and consider alternatives: (Suggestions are not in order of preference)
  › Add aprepitant if not previously included.
  › Add other concomitant antiemetics, (eg, dopamine antagonists such as metoclopramide or haloperidol).
  › Possibly adjust dose(s), either intensity or frequency, of the 5-HT3 antagonist. Based on the patient’s experiences, the chemotherapy regimen in question may actually be more emetogenic than generally classified (eg, Hesketh method).
  › Possibly switch to a different 5-HT3. Although not necessarily likely to be effective, anecdotal and limited investigational trial data suggest it may sometimes be efficacious.
  › If the goal of chemotherapy is non-curative, consider other appropriate regimens, if any, that might be less emetogenic.
  › It may be beneficial to add an anxiolytic agent in combination with the antiemetic agents.
• Consider antacid therapy if patient has dyspepsia (H2 blocker or proton pump inhibitor).
Discussion
This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/18/14

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.

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This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/18/14.
Overview
Chemotherapy-induced (or radiation-therapy induced) vomiting (emesis) and nausea can significantly affect a patient’s quality of life, leading to poor compliance with further chemotherapy or radiation therapy treatment. In addition, nausea and vomiting can result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of the patient’s performance status and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment.

The incidence and severity of nausea and/or vomiting in patients receiving chemotherapy or radiation therapy (or both) are affected by numerous factors, including: (1) the specific chemotherapeutic agents used; (2) dosage of the agents; (3) schedule and route of administration of the agents; (4) target of the radiation therapy (eg, whole body, upper abdomen); and (5) individual patient variability (eg, age, sex, prior chemotherapy, history of alcohol use).

More than 90% of patients receiving highly emetogenic chemotherapy will have episodes of vomiting. However, only about 30% of these patients will vomit if they receive prophylactic (preventive) antiemetic regimens before treatment. Antiemetic agents can block different neuronal pathways, exert their effects at different points during the course of emesis, or behave synergistically with other antiemetic agents to potentiate an antiemetic effect. When used at a certain concentration, each antiemetic agent predominantly blocks one receptor type. A final common pathway for emesis has yet to be identified. Therefore, no single agent can be expected to provide complete protection from the various emetic phases of chemotherapy.

Pathophysiology of Emesis
Vomiting results from stimulation of a multistep reflex pathway controlled by the brain. Vomiting is triggered by afferent impulses to the vomiting center (located in the medulla) from the chemoreceptor trigger zone, pharynx and gastrointestinal (GI) tract (via vagal afferent fibers), and cerebral cortex. Vomiting occurs when efferent impulses are sent from the vomiting center to the salivation center, abdominal muscles, respiratory center, and cranial nerves.

The chemoreceptor trigger zone, vomiting center, and GI tract have many neurotransmitter receptors. Activation of these receptors by chemotherapeutic agents or their metabolites may be responsible for chemotherapy-induced emesis. The principal neuroreceptors involved in the emetic response are the serotonin (5-hydroxytryptamine [5-HT3]) and dopamine receptors. Other neuroreceptors involved in emesis include acetylcholine, corticosteroid, histamine, cannabinoid, opiate, and neurokinin-1 (NK-1) receptors, which are located in the vomiting and vestibular centers of the brain.

Antiemetic agents can block different neuronal pathways, exert their effects at different points during the course of emesis, or behave synergistically with other antiemetic agents to potentiate an antiemetic effect. When used at a certain concentration, each antiemetic agent predominantly blocks one receptor type. A final common pathway for emesis has yet to be identified. Therefore, no single agent can be expected to provide complete protection from the various emetic phases of chemotherapy.

Nausea
With use of effective antiemetic regimens, patients receiving emetogenic chemotherapy often experience more nausea than...
Antiemesis

Vomiting and nausea are related; however, they may occur via different mechanisms. In general, younger patients are more likely to have nausea than older patients. Younger women receiving chemotherapy for breast cancer are more prone to nausea than other populations. Delayed nausea is more common than acute nausea, is often more severe, and tends to be resistant to treatment.

Types of Nausea and/or Vomiting

Chemotherapy-Induced Nausea and/or Vomiting

Nausea and/or vomiting induced by chemotherapy is commonly classified as acute, delayed, anticipatory, breakthrough, or refractory. Acute-onset nausea and/or vomiting usually occurs within a few minutes to several hours after drug administration and commonly resolves within the first 24 hours. The intensity of acute-onset emesis generally peaks after 5 to 6 hours. The occurrence of acute emesis is influenced by the patient's age and gender (females and younger patients [age < 50 years] are more prone to emesis), environment in which chemotherapy is administered, whether the patient has a history of chronic alcoholism (which decreases the incidence of emesis) or motion sickness, previous episodes of nausea and vomiting, dosage of the emetogenic agent, and efficacy of the antiemetic regimen.

Delayed-onset nausea and/or vomiting develop in patients more than 24 hours after chemotherapy administration. It occurs commonly with the administration of cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin. For cisplatin, emesis reaches its maximal intensity 48 to 72 hours after administration and can last 6 to 7 days.

Anticipatory nausea and/or vomiting occur before patients receive their next chemotherapy treatment. Because it is primarily considered a conditioned response, anticipatory emesis typically occurs after a negative past experience with chemotherapy. The incidence of anticipatory nausea and/or vomiting ranges from 18% to 57%, and nausea is more common than vomiting. Younger patients may be more susceptible to anticipatory nausea and vomiting, because they generally receive more aggressive chemotherapy and, overall, have poorer emesis control than older patients.

Breakthrough emesis refers to vomiting that occurs despite prophylactic treatment and/or requires “rescue” with antiemetic agents. Refractory emesis refers to emesis that occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles.

Radiation-Induced Nausea and/or Vomiting

Patients receiving whole body or upper abdominal radiation therapy have the greatest likelihood of developing nausea and/or vomiting. The GI tract (specifically, the small intestine) contains rapidly dividing cells that are particularly sensitive to radiation. In addition, the potential for nausea and/or vomiting increases with larger daily fractional doses of radiotherapy, larger total doses, and larger amounts of irradiated tissue. Total body irradiation, when given before bone marrow transplantation, commonly induces nausea and/or vomiting.

Emetogenicity of Chemotherapy

The frequency of chemotherapy-induced emesis depends primarily on the emetogenic potential of the specific chemotherapeutic agents used. Several classifications have been developed to define the emetogenicity of chemotherapy; however, none has been universally accepted.

