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Antiemesis

Clinical Practice Guidelines in Oncology

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Overview

Chemotherapy-induced (or radiotherapy-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. Nausea and vomiting can also result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of performance status and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment.[1–4]

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) specific chemotherapeutic agents used; 2) dosage of the agents; 3) schedule and route

NCCN Clinical Practice Guidelines in Oncology for Antiemesis

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, antiemesis, nausea and vomiting, chemotherapy-induced, 5-HT3–receptor antagonists, NK-1 receptor antagonists *(JNCCN* 2012;10:456–485)

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN 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® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Antiemesis Panel

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Antiemesis Panel members can be found on page 485. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

of administration of the agents; 4) target of the radiation therapy (e.g., whole body, upper abdomen); and 5) individual patient variability (e.g., age, sex, prior chemotherapy, history of alcohol use).[5,6] More than 90% of patients receiving highly emetogenic chemotherapy will have episodes of vomiting. However, only approximately 30% of these patients will vomit if they receive prophylactic (preventive) antiemetic regimens before treatment with highly emetogenic chemotherapy.[5,7,8] Although vomiting can often be prevented or substantially decreased with prophylactic antiemetic regimens, nausea is much harder to control.[9,10] These NCCN Guidelines are intended to provide an overview of the treatment principles for preventing chemotherapy-induced (or radiotherapy-induced) vomiting and nausea, and recommendations for antiemetic prophylaxis according to the emetogenic potential of antitumor therapies. These guidelines are updated yearly by a multidisciplinary panel of experts.

Pathophysiology of Emesis

Vomiting results from stimulation of a multistep reflex pathway controlled by the brain.[5] Vomiting is triggered by afferent impulses to the vomiting center (located in the medulla) from the chemoreceptor trigger zone, pharynx, gastrointestinal 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.[11]

Text continues on p. 470

PRINCIPLES OF EMESIS CONTROL FOR THE CANCER PATIENT

- Preventing nausea/vomiting is the goal.
- The risk for nausea/vomiting in persons undergoing 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 agonists 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-specific factors.
- Other potential causes of emesis in cancer patients 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- (e.g., vincristine) induced or other causes (e.g., diabetes)
  - Psychophysiologic:
    - Anxiety
    - Anticipatory nausea and vomiting
- For use of antiemetics for nausea and vomiting that are not related to radiation and/or chemotherapy, see the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Palliative Care (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).
- For multidrug regimens, select antiemetic therapy based on drug with the highest emetic risk. See Emetogenic Potential of Antineoplastic Agents (page 464).
- Consider using an H_2 blocker or proton pump inhibitor to prevent dyspepsia, which can mimic nausea.
- Lifestyle measures may help 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 "What You Should Know About Cancer Treatment, Eating Well, and Eating Problems" (www.cancer.gov/cancertopics/coping/eatinghints/page2).

HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY: ACUTE AND DELAYED EMESIS PREVENTION[a,b,c]

High[a] →

Start before chemotherapy[c,d]

- Serotonin (5-HT3) antagonist[e]
  - Dolasetron, 100 mg PO[f]
    or
  - Granisetron, 2 mg PO or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1[f] or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24-48 h prior to first dose of chemotherapy; maximum duration of patch is 7 d
    or
  - Ondansetron, 16-24 mg PO or 8-24 mg (max 32 mg/d) IV day 1[f]
    or
  - Palonosetron, 0.25 mg IV day 1 (preferred)

AND

- Steroid[g]
  - Dexamethasone, 12 mg PO or IV day 1, 8 mg PO daily days 2-4
    (with aprepitant, 125 mg or fosaprepitant, 115 mg IV day 1)
    or
  - Dexamethasone, 12 mg PO or IV day 1, 8 mg PO day 2, then 8 mg PO BID days 3 and 4
    (with fosaprepitant, 150 mg IV day 1)

AND

- Neurokinin 1 antagonist
  - Aprepitant, 125 mg PO day 1, 80 mg PO daily days 2-3
    or
  - Fosaprepitant, 150 mg IV day 1 only
    or
  - Fosaprepitant, 115 mg IV on day 1 only, then aprepitant, 80 mg PO daily days 2-3
- ± Lorazepam, 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4
- ± H_2 blocker or proton pump inhibitor

→ See Breakthrough Treatment (page 463)

[a] Data for post-cisplatin (≥ 50 mg/m^2) emesis prevention are category 1; others are category 2A.
[b] See Emetogenic Potential of Antineoplastic Agents (page 464).
[c] Antiemetic regimens should be chosen based on the drug with the highest emetic risk and patient-specific risk factors.
[d] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (page 468).
[e] Order of listed antiemetics is alphabetical and does not reflect preference.
[f] Some NCCN Member Institutions use a 5-HT3 antagonist on days 2-3.
[g] Use of steroids is contraindicated with drugs such as interleukin-2 (e.g., aldesleukin) and interferon.

MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY: EMESIS PREVENTIO N[b,c,i]

DAY 1

Start before chemotherapy[c,d]
- Serotonin (5-HT3) antagonist[e]
  - Dolasetron, 100 mg PO (category 1)
    or
  - Granisetron, 2 mg PO or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1 (category 1) or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24-48 h before first dose of chemotherapy; maximum duration of patch is 7 d
    or
  - Ondansetron, 16-24 mg PO or 8-12 mg (maximum 32 mg/day) IV (category 1)
    or
  - Palonosetron, 0.25 mg IV (category 1) day 1 only (preferred)[h]

AND
- Steroid[g]
  - Dexamethasone, 12 mg PO or IV

WITH/WITHOUT
- Neurokinin 1 antagonist (for selected patients, where appropriate)[i]
  - Aprepitant, 125 mg PO
  - or
  - Fosaprepitant, 115 mg IV day 1 only
- ± Lorazepam, 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H_2 blocker or proton pump inhibitor

DAYS 2 and 3

- Serotonin (5-HT3) antagonist monotherapy[e]
  - Dolasetron, 100 mg PO daily
    or
  - Granisetron, 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV
    or
  - Ondansetron, 8 mg PO BID or 16 mg PO daily or 8 mg (maximum 32 mg/day) IV

OR
- Steroid monotherapy[h]
  - Dexamethasone, 8 mg PO or IV daily

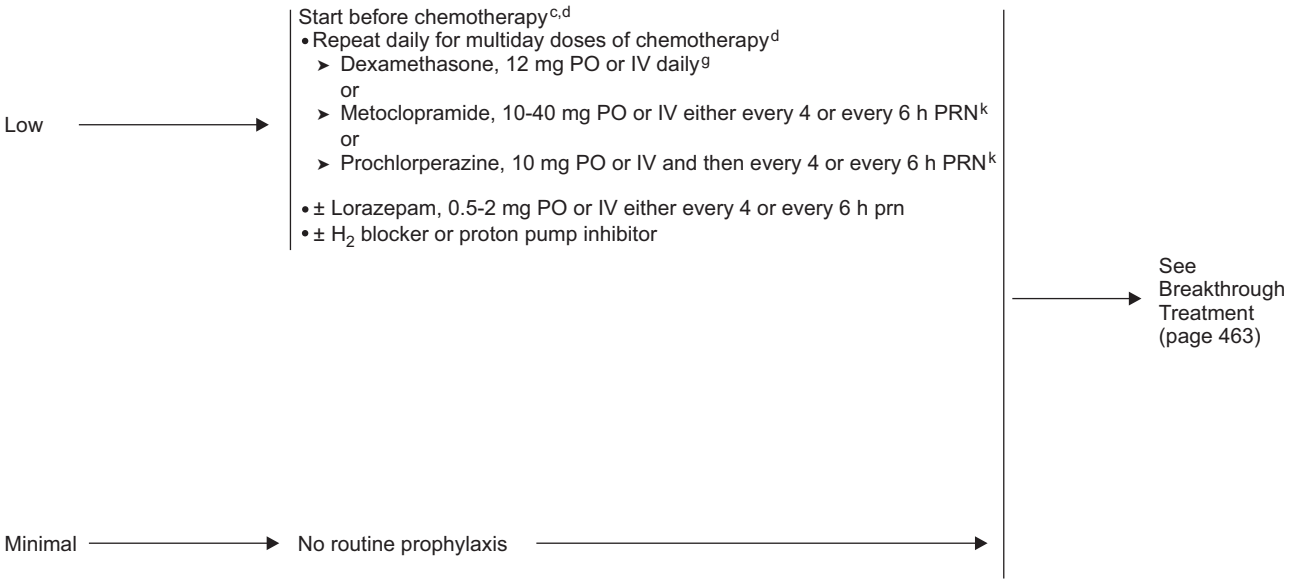
OR
- Neurokinin 1 antagonist ± steroid
(if neurokinin 1 antagonist used on day 1)[j]
  - Aprepitant, 80 mg PO ± dexamethasone 8 mg PO or IV daily

