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These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2006.
SUMMARY OF GUIDELINES UPDATES

Summary of changes in the 1.2007 version of the NCCN Antiemesis Guidelines from the 1.2006 version include:

- Footnote "b" was expanded to include patient specific risk factors (AE-2, AE-3, AE-4).
- Removal of the page designated to New Antiemetic Agents for Treating Nausea and Vomiting.
- Removal of the "preferred" indication following dexamethasone 8 mg PO or IV daily or 4 mg PO or IV bid on days 2-4 on page (AE-3), Moderate emetic risk chemotherapy - emesis prevention.
- Removal of metoclopramide ± diphenhydramine from page (AE-3).
- Added nabilone 1-2 mg PO bid as a breakthrough treatment for chemotherapy induced nausea/vomiting on page (AE-5).
- Expanded the table of emetogenic potential of antineoplastic agents pages (AE-6 and AE-7):
  - Added a footnote to imatinib for moderate emetic risk, stating "Daily use of antiemetics is not recommended based on clinical experience".
  - Moved bortezomib and trastuzumab from low to minimal emetic risk category.
  - Added paclitaxel-albumin to low emetic risk category.
  - Added decitabine, dasatinib, lenalidomide, nelarabine, sorafenib, sunitinib, and thalidomide to minimal emetic risk category.

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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.
PRINCIPLES OF EMESIS CONTROL IN THE CANCER PATIENT

- Prevention of nausea/vomiting is the goal.
- The risk of emesis and nausea for persons receiving chemotherapy of high and moderate emetic risk lasts for at least 4 days. Patients need to be protected throughout the full period of risk.
- Oral and IV antiemetic formulations have equivalent efficacy.
- Use the lowest fully efficacious dose of the antiemetic(s) prior to chemotherapy or radiation therapy.
- Consider the toxicity of the specific antiemetic(s).
- Choice of antiemetic(s) used should be based on the emetic risk of the therapy as well as 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, hyponatremia
  - Uremia
  - Concomitant drug treatments including opiates
  - Gastroparesis, tumor or chemotherapy (vincristine etc) induced.
  - Psychophysiological:
    - Anxiety
    - Anticipatory nausea and vomiting

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HIGH EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION\textsuperscript{b,c,d}

- Start before chemotherapy\textsuperscript{b,c,d}
  - Aprepitant 125 mg PO day 1, 80 mg PO daily days 2-3
  - Dexamethasone 12 mg PO or IV day 1, 8 mg PO or IV daily days 2-4
  - 5-HT3 antagonist:\textsuperscript{e}
    - Ondansetron 16-24 mg PO or 8-12 mg (maximum 32 mg) IV day 1
    - Granisetron 2 mg PO or 1 mg PO bid or 0.01 mg/kg (maximum 1 mg) IV day 1
    - Dolasetron 100 mg PO or 1.8 mg/kg IV or 100 mg IV day 1
    - Palonosetron 0.25 mg IV day 1
  - ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h days 1-4 (category 1, for combined regimen)

\textsuperscript{a} Data for post-cisplatin (> 50 mg/m\textsuperscript{2}) emesis prevention are category 1, others are category 2A.
\textsuperscript{b} Antiemetic regimens should be chosen based on emetogenic potential of the chemotherapy regimen as well as patient specific risk factors.
\textsuperscript{c} Lowest fully efficacious dose.
\textsuperscript{d} See Principles for Managing Multi-day Emetogenic Chemotherapy Regimens (AE-A).
\textsuperscript{e} Order of listed antiemetics does not reflect preference.