Hesketh and colleagues developed a classification of the acute emetogenicity of anticancer chemotherapeutic agents and developed an algorithm to define the emetogenicity of combination...
chemotherapeutic regimens. The classification was recently updated by Grunberg and colleagues; it divides chemotherapeutic agents into 4 levels according to the percentage of patients not receiving antiemetic prophylaxis who experience acute emesis. This classification, which is updated each year by the NCCN Guidelines Panel with recently introduced drugs, is used in these guidelines. Experts representing the panels of all of the published antiemetic treatment guidelines met to prepare a single consensus document. Although this process is ongoing, the consensus guidelines have been published. The NCCN Guidelines currently outline treatment using 4 categories of emetogenic potential for intravenous (IV) agents, which correspond to the Grunberg classification as follows:

- High emetic risk—90% or more 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—fewer than 10% of patients experience acute emesis.

In addition, the NCCN Guidelines attempt to define antiemetic regimens for particular chemotherapy drugs that cover the entire duration of time a patient is at risk for nausea and vomiting. Panel members were concerned that some patients may not receive adequate prophylaxis for delayed emesis; therefore, the NCCN Guidelines incorporate a dosing schedule that covers both acute and delayed emesis into a single algorithm. The NCCN Guidelines Panel members have also categorized the emetogenic potential of oral antineoplastic agents.

Types of Antiemetic Therapies

In general, to provide maximal protection against chemotherapy-induced emesis, antiemetic therapy should be initiated before chemotherapy. The antiemetic therapy should also be continued for the same length of time as the duration of the emetic activity of the chemotherapeutic agent being used. However, daily use of antiemetics is not recommended for some therapeutic agents that are taken long term (eg, imatinib, erlotinib). Antiemetic agents can be administered by the oral, rectal, IV, intramuscular, or transdermal route. Oral and IV 5-HT3 antagonists have equivalent efficacy when used at the appropriate doses. For patients at risk for CINV or unable to swallow or digest tablets because of emesis, IV antiemetics should be used. In selected patients who are unable to swallow, transdermal antiemetics may be of value. Although studies may show drugs to be equally effective on a population basis, individual patients may respond differently. Therefore, some drug options may be based on a patient’s individual experience.

Serotonin (5-HT3) Receptor Antagonists

The development of the 5-HT3–receptor antagonists (ie, dolasetron mesylate, granisetron, ondansetron, palonosetron) represents a significant advance in antiemetic therapy. All of these agents have been shown to be effective in controlling the acute nausea and/or vomiting associated with cancer chemotherapy.

Palonosetron is a 5-HT3 antagonist with an approximately 100-fold higher binding affinity for the 5-HT3 receptor compared to the other serotonin antagonists (ie, ondansetron, granisetron, and dolasetron). It has a half-life of approximately 40 hours, which is significantly longer than other commercially available 5-HT3 antagonists. Data suggest that palonosetron is associated with prolonged inhibition of the 5-HT3
receptor and thus differs from other 5-HT3 antagonists (eg, ondansetron, granisetron).  

Several large, multicenter, double-blind, randomized phase III trials have demonstrated the superiority of palonosetron compared with other 5-HT3 antagonists in preventing emesis associated with both moderate and high emetic risk chemotherapy regimens, particularly for delayed emesis. In these studies, the primary efficacy end point was complete response (CR), defined as having no emesis and no rescue treatments. A study in patients receiving moderately emetogenic chemotherapy (N=569 evaluable) showed that a single dose of palonosetron (0.25 mg IV) was comparable to a single dose of dolasetron (100 mg IV) for the prevention of acute chemotherapy-induced nausea and emesis (CR rate 63% vs. 53%, respectively); moreover, IV palonosetron was superior to dolasetron in preventing delayed emesis (CR rate 54% vs. 39%; P=0.004). Approximately 60% of patients in the palonosetron arms and 70% in the dolasetron arm had received anthracycline in combination with cyclophosphamide; only 6% and 5% of patients, respectively, received concomitant corticosteroids. In another study in patients receiving moderately emetogenic chemotherapy (N=563 evaluable), a single dose of palonosetron (0.25 mg IV) was found to be superior to a single dose of ondansetron (32 mg IV) in preventing both acute (CR rate 81% vs. 69%; P<0.01) and delayed emesis (CR rate 74% vs. 55%; P<0.01); no concomitant corticosteroids were given in this study. The safety and side-effect profiles of palonosetron were indistinguishable from the control 5-HT3 antagonists (ondansetron and dolasetron) using data submitted to the Food and Drug Administration (FDA). In a phase III randomized trial that compared palonosetron with ondansetron in patients receiving highly emetogenic chemotherapy (N=667), the majority (67%) had received dexamethasone on day 1 of antiemetic therapy. Among this subgroup of patients who received concomitant dexamethasone (n=447), palonosetron (0.25 mg IV) was similar to ondansetron (32 mg IV) in preventing acute emesis (CR rate 65% vs. 56%), but significantly more effective in preventing delayed emesis (CR rate 41% vs. 25%; P=0.021). In a more recent phase III randomized trial that compared palonosetron (at a higher dose of 0.75 mg IV) with granisetron (40 mcg/kg IV), both in combination with dexamethasone, in patients treated with highly emetogenic chemotherapy (N=1114 evaluable), palonosetron showed similar activity to granisetron in preventing acute emesis (CR rate 75% vs. 73%), with superior activity in preventing delayed emesis (CR rate 57% vs. 44.5%; P<0.0001). A 3-drug regimen using this higher dose of palonosetron (0.75 mg IV) in combination with dexamethasone and the neurokinin-1 receptor antagonist aprepitant was recently evaluated in a phase II study in patients with lung cancer undergoing highly emetogenic chemotherapy (see discussion section below, under “Neurokinin-1-Receptor Antagonist”). (Palonosetron (0.25 mg IV) is FDA approved as a single dose on day 1 for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy and for the prevention of acute nausea and vomiting associated with highly emetogenic chemotherapy. It is the preferred 5-HT3 antagonist for the prevention of acute and delayed emesis associated with high emetic risk IV chemotherapy and is also recommended (category 1) for emesis prevention when using moderate emetic risk IV chemotherapy (see Guidelines section on “High Emetic Risk Intravenous Chemotherapy - Acute and Delayed Emesis Prevention” and “Moderate Emetic Risk Intravenous Chemotherapy – Emesis Prevention; also see Discussion section below for “Prevention of Acute and Delayed Emesis”). It should be noted that the recommendation for palonosetron as the preferred 5-HT3 antagonist for antiemetic prophylaxis in the setting of high emetic risk chemotherapy is based upon data from randomized studies.
(discussed earlier) with the 2-drug combination of palonosetron and dexamethasone.

Several recent studies\textsuperscript{55-58} have evaluated the efficacy of a 3-drug combination regimen with palonosetron, dexamethasone and the neurokinin-1 receptor antagonist aprepitant, in the management of emesis in patients receiving moderately emetogenic and highly emetogenic chemotherapies (see discussion section below, under “Neurokinin-1-Receptor Antagonist”).