- ± Lorazepam, 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H_2 blocker or proton pump inhibitor

See Breakthrough Treatment (page 463)

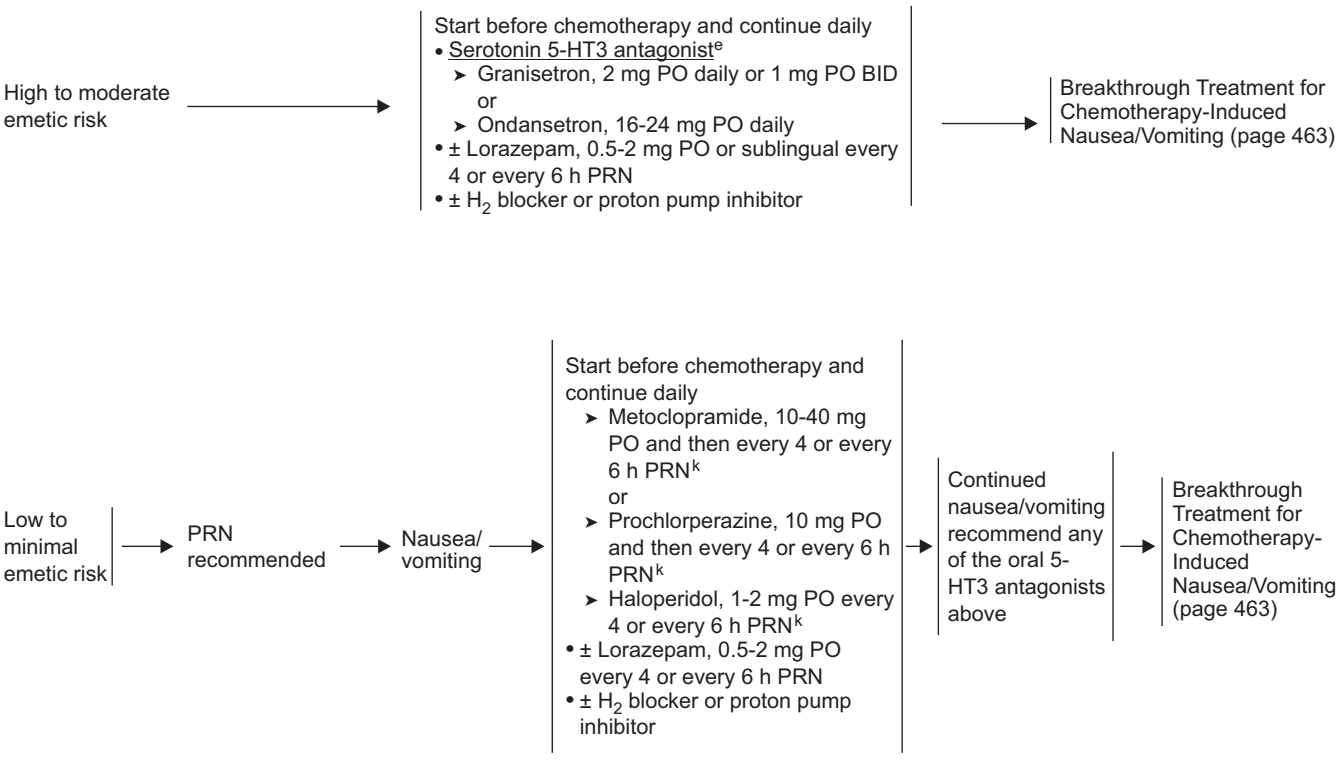
[b] See Emetogenic Potential of Antineoplastic Agents (page 464).
[c] Antiemetic regimens should be chosen based on the drug with the highest emetic risk and patient-specific risk factors.
[d] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (page 468).
[e] Order of listed antiemetics is alphabetical and does not reflect preference.
[g] Use of steroids is contraindicated with drugs such as interleukin-2 (e.g., aldesleukin) and interferon.
[h] Data with palonosetron is based on randomized studies with 2-drug combinations.
[i] Data for post-carboplatin, ≥ 300 mg/m^2; cyclophosphamide, ≥ 600-1000 mg/m^2; and doxorubicin, ≥ 50 mg/m^2 emesis prevention are category 1.
[j] As per high emetic risk prevention, aprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients receiving other chemotherapies of moderate emetic risk (e.g., carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, methotrexate); see page 459.