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MODERATE EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION

**Day 1**

- Start before chemotherapy
  - Aprepitant 125 mg PO in select patients
  - Dexamethasone 12 mg PO or IV and
  - 5-HT3 antagonist:
    - Palonosetron 0.25 mg IV (category 1)
    - Ondansetron 16-24 mg PO or 8-12 mg (maximum 32 mg) IV (category 1)
    - Granisetron 1-2 mg PO or 1 mg PO bid (category 1) or 0.01 mg/kg (maximum 1 mg) IV or
    - Dolasetron 100 mg PO or 1.8 mg/kg or 100 mg IV (category 1) and
  - ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h

**Days 2-4**

- Aprepitant 80 mg PO days 2-3 if used on Day 1 ± Dexamethasone 8 mg PO or IV daily or
- Dexamethasone 8 mg PO or IV daily or 4 mg PO or IV bid or
- 5-HT3 antagonist:
  - Ondansetron 8 mg PO bid or 16 mg PO daily or 8 mg (maximum 32 mg) IV or
  - Granisetron 1-2 mg PO daily or 1 mg PO bid or 0.01 mg/kg (maximum 1 mg) IV or
  - Dolasetron 100 mg PO daily or 1.8 mg/kg IV or ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h 100 mg IV

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b Antiemetic regimens should be chosen based on emetogenic potential of the chemotherapy regimen as well as patient specific risk factors.

c Lowest fully efficacious dose.

d See Principles for Managing Multi-day Emetogenic Chemotherapy Regimens (AE-A).

e Order of listed antiemetics does not reflect preference.

Data for post-carboplatin ≥ 300 mg/m², cyclophosphamide ≥ 600-1000 mg/m², doxorubicin ≥ 50 mg/m² emesis prevention are category 1.

Aprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for patients receiving the combination of an anthracycline and cyclophosphamide and select patients receiving other chemotherapies of moderate emetic risk (for example, carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan or methotrexate).

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LOW AND MINIMAL EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION

- Start before chemotherapy\(^{b,c,d}\)
- Repeat daily for fractionated doses of chemotherapy
  - Dexamethasone 12 mg PO or IV daily
  - Prochlorperazine 10 mg PO or IV every 4 or every 6 h or 15 mg spansule PO every 8 or every 12 h
  - Metoclopramide 20-40 mg PO either every 4 or every 6 h or 1-2 mg/kg IV either every 3 or every 4 h ± Diphenhydramine 25-50 mg PO or IV either every 4 or every 6 h
  - ± Lorazepam, 0.5-2 mg PO or IV either every 4 or every 6 h

Minimal → No routine prophylaxis → Nausea/emesis (0–24 h) → Consider using antiemetics listed under primary prophylaxis as treatment for low emetogenic-potential drugs

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## Antiemesis

### Breakthrough Treatment for Chemotherapy Induced Nausea/Vomiting

**No nausea/emesis**
- No change in antiemetic regimen

**Any nausea/emesis**
- General principle of breakthrough treatment is to give an additional agent from a different drug class prn
  - Prochlorperazine 25 mg supp pr every 12 h or 10 mg PO or IV every 4 or every 6 h or 15 mg Spansule PO every 5 or every 12 h
  - Metoclopramide 20-40 mg PO either every 4 or every 6 h or 1-2 mg/kg IV either every 3 or every 4 h ± Diphenhydramine 25-50 mg PO or IV either every 4 or every 6 h
  - Lorazepam 0.5-2 mg PO either every 4 or every 6 h
  - Ondansetron 16 mg PO or 8 mg IV daily
  - Granisetron 1-2 mg PO daily or 1 mg PO bid or 0.01 mg/kg (maximum 1 mg) IV
  - Dolasetron 100 mg PO daily or 1.8 mg/kg IV or 100 mg IV
  - Haloperidol 1-2 mg PO q 4-6 h or 1-3 mg IV either every 4 or every 6 h
  - Dronabinol 5-10 mg PO either every 3 or every 6 h
  - Nabilone 1-2 mg PO bid
  - Dexamethasone 12 mg PO or IV daily, if not previously given
  - Olanzapine 2.5-5 mg PO bid (category 2B)
  - Promethazine 12.5-25 mg PO or IV every 4 h

**Response to Breakthrough Antiemetic Treatment**

- Nausea and emesis controlled
  - Continue breakthrough medications, on a schedule, not prn

- Nausea and/or emesis uncontrolled
  - Consider changing antiemetic therapy to higher-level primary treatment

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\[c\]Lowest fully efficacious dose.

\[d\]See Principles for Managing Multi-day Emetogenic Chemotherapy Regimens (AE-A).

\[h\]See Principles of Managing Breakthrough Treatment (AE-B).