Intravenous palonosetron is superior to other 5-HT3 antagonists for preventing delayed nausea.\textsuperscript{15,51-54} Repeat dosing of palonosetron in the days after chemotherapy (ie, days 2 or 3) is likely to be safe. However, in the setting of multiple day (ie, multiday) chemotherapy, need for repeat dosing with palonosetron is not yet known (see Guidelines section on “Managing Multiday Emetogenic Chemotherapy Regimens”).

Many of the 5-HT3 antagonists can be delivered orally or intravenously. Although oral palonosetron has been approved by the FDA for moderately emetic risk chemotherapy, it is not available in the United States.\textsuperscript{59} Note that the IV dolasetron is no longer recommended for the prevention of nausea and vomiting because IV dolasetron has been associated with an increased risk for cardiac arrhythmias.\textsuperscript{60} Oral dolasetron is still recommended. Recently, the single IV dose of 32 mg ondansetron was removed from the prescription label based on FDA review of clinical data suggesting prolongation of the QT interval at this dose.\textsuperscript{61} At this time, the FDA recommends a maximum single IV dose of 16 mg with ondansetron; the dose recommendations for oral administration of this agent remains unchanged.\textsuperscript{61}

In addition, the FDA has approved the use of a granisetron transdermal system for chemotherapy-induced nausea and vomiting.\textsuperscript{62} The patch containing 34.3 mg of granisetron is applied approximately 24 to 48 hours before the first dose of chemotherapy; the maximum duration of the patch is 7 days. A phase III randomized study compared the patch to oral granisetron in patients receiving either highly emetogenic or moderately emetogenic chemotherapy. The patch proved non-inferior to repeat dosing of the oral antiemetic granisetron over 3 to 5 days.\textsuperscript{63,64}

Many clinical trials directly comparing ondansetron, granisetron, dolasetron mesylate, and palonosetron have been conducted. These trials have used various doses, routes, and schedules of administration.\textsuperscript{51-54,65-78} A meta-analysis found no difference in efficacy between ondansetron, granisetron, and dolasetron mesylate.\textsuperscript{79} A recent meta-analysis of studies comparing ondansetron with granisetron has also confirmed the similar efficacy of these 5-HT3 antagonists in controlling acute and delayed nausea and vomiting, with similar safety profiles between these agents.\textsuperscript{60} The most recent meta-analysis of randomized controlled trials comparing palonosetron with other available 5-HT3 antagonists demonstrated that palonosetron was significantly more effective in preventing acute and delayed nausea and vomiting for both moderately and highly emetogenic chemotherapy agents.\textsuperscript{81}

The addition of dexamethasone improves the efficacy of the antiemetic regimen containing 5-HT3 antagonists; however, dexamethasone is associated with side effects (such as insomnia). A recent randomized trial suggests that the dose of dexamethasone can be decreased to 8 mg on day 1 and also eliminated on days 2-3 when used with palonosetron for moderately emetic chemotherapy.\textsuperscript{82}

Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis but appear to be less effective for delayed emesis. A meta-analysis of randomized controlled trials found that adding a 5-HT3

\textsuperscript{51-54,65-78}
antagonist to dexamethasone did not improve the antiemetic effect of dexamethasone for preventing delayed emesis. Another study found that 5-HT3 antagonists (except palonosetron, which was not studied) were not more effective than prochlorperazine for preventing delayed emesis. Intravenous palonosetron appears to be effective for preventing both delayed and acute emesis.

5-HT3–receptor antagonists have been associated with an increased risk for developing abnormal electrical activity of the heart (detectable on ECG, including prolongation of electrocardiographic intervals such as PR or QT intervals). Although the ECG changes can be reversible and asymptomatic, abnormal activity can also result in potentially fatal cardiac arrhythmias (including Torsade de Pointes) in some cases. Patients who may be particularly at risk for developing Torsade include those with congenital long QT syndrome or other underlying cardiac diseases, congestive heart failure, bradycardia, those with electrolyte abnormalities (eg, hypokalemia or hypomagnesemia), and those taking other medications that can lead to QT prolongation. It is recommended that these patients undergo routine ECG monitoring during treatment with regimens that include 5-HT3–receptor antagonists.

Neurokinin-1–Receptor Antagonist
Aprepitant selectively blocks the binding of substance P at the NK-1 receptor in the central nervous system. Thus, aprepitant provides a different and complementary mechanism of action to other commercially available antiemetics. Aprepitant has been shown to augment the antiemetic activity of the 5-HT3–receptor antagonists and the corticosteroid dexamethasone to prevent both acute and delayed cisplatin-induced emesis. In a randomized phase III trial comparing a standard antiemetic regimen (ondansetron 32 mg IV and oral dexamethasone) with or without the addition of aprepitant in patients receiving emetogenic chemotherapy with high-dose cisplatin (N=521 evaluable), the addition of aprepitant was significantly more effective than the 2-drug regimen in controlling both acute (CR rate 89% vs. 78%; P<0.001) and delayed emesis (CR rate 75% vs. 56%; P<0.001). Another similarly designed randomized phase III study (N=523 evaluable) also showed a significant benefit of adding aprepitant to ondansetron and dexamethasone compared with the 2-drug regimen alone for controlling both acute (CR rate 83% vs. 68%; P<0.001) and delayed emesis (CR rate 68% vs. 47%; P<0.001). A pooled analysis of data combined from these two phase III trials found that the aprepitant regimen was particularly beneficial in improving CR rates for patients receiving concomitant emetogenic therapy with doxorubicin and/or cyclophosphamide, along with high-dose cisplatin therapy.

A meta-analysis (of 7 randomized controlled trials) in patients receiving highly emetogenic chemotherapy found that NK-1 receptor antagonists used alone or with standard therapy did not significantly increase protection from acute emesis or nausea; however, for delayed emesis and nausea, NK-1 receptor antagonists was associated with significantly increased protection compared with control. A recent meta-analysis (of 17 randomized controlled trials) that evaluated outcomes with standard antiemetic therapy with or without NK-1 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy, the addition of NK-1 receptor antagonists was associated with significantly improved CR (no emetic episodes and no rescue medication) rate compared with standard therapy (72% vs. 54%; P<0.001) during the overall time frame from 0 to 120 hours after starting chemotherapy. The significant increase in CR rate associated with NK-1 receptor antagonists was observed for both the acute and delayed periods. Based on data from 3 trials that reported on infectious
complications, NK-1 receptor antagonists was associated with higher rates of severe infections compared with standard therapy (6% vs. 2%; \( P < 0.001 \)); the risk of febrile neutropenia or other hematologic toxicities were not increased.\(^{92}\)

A randomized phase III trial (N=866) showed that an aprepitant regimen was more effective than a standard regimen for preventing vomiting in patients receiving moderately emetogenic chemotherapy (non-cisplatin based) during 120 hours after initiation of chemotherapy (CR rate 51% vs. 43%, \( P = 0.015 \)); However, approximately 40% of patients (receiving either regimen) still experienced significant nausea.\(^{93}\) The aprepitant regimen included aprepitant, ondansetron, and dexamethasone; the standard regimen included ondansetron and dexamethasone.