LOW AND MINIMAL EMETIC RISK INTRAVENOUS CHEMOTHERAPY: EMESIS PREVENTION[c,d,l]



[c]Antiemetic regimens should be chosen based on the drug with the highest emetic risk and patient-specific risk factors.
[d]See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (page 468).
[g]Use of steroids is contraindicated with drugs such as interleukin-2 (e.g., aldesleukin) and interferon.
[k]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.
[l]See Emetogenic Potential of Antineoplastic Agents (page 464).

ORAL CHEMOTHERAPY: EMESIS PREVENTION[c,d,m,n]



[c]Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[d]See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (page 468).
[e]Order of listed antiemetics is alphabetical and does not reflect preference.
[k]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.
[m]See Emetogenic Potential of Oral Antineoplastic Agents (page 465).
[n]These antiemetic recommendations apply to oral chemotherapy only. When combined with IV agents in a combination chemotherapy regimen, the antiemetic recommendations for the agent with the highest level of emetogenicity should be followed. If multiple oral agents are combined, emetic risk may increase and require prophylaxis.

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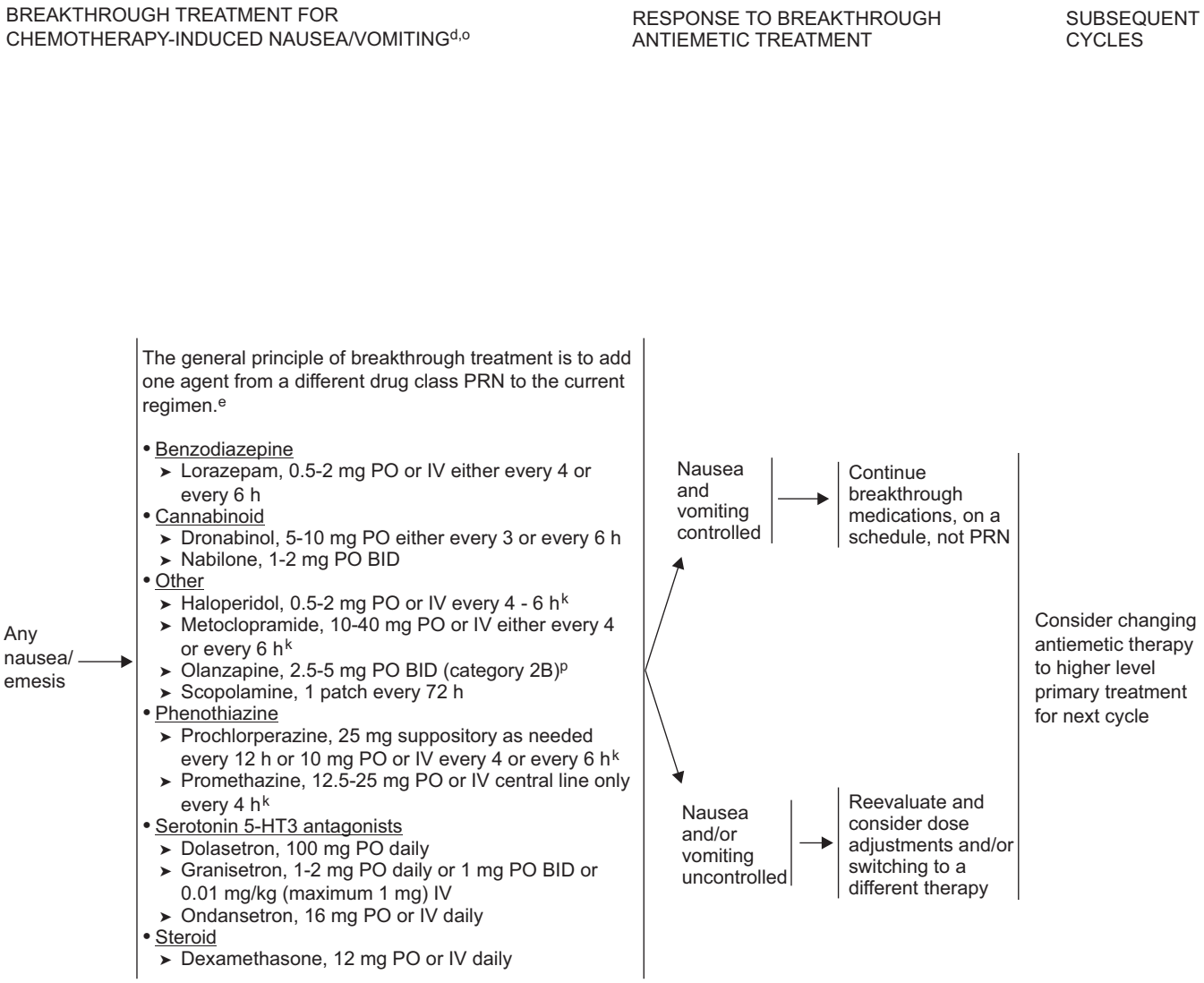