\[i\]See blackbox warning/label indication regarding type II diabetes and hyperglycemia.
## EMETOGENIC POTENTIAL OF ANTINEOPLASTIC AGENTS

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>AGENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High emetic risk (&gt; 90% frequency of emesis)</td>
<td></td>
</tr>
<tr>
<td>• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide</td>
<td>• Dacarbazine</td>
</tr>
<tr>
<td>• Altretamine</td>
<td>• Mechlorethamine</td>
</tr>
<tr>
<td>• Carmustine &gt; 250 mg/m²</td>
<td>• Procarbazine (oral)</td>
</tr>
<tr>
<td>• Cisplatin ≥ 50 mg/m²</td>
<td>• Streptozocin</td>
</tr>
<tr>
<td>• Cyclophosphamide &gt; 1,500 mg/m²</td>
<td></td>
</tr>
</tbody>
</table>

| Moderate emetic risk (30-90% frequency of emesis) |       |
| • Aldesleukin > 12-15 million units/m²            | • Epirubicin |
| • Amifostine > 300 mg/m²                          | • Etoposide (oral) |
| • Arsenic trioxide                                | • Idarubicin |
| • Azacitidine                                    | • Ifosfamide |
| • Busulfan > 4 mg/d                              | • Imatinib (oral) k |
| • Carboplatin                                    | • Irinotecan |
| • Carmustine ≤ 250 mg/m²                         | • Lomustine |
| • Cisplatin < 50 mg/m²                           | • Melphalan > 50 mg/m² |
| • Cyclophosphamide ≤ 1,500 mg/m²                 | • Methotrexate 250 - 1,000 mg/m² |
| • Cyclophosphamide (oral)                        | • Oxaliplatin > 75 mg/m² |
| • Cytarabine > 1 g/m²                            | • Temozolomide (oral) |
| • Dactinomycin                                   | • Vinorelbine (oral) |
| • Daunorubicin                                   |       |
| • Doxorubicin                                    |       |

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1Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis

2Daily use of antiemetics is not recommended based on clinical experience.

Adapted with permission from:

Low emetic risk, level 2 (See AE-7)

Minimal emetic risk, level 1 (See AE-7)
### Antiemesis

#### EMETOGENIC POTENTIAL OF ANTINEOPLASTIC AGENTS

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>AGENT</th>
</tr>
</thead>
</table>
| **Low emetic risk**  
(10-30 % frequency of emesis)\(^j\) | *Amifostine ≤ 300 mg*  
*Bexarotene*  
*Capecitabine*  
*Cetuximab*  
*Cytarabine (low dose) 100-200 mg/m\(^2\)*  
*Docetaxel*  
*Doxorubicin (liposomal)*  
*Etoposide*  
*Fludarabine (oral)*  
*5-Fluorouracil*  
*Gemcitabine*  
*Methotrexate > 50 mg/m\(^2\) < 250 mg/m\(^2\)*  
*Mitomycin*  
*Mitoxantrone*  
*Paclitaxel*  
*Paclitaxel-albumin*  
*Pemetrexed*  
*Topotecan* |
| **Minimal emetic risk**  
(< 10 % frequency of emesis)\(^j\) | *Alemtuzumab*  
*Alpha Interferon*  
*Asparaginase*  
*Bevacizumab*  
*Bleomycin*  
*Bortezomib*  
*Busulfan*  
*Chlorambucil (oral)*  
*Cladribine (2-chlorodeoxyadenosine)*  
*Decitabine*  
*Denileukin difftox*  
*Dasatinib*  
*Dexrazoxane*  
*Erlotinib*  
*Fludarabine*  
*Gefitinib*  
*Gemtuzumab ozogamicin*  
*Hydroxyurea (oral)*  
*Lenalidomide*  
*Melphalan (oral low-dose)*  
*Methotrexate ≤ 50 mg/m\(^2\)*  
*Nelarabine*  
*Pentostatin*  
*Rituximab*  
*Sorostatin*  
*Sunitinib*  
*Thalidomide*  
*Thioguanine (oral)*  
*Trastuzumab*  
*Valrubicin*  
*Vinblastine*  
*Vincristine*  
*Vinorelbine* |