A phase II study (N=58) found that combining palonosetron (0.25 mg IV day 1), aprepitant (125 mg day 1; 80 mg days 2, 3), and dexamethasone (12 mg day 1; 8 mg days 2, 3) was effective for preventing both acute and delayed emesis and nausea when using various chemotherapeutic regimens (moderate to moderate-highly emetogenic); 78% of patients had a CR (no emetic episodes and no rescue medication) during the overall time frame, from 0 to 120 hours after initiation of emetogenous therapy.\(^{56}\) A phase II study in patients with breast cancer (N=41) receiving moderately emetogenic chemotherapy also found that a single-day regimen of palonosetron (0.25 mg IV), aprepitant (285 mg oral), and dexamethasone (20 mg) was effective; 76% and 66% of patients had a CR during the acute and delayed phases, respectively.\(^{57}\) A 3-drug antiemetic regimen with palonosetron, dexamethasone and aprepitant has also been investigated in patients undergoing treatment with highly emetogenic chemotherapies. A phase II study in patients receiving highly emetogenic chemotherapy with cisplatin-containing regimens (N=222) showed that the 3-drug combination of palonosetron (0.25 mg IV day 1), aprepitant (125 mg day 1; 80 mg days 2, 3), and dexamethasone (20 mg IV day 1; 4 mg PO days 2, 3) resulted in a CR rate (no emetic episodes and no rescue medication) of 70% during the overall study period (0–120 hours).\(^{58}\) In addition, 93% of patients had no emesis and 60% had no nausea during the study period. Constipation was the most commonly reported adverse event (39%).\(^{58}\) In a recent phase II study that evaluated a higher dose of palonosetron (0.75 mg IV day 1) with aprepitant (125 mg day 1; 80 mg days 2, 3), and dexamethasone (10 mg PO day 1; 8 mg PO days 2–4) in patients with lung cancer undergoing highly emetogenic chemotherapy (N=63), the CR rate during the overall study period (0–120 hours) was 81%.\(^{55}\) The CR rates during the acute and delayed phases were 97% and 81%, respectively. In addition, 54% of patients had no nausea during the overall study period. Grade 1 or 2 constipation was the most commonly reported adverse event.\(^{55}\)

A randomized double-blind phase III study compared the effectiveness of combining ondansetron (8 mg PO BID day 1), aprepitant (125 mg day 1; 80 mg days 2, 3) and dexamethasone (12 mg day 1) versus standard therapy with ondansetron (8 mg PO BID days 1-3) and dexamethasone (20 mg day 1) in patients receiving moderately emetogenic chemotherapy (N=585).\(^{94}\) Dexamethasone was only given on day 1 for both treatment groups. A significantly higher proportion of patients in the 3-drug regimen with aprepitant had no vomiting compared with the standard group (76% vs. 62%; \( P < 0.001 \)) during the overall time frame from 0 to 120 hours after starting chemotherapy. In addition, the CR (no emetic episodes, no rescue medications) rate was significantly increased in the aprepitant group (69% vs. 56%; \( P < 0.001 \)) during the overall time period. The significant improvement in antiemetic activity (with regards to no emesis as well as CR rate) in the aprepitant group was observed for both the acute and delayed phases. The 3-drug
regimen was well tolerated, and the incidence of adverse events was similar between treatment groups.94

Oral aprepitant is approved by the FDA for the prevention of nausea and vomiting in patients receiving highly (eg, cisplatin-containing) and moderately emetogenic chemotherapy.95 The oral doses of aprepitant are 125 mg on day 1 (before chemotherapy) and then 80 mg on days 2 and 3 (after chemotherapy).95,96 An IV version of aprepitant (fosaprepitant dimeglumine), which can be given on day 1 only, is also approved by the FDA. IV fosaprepitant is given 30 minutes before chemotherapy on day 1 only, per the package insert.97 If a higher dose of fosaprepitant is used (150 mg IV) on day 1, then it is not necessary to give oral aprepitant on days 2-3.98,99 Note that the dexamethasone dosing is slightly different on days 3 and 4 (8 mg PO twice daily) when using the higher dose of fosaprepitant (150 mg IV) per the package insert.97 A single dose of 150 mg IV fosaprepitant was shown to be non-inferior to the standard regimen with 3-day oral aprepitant in a recent randomized study.100 There are no studies showing efficacy or safety of chronic dosing with aprepitant. It is possible that the drug-drug interaction profile may change with chronic dosing.

Drug Interactions
Aprepitant is simultaneously a substrate, moderate inducer, and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4); aprepitant also induces CYP2C9.101 Thus, aprepitant can alter the metabolism of certain drugs and change their plasma concentrations (ie, AUCs [area under the curve]). These interactions are more significant with orally administered forms of these drugs than with IV forms because of first-pass metabolism. Patients should not take aprepitant with pimozide, terfenadine, astemizole, or cisapride; these combinations are contraindicated, because they may cause "serious or life-threatening reactions" (see the aprepitant package insert).95

Chemotherapeutic agents known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. In clinical trials, aprepitant was used concurrently with etoposide, vinorelbine, or paclitaxel; although chemotherapy doses were not adjusted for potential drug interactions in phase III trials, caution is urged when using any chemotherapeutic agent that is metabolized by CYP3A4. Aprepitant has been shown to interact with several non-chemotherapeutic drugs (including warfarin, dexamethasone, methylprednisolone, oral contraceptives). Again, these interactions are more significant with orally administered forms of these drugs than with IV forms because of first-pass metabolism.

Induction of warfarin metabolism by aprepitant may lead to clinically significant reductions in INR (international normalized ratio) values, particularly for patients on therapeutic (as compared to prophylactic) warfarin regimens. These changes, although brief in duration, may require increased patient monitoring.95 Aprepitant decreases the AUC for patients taking oral contraceptives; thus, other methods of birth control should be used during treatment with aprepitant and for 1 month after the last dose of aprepitant.95 Additionally, certain drugs can affect the AUCs of aprepitant. Concomitant administration with CYP3A4 inhibitors (eg, ketoconazole,itraconazole, and erythromycin) may lead to increased aprepitant AUCs, whereas concomitant administration with CYP3A4 inducers (eg, carbamazepine, rifampin, and phenytoin) may lead to decreased levels of aprepitant.