[d] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (page 468).
[e] Order of listed antiemetics is alphabetical and does not reflect preference.
[k] Monitor for dystonic reactions; use diphenhydramine, 25-50 mg PO or IV either every 4 or every 6 h for dystonic reactions. If allergic 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.
[o] See Principles for Managing Breakthrough Treatment (page 469).
[p] See blackbox warning/label indication regarding type II diabetes, hyperglycemia, and death in elderly patients with dementia.

EMETOGENIC POTENTIAL OF ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT	
High emetic risk (> 90% frequency of emesis)[q,r]	• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide[q] • Carmustine (> 250 mg/m^2) • Cisplatin (≥ 50 mg/m^2) • Cyclophosphamide (> 1500 mg/m^2) • Dacarbazine	• Doxorubicin (> 60 g/m^2) • Epirubicin (> 90 g/m^2) • Ifosfamide (≥ 10 g/m^2) • Mechlorethamine • Streptozocin
Moderate emetic risk (30%-90% frequency of emesis)[q,s]	• Aldesleukin (> 12-15 million IU/m^2) • Amifostine (> 300 mg/m^2) • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin[s] • Carmustine[s] (≤ 250 mg/m^2) • Cisplatin[s] (< 50 mg/m^2) • Clofarabine • Cyclophosphamide (≤ 1500 mg/m^2) • Cytarabine (> 200 mg/m^2)	• Dactinomycin[s] • Daunorubicin[s] • Doxorubicin[s] (≤ 60 mg/m^2) • Epirubicin[s] (≤ 90 mg/m^2) • Idarubicin • Ifosfamide[s] (< 10 g/m^2) • Interferon alfa (≥ 10 million IU/m^2) • Irinotecan[s] • Melphalan • Methotrexate[s] (≥ 250 mg/m^2) • Oxaliplatin • Temozolomide
Low emetic risk (10%-30% frequency of emesis)[q]	• Amifostine (≤ 300 mg) • Aldesleukin (≤ 12 million IU/m^2) • Cabazitaxel • Cytarabine (low-dose) (100-200 mg/m^2) • Docetaxel • Doxorubicin (liposomal) • Eribulin • Etoposide • 5-Fluorouracil • Floxuridine • Gemcitabine • Interferon alfa (> 5 < 10 million IU/m^2)	• Ixabepilone • Methotrexate (> 50 mg/m^2 < 250 mg/m^2) • Mitomycin • Mitoxantrone • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Thiotepa • Topotecan
Minimal emetic risk (< 10% frequency of emesis)[q]	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine (2-chlorodeoxyadenosine) • Cytarabine (< 100 mg/m^2) • Decitabine • Denileukin diftitox • Dexrazoxane • Fludarabine • Interferon alpha (≤ 5 million IU/m^2) • Ipilimumab	• Methotrexate (≤ 50 mg/m^2) • Nelarabine • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Rituximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vinorelbine

Adapted with permission from Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Onc 1997;15:103-109; and Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--an update. Support Care Cancer 2011;19(Suppl 1):S43–47.