\(^j\)Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis

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EMETOGENIC POTENTIAL

<table>
<thead>
<tr>
<th>TYPE OF RADIATION THERAPY</th>
<th>EMESIS PREVENTION</th>
<th>BREAKTHROUGH TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT - upper abdomen</td>
<td>Start pretreatment for each day of RT treatment:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ondansetron 8 mg PO bid-tid or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone 2 mg PO tid or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Granisetron 2 mg PO daily</td>
<td></td>
</tr>
<tr>
<td>Total body irradiation</td>
<td>Start pretreatment for each day of RT treatment:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ondansetron 8 mg PO bid-tid or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Granisetron 2 mg PO daily, or 3 mg IV daily (category 2B)</td>
<td></td>
</tr>
<tr>
<td>Radiation-induced nausea/vomiting</td>
<td>See emesis prevention for chemotherapy-induced nausea/vomiting (High AE-2, Moderate AE-3 and Low AE-4)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy and RT</td>
<td>See Principles of Emesis Control (AE-1)</td>
<td></td>
</tr>
<tr>
<td>RT - Other sites</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

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©Lowest fully efficacious dose
ANTICIPATORY EMESIS PREVENTION/TREATMENT

Prevention:
• Use optimal antiemetic therapy during every cycle of treatment

Behavioral therapy:
• Relaxation/systematic desensitization
• Hypnosis/guided imagery
• Music therapy
• Accupuncture/accupressure

Alprazolam 0.5-2 mg PO tid on the night before treatment

Lorazepam 0.5-2 mg PO on night before and morning of treatment

See primary and breakthrough treatments for chemotherapy-induced nausea/vomiting (Antiemeses TOC)

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PRINCIPLES OF MANAGING MULTI-DAY EMETOGENIC CHEMOTHERAPY REGIMENS

- Patients receiving multi-day chemotherapy are at risk for both acute and delayed nausea and emesis based upon the emetogenic potential of the individual chemotherapy agents 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. The period of risk for delayed emesis after chemotherapy administration has concluded also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen.

- Examples illustrating the above include BEP (bleomycin 30 units IV weekly, etoposide 100 mg/m² IV days 1-5 and cisplatin 20 mg/m² IV days 1-5) versus ASHAP (doxorubicin 25 mg/m² IV day 1, methylprednisolone 500 mg/day IV days 1-5, cisplatin 25 mg/m² IV continuous infusion days 1-4 followed by cytarabine 2000 mg/m² on day 5). BEP is moderately emetogenic with risk for emesis on days 1-8) whereas ASHAP is moderately emetogenic on days 1-4 but becomes highly emetogenic on day 5 due to the administration of high-dose cytarabine). Risk for acute and delayed emesis for ASHAP may last up to 10 days.

Accordingly, the panel recommends the following as general principles (category 2B).

- A 5-HT3 receptor antagonist should be administered prior to each days 1st dose of moderately or highly-emetogenic chemotherapy.
- Dexamethasone should be administered once daily either orally or intravenously for every day of moderately or highly emetogenic chemotherapy and for 2-3 days after chemotherapy for regimens that are likely to cause significant delayed-emesis.
- Dexamethasone should not be added when the chemotherapy regimen already includes a corticosteroid (as in ASHAP illustrated above).
- Palonosetron may be used prior to the start of a three day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT3 receptor antagonists. Repeat dosing of palonosetron 0.25 mg is likely to be safe, based upon the dose ranging Phase II trial where up to 30 times the FDA approved dose (90 mcg/kg) was administered and the 3 Phase III trials that evaluated palonosetron 0.75 mg as a single fixed dose. Compared to the approved dose of palonosetron 0.25 mg, these higher doses were not associated with significantly different grades or durations of adverse events. In terms of efficacy, need for repeat dosing with palonosetron, either daily or less frequently, in the setting of multi-day chemotherapy is not yet known.
- Aprepitant may be used for multi-day 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 one, 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. Based upon Phase II data, aprepitant 80 mg may be safely administered on days 4 and 5 after chemotherapy. It is not yet known if dosing aprepitant after day 3 improves control of nausea or emesis in this clinical setting.