Other Non–5-HT3–Receptor Antagonist Antiemetics
Before the advent of the 5-HT3–receptor antagonists, the available antiemetic agents included phenothiazines,102 substituted benzamides,103,104 antihistamines,105 butyrophenones,106 corticosteroids,107-109 benzodiazepines,110,111 and cannabinoids.112,113 Most
drugs used to prevent chemotherapy-induced emesis are classified as dopamine antagonists, serotonin antagonists, and other antagonists. Other agents such as gabapentin have also been evaluated as part of antiemetic regimens. Combination antiemetic therapy is generally more effective than single-agent therapy.

Olanzapine (thiobenzodiazepine) was found to be effective for preventing acute and delayed emesis in a phase II trial in patients (N=30) who received cyclophosphamide, doxorubicin, and/or cisplatin; other studies have also showed the value of olanzapine for delayed and refractory emesis and nausea. Several studies have demonstrated the activity of olanzapine combined with a 5-HT3 receptor antagonist and dexamethasone in controlling emesis in patients receiving emetogenic chemotherapy regimens. A phase II study evaluated the combination of olanzapine with palonosetron and dexamethasone in patients receiving highly emetogenic chemotherapy (N=40). Among patients undergoing highly emetogenic chemotherapy (n=8), the CR rate was 75% during the overall study period (0–120 hours); the CR rates for the acute phase (0–24 hours) and delayed phase (24–120 hours) were 100% and 75%, respectively. The corresponding CR rates among the patients receiving moderately emetogenic chemotherapy (n=32) were 72%, 97%, and 75%, respectively. More recently, a randomized phase III study evaluated the effectiveness of olanzapine (10 mg PO day 1–4) versus aprepitant (125 mg PO day 1, 80 mg PO days 2, 3) for preventing acute and delayed emesis in patients (N=251) receiving highly emetogenic chemotherapy (cisplatin, cyclophosphamide and doxorubicin); both treatment arms included the 5-HT3–receptor antagonist palonosetron (0.25 mg IV day 1) and dexamethasone. The CR (no emesis, no rescue) rate was similar between the olanzapine and aprepitant regimens, both during the acute (97% vs. 87%) and delayed (77% vs. 73%) periods. The proportion of patients without nausea was similar for the acute period (87% in each study arm) but the olanzapine regimen was associated with a higher rate of nausea control during the delayed period (69% vs. 38%) compared with the aprepitant regimen. However, 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 about type II diabetes and hyperglycemia).

Gabapentin is an anticonvulsant agent with analgesic and anti-seizure activities, and is indicated for the management of postherpetic neuralgia in adults and as adjunctive treatment for partial seizures associated with epilepsy. A recent randomized, double-blind controlled pilot study evaluated the activity and safety of adding gabapentin (versus placebo) to an antiemetic regimen (comprising ondansetron dexamethasone and ranitidine) in patients receiving moderately or highly emetogenic chemotherapy (N=80). The CR rate (complete protection from vomiting or nausea) during the course of the study (days 1 to 5) was higher in the gabapentin arm compared with the placebo arm (62.5% vs. 40%). In addition, among the patients who had a CR during the acute period, the CR rate for the delayed period (24-120 hours post-chemotherapy) was also improved with gabapentin (89% vs. 61%).

**Treatment Issues**

As new data on the use of antiemetics in patients receiving chemotherapy become available, clinicians should consider these data when caring for such patients, even if the information has not been included in the guidelines. In contrast to other NCCN Guidelines in which most of the recommendations are category 2A, many of the recommendations for antiemetic management are classified as category...
Principles of Emesis Control

These principles are described in the algorithm and are summarized here (see Guidelines section on “Principles of Emesis Control for the Cancer Patient”). The goal of emesis control is to prevent nausea and/or vomiting. Antiemetic regimens should be chosen based on the drug with the highest emetic risk in the chemotherapy regimen, previous experience with antiemetics, and patient-specific risk factors. Patients need to be protected throughout the entire period of risk, which lasts for at least 3 days for high emetic risk and 2 days for moderate emetic risk agents after the last dose of chemotherapy.

In addition to using antiemetic regimens, patients can adjust their eating habits and adopt other lifestyle measures that may alleviate nausea and vomiting (see “Eating Hints: Before, During, and After Cancer Treatment” from the National Cancer Institute). Suggestions include eating small frequent meals, food that is “easy on the stomach”, full liquid foods, and food at room temperature; patients can also avoid foods that make them feel nauseous.

Prevention of Acute and Delayed Emesis

To prevent acute emesis, antiemetic therapy should start before the administration of chemotherapy and then should cover the first 24 hours. In the NCCN Guidelines for Antiemesis, the specific antiemetic regimens are described for highly emetogenic IV drugs, moderately emetogenic IV drugs, low, and minimally emetogenic IV drugs. Emesis prevention for oral chemotherapeutic agents is also described in the NCCN Guidelines. This section discusses prechemotherapy and postchemotherapy emesis prevention rather than primary treatment.

Prechemotherapy Emesis Prevention

The NCCN Guidelines specify different prophylactic antiemetic regimens for cancer patients receiving chemotherapy of different emetogenic potential (ie, high, moderate, low, and minimal). Prophylactic antiemetics should be administered before chemotherapy. The recommendations for prophylactic antiemetic treatment include drug dosages. The guidelines reflect accumulating experience with the 5-HT3 antagonists, demonstrating their effectiveness in a range of doses. Unless indicated, the order of listed antiemetics in the NCCN Guidelines does not reflect preference.

Highly emetogenic IV drugs in the NCCN Guidelines include carmustine (>250 mg/m²), cisplatin (any dose), cyclophosphamide (>1500 mg/m²), dacarbazine, doxorubicin (≥ 60 mg/m²), epirubicin (≥ 90 mg/m²), ifosfamide (≥ 2 g/m² per dose), mechlorethamine, streptozocin, or anthracycline plus cyclophosphamide (AC) combinations (eg, doxorubicin or epirubicin with cyclophosphamide). Although most of these drugs are also considered highly emetogenic by the Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO) guidelines, the NCCN Guidelines for highly, moderately, low, and minimally emetogenic agents differ slightly based on the experience and expertise of the panel members. The antiemetic regimen for these highly emetogenic drugs on day 1 includes aprepitant (or fosaprepitant), dexamethasone, and a 5-HT3 antagonist (category 1 for the combined regimen) with or without lorazepam and with or without either an H2 blocker or a proton pump inhibitor. Note that the regimen and doses are often modified on days 2 to 4 after chemotherapy. An alternative antiemetic regimen for highly emetogenic agents on day 1 includes olanzapine, palonosetron, and dexamethasone. Although it is not recommended as a single agent, lorazepam is a useful adjuvant because it decreases anxiety.
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Lorazepam is also recommended for patients who are at risk for anticipatory nausea and/or vomiting (see Guidelines section on “Anticipatory Emesis Prevention/Treatment”). Antacid therapy (eg, proton pump inhibitors, H2 blockers) should be considered if patients have dyspepsia, because patients sometimes have difficulty discriminating heartburn from nausea.