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PRINCIPLES FOR MANAGING BREAKTHROUGH EMESIS

- The general principle of breakthrough treatment is to give an additional agent from a different drug class.
- The PO route is not likely to be feasible due to ongoing vomiting, therefore, rectal or IV therapy is often required.
- Breakthrough emesis presents a difficult situation as correction of refractory ongoing nausea and vomiting is often challenging to reverse. It is generally far easier to prevent nausea and vomiting than to treat it.
- Multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary. Dopamine antagonists, eg, metoclopramide, thiethylperazine, butyrophenones (eg, haloperidol), corticosteroids and agents such as lorazepam may be required.
- One should strongly consider routine, around the clock, administration rather than PRN dosing.
- 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 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 chemo antiemetic regimen which did not protect the patient during the present cycle and consider alternatives: (Suggestions are not in order of preference)
  - Addition of aprepitant
  - Additional other concomitant antiemetics, eg, dopamine antagonists or butyrophenones such as haloperidol
  - Possibly adjusting 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 switching 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 palliative or adjuvant, consider other appropriate regimens, if any, which might be less emetogenic.
  - Addition of an anxiolytic agent in combination with the antiemetic agents.
- If patient has dyspepsia consider antacid therapy (H2 blocker or proton pump inhibitor).
Overview
Chemotherapy-induced nausea and vomiting (emesis) can significantly affect a patient’s quality of life, leading to poor compliance with further chemotherapy 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.1-4 The incidence and severity of nausea and/or vomiting in patients receiving chemotherapy 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; and (4) individual patient variability (eg, age, sex, prior chemotherapy, history of alcohol use). Approximately 70% to 80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting, whereas 10% to 44% experience anticipatory nausea and/or vomiting.7-10 Patients often experience more nausea than vomiting.11

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 (CTZ), 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.12 The CTZ, 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.13, 14 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.15 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.

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, 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 emesis develops 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 chemotherapy and can last 6 to 7 days.

Anticipatory nausea and/or vomiting is the occurrence of nausea and/or vomiting before patients receive their next chemotherapy treatment. Because it is a conditioned response, anticipatory emesis can occur only 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.” 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 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, also 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 and divides chemotherapeutic agents into 4 levels according to the percentage of patients not receiving antiemetic prophylaxis who experience acute emesis. This classification, which has been updated with recently introduced drugs, is used in these NCCN practice guidelines. Panel members from 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. NCCN guidelines currently outline treatment using 4 categories of emetogenic potential (see AE-6 and AE-7), 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 algorithms were revised for high and moderate emetogenic potential agents to incorporate a dosing schedule that covers both acute and delayed emesis into a single algorithm.

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, bortezomib, trastuzumab) (see AE-6). Antiemetic agents can be administered by the oral, rectal, intravenous (IV), or intramuscular route. When compared with other routes of administration, oral formulations of antiemetic agents are equally effective, safe, more convenient, and less costly. For patients unable to swallow or digest tablets because of emesis, IV antiemetics are required. The lowest, maximally effective dose of an antiemetic should be used. 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 (such as ondansetron, granisetron, dolasetron mesylate, palonosetron) represents a significant advance in antiemetic therapy.31-33 All of these agents have been shown to be effective in controlling the acute nausea and/or vomiting associated with cancer chemotherapy.33-47 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.33 Initial studies in patients receiving moderately emetogenic chemotherapy showed that a single IV dose of palonosetron was comparable to a single IV dose of dolasetron for the prevention of acute chemotherapy-induced nausea and emesis; however, palonosetron was superior to dolasetron in preventing delayed emesis.48 The safety and side-effect profiles of palonosetron were indistinguishable from the control 5-HT3 antagonists (ondansetron and dolasetron) using data submitted to the FDA. Palonosetron is administered intravenously and is FDA approved as a single dose of 0.25 mg IV over 30 seconds on day 1; it is recommended (category 1) for acute and delayed emesis prevention when using moderate emetic risk chemotherapy.48 Palonosetron is superior to other 5-HT3 antagonists for preventing delayed nausea. However, repeat dosing of palonosetron in the days after chemotherapy (ie, days 2 or 3) is not supported by the scientific literature. Repeat dosing of palonosetron in the setting of multiday chemotherapy regimens has not been studied.