For IV regimens with high emetogenic potential, aprepitant is used at an oral dosage of 125 mg on day 1 and then 80 mg on days 2 and 3. When given with aprepitant, dexamethasone is used at a dosage of 12 mg on day 1; the dose can be oral or IV. Note that IV fosaprepitant may be substituted for oral aprepitant on day 1 only. If appropriate, lorazepam (0.5–2 mg either every 4 or every 6 hours on days 1–4; either oral, IV, or sublingual) may be used with each of these regimens (ie, high, moderate, or low). As previously discussed, a recent phase III randomized trial suggested that palonosetron is preferred over granisetron for high emetic risk chemotherapy in combination with dexamethasone. This trial has been criticized because: 1) the control arm was not adequately dosed; thus, the trial “stacked the deck” in favor of palonosetron; 2) a larger non-FDA-approved dose of palonosetron was used (ie, 0.75 mg IV); and 3) aprepitant was not used in this study.

The antiemetic regimen for moderately emetogenic IV drugs on day 1 includes dexamethasone and a 5-HT3 antagonist with or without lorazepam and with or without either an H2 blocker or a proton pump inhibitor. Aprepitant (or fosaprepitant) should be added (to dexamethasone and a 5-HT3 antagonist) for select patients receiving certain moderate emetic risk chemotherapy (eg, carboplatin, carmustine ≤ 250 mg/m², dacarbazine, daunorubicin, doxorubicin <60 mg/m², epirubicin ≤ 90 mg/m², ifosfamide <2 g/m² per dose, irinotecan, or methotrexate), because these agents are more emetogenic than the other moderately emetogenic agents. IV fosaprepitant may be substituted for oral aprepitant on day 1 only. Any one of the 5-HT3 antagonists can be used, because they are all category 1 for day 1. However, as previously mentioned, palonosetron was shown in a recent meta-analysis to be more effective than other available 5-HT3 antagonists in preventing acute and delayed nausea and vomiting for both high and moderately emetogenic chemotherapy agents; hence, the NCCN Panel recommends palonosetron as the preferred 5-HT3 antagonist in the setting of moderately emetogenic chemotherapy. Similar to the setting of highly emetogenic chemotherapy regimens, an alternative antiemetic regimen for patients receiving moderately
emetogenic chemotherapy includes olanzapine (10 mg PO days 1–4) with palonosetron (0.25 mg IV day 1 only) and dexamethasone (20 mg IV day 1 only).\textsuperscript{119,121}

The antiemetic regimen for low emetogenic IV drugs (see the NCCN 2014 Antiemesis algorithm) includes orally administered 5-HT3 receptor antagonists or agents such as dexamethasone, prochlorperazine, or metoclopramide, with or without lorazepam, and with or without either an H2 blocker or a proton pump inhibitor. When using prochlorperazine or metoclopramide, patients should be monitored for dystonic reactions.\textsuperscript{128-130} Diphenhydramine can be used for dystonic reactions.\textsuperscript{131,132} Benztropine may be used in patients who are allergic to diphenhydramine.\textsuperscript{129} If appropriate, lorazepam (0.5-2 mg either every 4 or every 6 hours on days 1-4; either oral, IV, or sublingual) may be used with each of these regimens (ie, high, moderate, or low).

The emetogenic potential of oral chemotherapeutic agents is shown in the NCCN Guidelines. Antiemetic prophylaxis is recommended for the following oral agents: altretamine, busulfan (≥ 4 mg/day), crizotinib, cyclophosphamide (≥100 mg/m\textsuperscript{2}/day), estramustine, etoposide, lomustine (single day), mitotane, procarbazine, temozolomide (> 75 mg/m\textsuperscript{2}/day or ≤ 75 mg/m\textsuperscript{2}/day with concurrent radiotherapy) and vismodegib. For high or moderate emetic risk oral agents, recommended prophylaxis includes oral 5-HT3 antagonists (such as granisetron or ondansetron) with or without lorazepam and with or without either an H2 blocker or a proton pump inhibitor. For low or minimal emetic risk oral agents, recommended prophylaxis includes oral 5-HT3 antagonists, metoclopramide, prochlorperazine, or haloperidol with or without lorazepam and with or without either an H2 blocker or a proton pump inhibitor; prophylaxis is given before chemotherapy is started and then on an as needed basis only (ie, PRN).

Postchemotherapy/Delayed Emesis Prevention
The best management for delayed emesis is prevention.\textsuperscript{133} For chemotherapeutic agents with high emetogenic potential, the prophylactic treatment (ie, dexamethasone and aprepitant) is continued through the period when delayed emesis may occur. Using this strategy, prophylaxis continues for 2 to 4 days after completion of a chemotherapy cycle. However, 5-HT3 antagonists are given on day 1 only.

For drugs with moderate emetogenic potential, postchemotherapy prevention depends on which antiemetics were used before chemotherapy. For example, palonosetron (category 1) is only administered on day 1.\textsuperscript{133} If either aprepitant or fosaprepitant was used on day 1, then aprepitant is continued on days 2 and 3.

Recently, a randomized double-blind trial was conducted to evaluate the effectiveness of 4 different antiemetic regimens in preventing delayed nausea in patients receiving moderate or high emetic risk chemotherapy (N=1021; n=944 evaluable).\textsuperscript{134} The 4 regimens evaluated included the following: Group 1 with palonosetron and dexamethasone day 1, prochlorperazine days 2, 3; Group 2 with granisetron and dexamethasone day 1, prochlorperazine days 2, 3; Group 3 with palonosetron, aprepitant and dexamethasone day 1, aprepitant and dexamethasone days 2, 3; and Group 4 with palonosetron and dexamethasone day 1, prochlorperazine and dexamethasone days 2, 3. Severity of nausea was measured using a 7-point semantic rating scale; mean and maximum severity scores were obtained from measurements taken throughout day 1 (for acute nausea) and throughout days 2 and 3 (for delayed nausea). The trial was designed to address several specific research objectives for controlling delayed nausea, including the comparison of palonosetron with granisetron (Group 1 vs. Group 2), activity of adding dexamethasone to prochlorperazine on days 2, 3.
(Group 1 vs. Group 4), and activity of aprepitant compared with prochlorperazine when both agents are combined with palonosetron and dexamethasone (Group 3 vs. Group 4).\textsuperscript{134} Data from this trial showed no significant differences between palonosetron and granisetron in the mean or maximum severity of delayed nausea, when these agents were used with dexamethasone and prochlorperazine. Similarly, no significant differences were observed between aprepitant and prochlorperazine in controlling delayed nausea, when these agents were combined with palonosetron and dexamethasone.\textsuperscript{134} This trial also showed that the addition of dexamethasone to prochlorperazine on days 2 and 3 (for a regimen with palonosetron and dexamethasone on day 1) improved the severity of both mean and maximum delayed nausea compared with prochlorperazine alone.