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.48-68 Studies have demonstrated that the 5-HT3 antagonists are equally effective and have mild, infrequent side effects. A recent meta-analysis found no difference in efficacy, except that granisetron may be more efficacious than tropisetron during the first 24 hours.69 The addition of dexamethasone improves the efficacy of the
antiemetic regimen containing 5-HT3 antagonists. Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis but appear to be less effective for delayed emesis. However, palonosetron is effective for preventing both delayed and acute emesis. A recent meta-analysis of randomized controlled trials found that adding a 5-HT3 antagonist to dexamethasone did not improve the antiemetic effect of dexamethasone for preventing delayed emesis. Another recent study found that 5-HT3 antagonists (except palonosetron, which was not studied) were not more effective than prochlorperazine for preventing delayed emesis.

**NK-1–Receptor Antagonist**

In March 2003, the Food and Drug Administration (FDA) approved aprepitant, which 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 all other commercially available antiemetics. Aprepitant has been shown to augment the antiemetic activity of the 5-HT3–receptor antagonists and the corticosteroid dexamethasone to inhibit both acute and delayed cisplatin-induced emesis. When combined with 5-HT3 antagonists and dexamethasone on day 1 before cisplatin-based highly emetogenic chemotherapy and continued orally along with dexamethasone on days 2 and 3 after chemotherapy, aprepitant significantly improved control of acute and delayed chemotherapy-induced nausea and emesis. The oral doses of aprepitant are 125 mg on day 1 (before chemotherapy) and then 80 mg on days 2 and 3 (after chemotherapy). There are no studies documenting efficacy or safety of chronic dosing with aprepitant. It is possible that the drug-drug interaction profile may change with chronic dosing.

A recent phase III study (866 patients) showed that an aprepitant regimen is better than a standard regimen for preventing vomiting in patients receiving moderately emetogenic chemotherapy (non-cisplatin based) during 120 hours after initiation of chemotherapy (complete response, 50.8% versus 42.5%, \( P=.015 \)); however, 40% of patients (receiving either regimen) still had significant nausea. The aprepitant regimen included aprepitant, ondansetron, and dexamethasone; the standard regimen included ondansetron and dexamethasone. An analysis of 2 phase III randomized trials found that an aprepitant regimen is useful for patients receiving moderately emetogenic chemotherapy plus high-dose cisplatin. The FDA has approved the use of aprepitant for preventing emesis in patients receiving moderately emetogenic chemotherapy. A meta-analysis (7 randomized controlled trials) in patients receiving highly emetogenic chemotherapy found that NK-1 receptor antagonists used alone or with standard therapy for acute emesis were not better than the control; however, for delayed emesis, NK-1 receptor antagonists were better than the control. A recent phase II study (39 patients) found that combining palonosetron, aprepitant, and dexamethasone was useful for various chemotherapeutic regimens (moderate to moderate-highly emetogenic); 80% of patients had a complete response (no emetic episodes and no rescue medication).

**Drug Interactions**

Aprepitant is simultaneously a substrate, moderate inducer, and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4); aprepitant also induces CYP2C9. 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 http://www.merck.com/product/usa/pi_circulars/e/emend/emend_pi.pdf.)
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 nonchemotherapeutic drugs (including warfarin, dexamethasone, methylprednisolone, oral contraceptives). 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.


When given with aprepitant, the AUC of dexamethasone is increased; thus, the NCCN guidelines include reduced dose recommendations for dexamethasone in this setting. The AUC of methylprednisolone is also increased when given with aprepitant; thus, the methylprednisolone dose should also be decreased in this setting. However, if dexamethasone (or prednisone or any corticosteroid) is being administered as part of anticancer therapy (eg, CHOP regimen), the corticosteroid dose should not be reduced.

Aprepitant decreases the AUC for patients taking oral contraceptives; the package insert should be consulted in this setting.