The antiemetic regimens in the NCCN Guidelines include different options on days 2 to 3 for moderate emetic risk agents.\textsuperscript{23,26,133} There are 3 possible regimens on days 2 to 3 including: 1) aprepitant (if used on day 1); 2) dexamethasone; or 3) 5-HT3 antagonist, such as ondansetron, granisetron, or dolasetron.\textsuperscript{133} Each of these regimens may also include the following: ± lorazepam and ± either an H2 blocker or a proton pump inhibitor. It is important to note that the doses of both aprepitant (80 mg PO) and dexamethasone (8 mg PO or IV) are decreased when used on days 2 to 3 (when compared with the doses given on day 1). Note that palonosetron is not given on days 2 to 3. Fosaprepitant is also not given on days 2 to 3.

The NCCN, MASCC, and American Society of Clinical Oncology (ASCO) guidelines all recommend using aprepitant to prevent delayed nausea and/or vomiting when giving AC regimens.\textsuperscript{8,26,135} Note that the MASCC guidelines are updated on a biannual basis following the publication of the initial consensus guidelines, which were based on the Perugia Consensus Conference on Antiemetic Therapy held in June 2009.

**Breakthrough Treatment**

Breakthrough emesis presents a difficult situation, because refractory ongoing nausea and/or vomiting is often challenging to reverse (see Guidelines section on “Principles for Managing Breakthrough Emesis”). Generally, it is much easier to prevent nausea and/or vomiting than to treat it. Thus, routine around-the-clock administration of antiemetics should be strongly considered to prevent emesis, rather than PRN (as required) dosing. The general principle of breakthrough treatment is to give an additional agent as needed from a different drug class.\textsuperscript{23} However, no single treatment is better than another for managing breakthrough emesis. Some patients may require several agents using different mechanisms of action. The oral route may not be feasible because of ongoing vomiting; therefore, rectal or IV therapy is often required. Nasal sprays might be useful for treatment of breakthrough emesis, because they provide acute delivery of agents.\textsuperscript{136,137} Multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary.

Miscellaneous agents (eg, haloperidol, metoclopramide, olanzapine, scopolamine transdermal patch), corticosteroids, and agents such as lorazepam may be incorporated for breakthrough treatment. In a recent randomized double-blind phase III study, the effectiveness of olanzapine (10 mg/day PO for 3 days) as treatment for breakthrough emesis was compared with metoclopramide in patients treated with highly emetogenic chemotherapy regimens who developed breakthrough emesis or nausea despite antiemetic prophylaxis (comprising palonosetron, dexamethasone and fosaprepitant; N=112; n=108 evaluable).\textsuperscript{138,139} Patients were observed for emesis and nausea...
During the 72 hours after treatment with olanzapine or metoclopramide. During this observation period, a higher proportion of patients had no emesis (70% vs. 31%; \(P<0.01\)) and no nausea (68% vs. 23%; \(P<0.01\)) with olanzapine than metoclopramide.\(^{139}\) Thus, olanzapine was more effective in controlling breakthrough emesis and nausea compared with metoclopramide in this patient population. Dronabinol and nabilone (which are cannabinoids) are approved by the FDA for nausea and vomiting in patients who have not responded to conventional antiemetic agents. Adequate hydration or fluid repletion should be ensured, and any possible electrolyte abnormalities should be assessed and corrected. Before administering the next cycle of chemotherapy, the patient should be reassessed for other possible non-chemotherapy-related reasons for breakthrough emesis with the current cycle (eg, brain metastases, electrolyte abnormalities, tumor infiltration of the bowel or other GI abnormality, and other comorbidities; see Guidelines section on “Principles for Managing Breakthrough Emesis”).

In addition, before the next cycle of chemotherapy, the antiemetic regimen (both the day 1 and postchemotherapeutic) that did not protect the patient during the present cycle should be assessed and alternatives should be considered (see Guidelines section on “Principles for Managing Breakthrough Emesis”). Because patients sometimes have difficulty discriminating heartburn from nausea, use of antacid therapy (eg, proton pump inhibitors, H2 blockers) should be considered.

### Radiation-Induced Nausea and/or Vomiting

Prophylaxis for radiation-induced nausea and/or vomiting is based on the site of radiation and whether it is combined with chemotherapy.\(^{24,140,141}\) When radiation is combined with chemotherapy, prophylaxis is dictated by the emetogenic potential of the chemotherapy regimen. Recent MASCC/ESMO guidelines state that total body irradiation is associated with the highest risk for emesis and that upper abdominal radiation is associated with moderate risk.\(^{24}\) A recent meta-analysis suggests that 5-HT3 antagonists are the preferred agents for preventing radiation-induced vomiting.\(^{142}\)

Patients undergoing radiation therapy to the upper abdomen may receive antiemetic prophylaxis with oral ondansetron or oral granisetron, with or without oral dexamethasone.\(^{8,24}\) A randomized study compared oral ondansetron with placebo in patients receiving daily fractionated radiotherapy including the abdomen. In this study, 67% of patients given ondansetron had complete control of emesis compared with 45% of patients who received placebo (\(P<0.05\)).\(^{143}\) A study showed that the addition of oral dexamethasone (4 mg daily) to the ondansetron regimen decreases emesis and nausea, although the effect is modest.\(^{144}\) Another randomized study in patients receiving radiotherapy to the upper abdomen found that oral granisetron decreased emesis and nausea when compared with placebo.\(^{145}\)

Patients undergoing total body irradiation may receive antiemetic prophylaxis with either ondansetron or granisetron; either agent can be given with or without oral dexamethasone.\(^{8,24,146}\) Treatment of breakthrough radiation-induced emesis is similar to chemotherapy-induced emesis. Patients who do not receive primary prophylaxis and experience breakthrough nausea and/or vomiting may be treated with ondansetron, similar to primary prophylaxis.

### Anticipatory Nausea and/or Vomiting

About 20% of patients develop anticipatory nausea and/or vomiting. However, the rate of anticipatory nausea and/or vomiting appears to be decreasing (when compared with older studies) with current use of more effective antiemetic regimens.\(^{8}\) The most effective way to treat anticipatory nausea and/or vomiting is to prevent it by using optimal
antiemetic therapy during every cycle of treatment. Behavioral therapy has been used in patients with anticipatory nausea and/or vomiting. Systematic desensitization may also be helpful. Hypnosis with guided imagery is another behavioral technique that has shown some success in treating this condition.

The antianxiety agents lorazepam and alprazolam have been combined with antiemetics for anticipatory nausea and/or vomiting. The usual starting dose of alprazolam for anxiety is 0.25 to 0.5 mg orally 3 times daily, beginning on the night before treatment. In elderly patients, patients with debilitating disease, and patients with advanced liver disease, the usual starting dose of alprazolam is 0.25 mg orally 2 or 3 times daily for treatment of anxiety. This dose may be gradually increased if needed. Note that the elderly are especially sensitive to the effects of benzodiazepines. The dose should be gradually reduced when decreasing or discontinuing alprazolam therapy.