Certain drugs can affect the AUCs of aprepitant. Concomitant administration with CYP3A4 inhibitors (eg, ketoconazole, itraconazole, erythromycin) may lead to increased aprepitant AUCs, whereas concomitant administration with CYP3A4 inducers (eg, carbamazepine, rifampin, 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,80 substituted benzamides,81, 82 antihistamines,83 butyrophenones,84 corticosteroids,85-87 benzodiazepines,88, 89 and cannabinoids.90, 91 Most drugs used to prevent chemotherapy-induced emesis are classified as dopamine antagonists, serotonin antagonists, and other antagonists. Combination antiemetic therapy is more effective than single-agent therapy.

Recently, olanzapine (thiobenzodiazepine) was found to be effective for acute and delayed emesis in a phase II trial in patients (n = 30) who received cyclophosphamide, doxorubicin, and/or cisplatin;92, 93 other studies have also showed the value of olanzapine for delayed and refractory emesis as well as nausea.94-97 However, olanzapine should be used with caution in elderly patients (see boxed warning/label indication regarding type II diabetes and hyperglycemia [http://pi.lilly.com/us/zyprexa-pi.pdf]).98

Treatment Issues

Selected issues that arose in the panel’s deliberations on the guidelines are discussed in the following sections. As new data about 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 1, reflecting the
large number of randomized controlled trials that have focused on antiemetic management.

**Principles of Emesis Control**

These principles are discussed in the algorithm (see AE-1).

- The goal is to prevent nausea and/or vomiting.
- The risk of emesis and nausea lasts for at least 4 days for persons receiving chemotherapy of high and moderate emetogenic potential. Patients need to be protected throughout the full period of risk.
- Oral and IV antiemetic formulations have equivalent efficacy.
- The lowest, maximally effective dose of the antiemetic(s) is recommended before chemotherapy or radiation therapy.
- The toxicity of the specific antiemetic(s) should be considered.
- Antiemetic regimens should be chosen based on the emetogenic potential of the chemotherapy regimen, as well as patient-specific risk factors.

In addition to emesis induced by chemotherapy, emesis in cancer patients can also potentially be caused by:

- Partial or complete bowel obstruction
- Vestibular dysfunction
- Brain metastases
- Electrolyte imbalance: hypercalcemia, hyperglycemia, hyponatremia
- Uremia
- Concomitant drug treatments, including opiates
- Gastroparesis induced by a tumor or chemotherapy, such as vincristine.
- Psychophysiologic factors, including anxiety as well as anticipatory nausea and vomiting.

**Prevention of Acute Emesis**

To prevent acute emesis, antiemetic therapy should start before the administration of chemotherapy and then should cover the first 24 hours. For highly emetogenic drugs, the regimens are described on AE-2. For moderately emetogenic drugs, the regimens are described on AE-3. For low and minimally emetogenic drugs, the regimens are described on AE-4. This section discusses prechemotherapy and postchemotherapy emesis prevention rather than primary treatment.

**P**re**c**hemotherapy Emesis Prevention

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

Highly emetogenic drugs include altretamine, carmustine > 250 mg/m², cisplatin at 50 mg/m² or more, cyclophosphamide > 1500 mg/m², dacarbazine, mechlorethamine, procarbazine (oral), streptozocin, or AC combinations (doxorubicin or epirubicin with cyclophosphamide). The antiemetic regimen for these highly emetogenic drugs on day 1 includes aprepitant, dexamethasone, and a 5-HT3 antagonist with or without lorazepam (category 1 for the combined regimen [see AE-2]); note that the regimen and doses are often modified on days 2 to 4 after chemotherapy.

A recent Canadian meta-analysis suggests that it is not cost-effective to use 5-HT3 antagonists (ie, ondansetron) on days 2 to 4 to prevent delayed emesis; however, ondansetron (when used alone) did protect...
against delayed emesis in this meta-analysis. Palonosetron was not assessed in these studies. The NCCN panel recommends the use of 5-HT3 antagonists as one of several options to prevent delayed emesis for moderately emetogenic agents (see AE-3).

The antiemetic regimen for moderately emetogenic drugs on day 1 (see AE-6) includes dexamethasone and a 5-HT3 antagonist with or without lorazepam; aprepitant should be added for patients receiving the combination of an anthracycline and cyclophosphamide and for select patients receiving other chemotherapies of moderate emetic risk (eg, carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate) (see AE-3). Any one of the 5-HT3 antagonists can be used, because they are all category 1. Note that the regimens differ on days 2 to 4.