Managing Multiday Emetogenic Chemotherapy Regimens

Patients receiving multiple day (ie, multiday) chemotherapy are at risk for both acute and delayed nausea and/or vomiting based on the emetogenic potential of the individual chemotherapy agents and their sequence. It is difficult to recommend a specific antiemetic regimen for each day, especially because acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy. The period of risk for delayed emesis following completion of chemotherapy also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. For multi-drug regimens, antiemetic therapy should be selected based on the drug with the highest emetic risk. General principles for managing multiday emetogenic chemotherapy regimens recommended by the panel are described in the algorithm (see Guidelines section on “Principles for Managing Multiday Emetogenic Chemotherapy Regimens”).

For antiemetic prophylaxis of multiday emetogenic chemotherapy regimens (eg, cisplatin-containing regimens), the combination of a 5-HT3 antagonist with dexamethasone has been the standard treatment. Dexamethasone should be administered once daily either orally or intravenously for every day of moderately or highly emetogenic chemotherapy and for 2 to 3 days after chemotherapy for regimens that are likely to cause significant delayed emesis. However, dexamethasone should not be added when the chemotherapy regimen already includes a corticosteroid. Steroids should also be avoided when using regimens containing interleukin-2 (IL-2, aldesleukin) and interferon.

A 5-HT3 receptor antagonist should be administered each day before the first dose of moderately or highly emetogenic chemotherapy. Intravenous palonosetron may be used before the start of a 3-day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT3 receptor antagonists. Repeat dosing of palonosetron (0.25 mg IV) is likely to be safe, based on the dose ranging phase II trial and the 3 phase III trials using palonosetron as a single fixed dose (0.75 mg IV). Compared to the approved dose of palonosetron of 0.25 mg IV, these higher doses were not associated with significantly different adverse events.

The need for repeat dosing with palonosetron, either daily or less frequently, in the setting of multiday chemotherapy is not yet known. In one study, patients receiving highly emetogenic multiday cisplatin-based chemotherapy for testicular cancer (N=41) received multiday dosing of palonosetron (0.25 mg IV on days 1, 3, and 5) and dexamethasone, which prevented nausea and emesis in most patients.
on days 1 to 5 (51%) and on days 6 to 9 (83%); the most common adverse events were mild headache and constipation. A recent study assessed palonosetron given for 1, 2, or 3 days in combination with dexamethasone for patients receiving multiday high-dose chemotherapy prior to stem cell transplantation for multiple myeloma (N=73); during the 7-day emesis prevention period, about 40-45% of patients had no emesis (with no differences observed between palonosetron treatment groups), and no serious adverse events were reported. However, even among the patients who received either 2 or 3 days of palonosetron, only 20% had a complete response (ie, emesis free without rescue medication). Another study found that a palonosetron/dexamethasone regimen appeared to be more effective for multiday chemotherapy than an ondansetron/dexamethasone regimen; patients received a second dose of palonosetron for breakthrough emesis, which was effective in 67% of patients who experienced nausea or vomiting. Further studies are needed to define whether a need exists for repeat dosing of palonosetron in the setting of multiday chemotherapy.

The potential role of NK-1 antagonists in the antiemetic management of multiday chemotherapy regimens has been investigated in several studies. In one study, the addition of the NK-1 antagonist aprepitant to granisetron and dexamethasone was evaluated in patients receiving multiday high and moderate emetogenic chemotherapy (N=78); in this study, the 3-drug antiemetic regimen was given during chemotherapy, and aprepitant and dexamethasone was given for an additional 2 days following chemotherapy, which was effective in 67% of patients who experienced nausea or vomiting. Further studies are needed to define whether a need exists for repeat dosing of palonosetron in the setting of multiday chemotherapy.

During cycle 1 of chemotherapy, 96% of patients had no emesis on day 1 and 82% had no emesis during days 1 to 7. In addition, 71% had no nausea on day 1 of cycle 1, and 27% had no nausea during days 1 to 7. Over 80% of patients had no emesis on any given day of any given chemotherapy cycle. No unexpected or serious adverse events were reported. In a recent double-blind, randomized, placebo-controlled phase III cross-over trial, the efficacy of adding aprepitant (versus placebo) to an antiemetic regimen with 5-HT3 receptor antagonist and dexamethasone was evaluated in patients with testicular cancer undergoing 2 cycles of a 5-day cisplatin combination chemotherapy regimen (N=71; n=69 evaluable). Patients were randomized to receive aprepitant (125 mg PO day 3, 80 mg PO days 4–7) or placebo, combined with a 5-HT3 antagonist (days 1–5) and dexamethasone (20 mg days 1, 2) during the first cycle, and then crossed over to the opposite antiemetic regimen during the second cycle of chemotherapy. Thus, patients served as their own controls after receiving either aprepitant or placebo for cycle 1. Palonosetron was excluded from the options for 5-HT3 antagonists due to its longer half-life. The primary endpoint of the study was CR (no emetic episodes and no rescue medication) during the overall study period (days 1–8). The CR rate for the overall study period was significantly higher with aprepitant compared with placebo (42% vs. 13%; P<0.001). The CR rates were also higher with aprepitant during the acute phase (days 1–5; 47% vs. 15%; P<0.001) and delayed phase (days 6–8; 63% vs. 35%; P<0.001). No statistically significant differences were observed between treatment regimens in terms of nausea (based on patient-reported visual analog scale). Importantly, no increase in toxicity with aprepitant compared with placebo was reported.
Aprepitant may be used for multiday chemotherapy regimens likely to be highly emetogenic and associated with significant risk for delayed nausea and emesis. As per the labeled indication, aprepitant should be administered 125 mg orally 1 hour prior to chemotherapy on day 1, along with a 5-HT3 receptor antagonist and dexamethasone. Aprepitant 80 mg should be administered daily on days 2 and 3 after the start of chemotherapy along with dexamethasone.\textsuperscript{158} Repeated dosing of aprepitant over multiple cycles of cisplatin-based chemotherapy was shown to be feasible and well tolerated; importantly, protection from emesis and from significant nausea was maintained during the subsequent cycles of emetogenic chemotherapy.\textsuperscript{95,158} Based on phase II data, aprepitant 80 mg may be safely administered beyond day 3 of initiating chemotherapy.\textsuperscript{96,170} Alternatively, for highly emetogenic chemotherapy regimens, fosaprepitant 150 mg IV with dexamethasone may be given on day 1 with no need for oral aprepitant on days 2 and 3 with recommended dosing of dexamethasone.
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