The antiemetic regimen for low emetogenic drugs (see AE-7) includes non–5-HT3 antagonists, such as dexamethasone, prochlorperazine, or metoclopramide, with or without lorazepam (see AE-4).

For 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 (see AE-2). When given with aprepitant, dexamethasone is used at a dosage of 12 mg on day 1 and then 8 mg on days 2 to 4; the dose can be oral or IV. Because aprepitant increases dexamethasone levels, it is necessary to reduce the dose of dexamethasone when using it as an antiemetic with aprepitant. However, if dexamethasone (or any corticosteroid) is being administered as part of anticancer therapy, the corticosteroid dose should not be reduced. All 4 5-HT3–receptor antagonists (ie, ondansetron, granisetron, dolasetron, palonosetron) are considered to have similar effectiveness for control of acute emesis. 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).

Postchemotherapy/Delayed Emesis Prevention
The best management for delayed emesis is prevention. For chemotherapy involving agents with high emetogenic potential, the primary treatment is continued through the period when delayed emesis may occur. Using this strategy, prophylaxis continues for 2 to 3 days after completion of a chemotherapy cycle.

For drugs with moderate emetogenic potential, postchemotherapy prevention depends on what antiemetics were used before chemotherapy. For example, palonosetron (category 1) is only administered on day 1 (see AE-3). If aprepitant was used on day 1, then it is continued on days 2 and 3 and is given with or without dexamethasone or lorazepam. Alternatively, either dexamethasone, or a 5-HT3 antagonist can be used; lorazepam may be used with either agent.

Breakthrough Treatment
Breakthrough emesis presents a difficult situation, because refractory ongoing nausea and/or vomiting is often challenging to reverse (see AE-B). 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. The oral route is not likely to be feasible because of 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, metoclopramide, butyrophenones (eg, haloperidol), cannabinoids, corticosteroids, and agents such as lorazepam may be required. Nabilone (cannabinoid) was recently 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 with attention to various possible nonchemotherapy-related reasons for breakthrough emesis with the current cycle, such as brain metastases, electrolyte abnormalities, tumor infiltration of the bowel or other GI abnormality, and other comorbidities (see AE-1). 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 AE-B). Consider using antacid therapy (eg, proton pump inhibitors, H2 blockers) if patients have dyspepsia, because patients sometimes have difficulty discriminating heartburn from nausea.

**Radiation-Induced Nausea and/or Vomiting**

Primary prophylaxis for radiation-induced nausea and/or vomiting is based on the site of radiation and whether it is combined with chemotherapy (see AE-8). When radiation is combined with chemotherapy, prophylaxis is dictated by the emetogenic potential of the chemotherapy regimen.

Radiation to the upper abdomen may be treated with oral ondansetron (8 mg 2 to 3 times daily), based on the results of a randomized study comparing oral ondansetron, 8 mg 2 times daily, 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. Other options are oral dexamethasone (2 mg 3 times daily) or oral granisetron (2 mg every day).

Total body irradiation may be treated with either ondansetron (8 mg 2 to 3 times daily) or granisetron; either agent can be given with or without oral dexamethasone (2 mg 3 times daily). The dose of granisetron is either 2 mg oral every day or 3 mg IV every day (category 2B recommendation, because this dose of granisetron is higher than the dose typically used). No primary treatment is recommended for patients receiving irradiation to other sites.

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**

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 (see AE-9). 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 both been combined with antiemetics for anticipatory nausea and/or vomiting with mixed results. The usual starting dose of alprazolam is 0.5 mg oral 3 times daily, given 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 oral 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 multiday chemotherapy are at risk for both acute and delayed nausea as well as emesis 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 after chemotherapy administration has concluded also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. General principles for managing multiday emetogenic chemotherapy regimens recommended (category 2B) by the panel are described in the algorithm (see AE-A).

Disclosures for the NCCN Antiemesis Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers’ bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Amgen Inc.; Genentech, Inc; GlaxoSmithKline; Merck & Co., Inc; MGI PHARMA, INC.; Ortho Biotech Products, L.P.; and sanofi-aventis. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
References