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

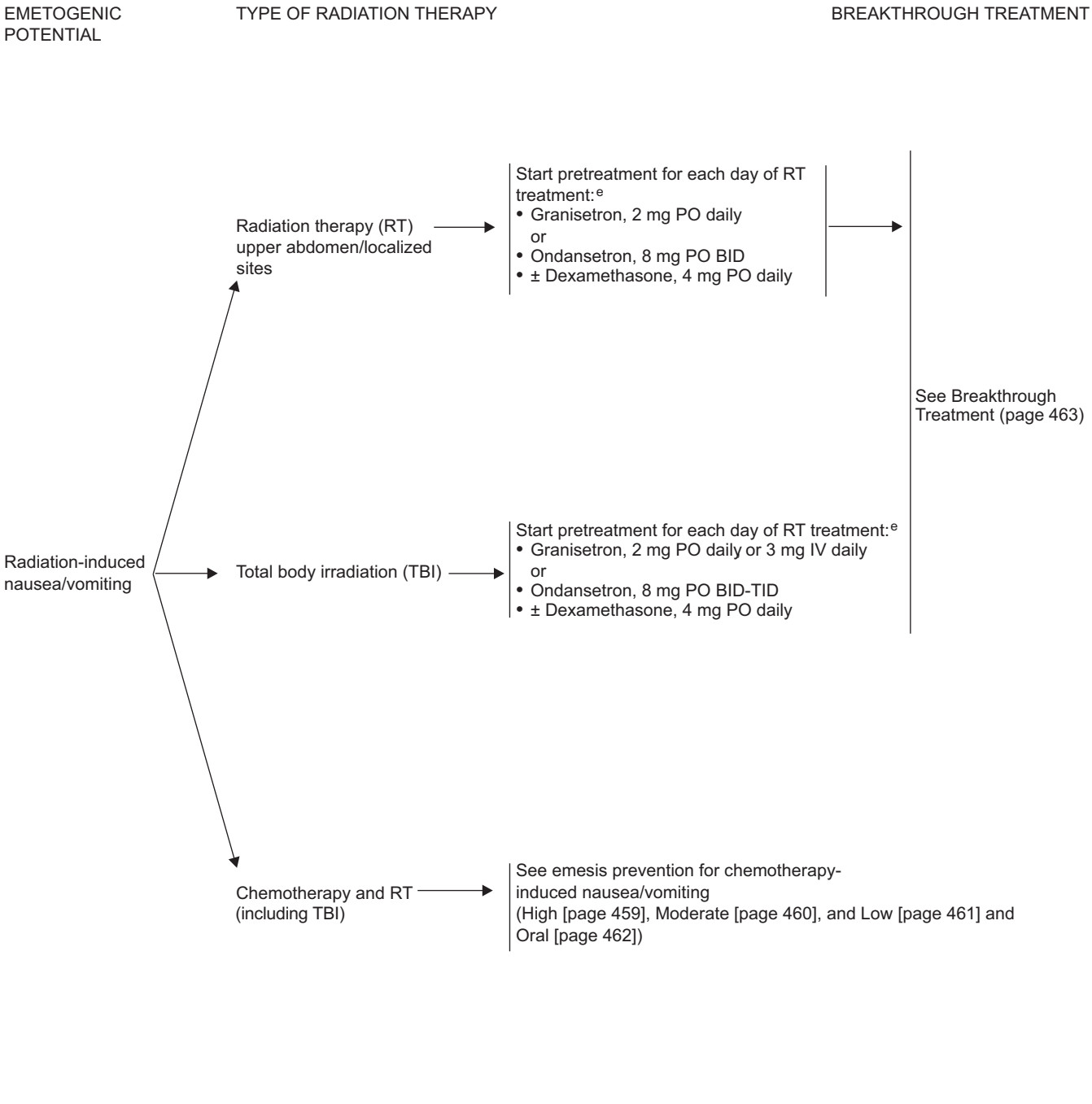
EMETOGENIC POTENTIAL OF ORAL ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT
Moderate to High	• Altretamine • Busulfan (≥ 4 mg/d) • Cyclophosphamide (≥ 100 mg/m^2/d) • Estramustine • Etoposide • Lomustine (single day) • Procarbazine • Temozolomide (> 75 mg/m^2/d)
Minimal to Low	• Bexarotene • Busulfan (< 4 mg/d) • Capecitabine • Chlorambucil • Cyclophosphamide (< 100 mg/m^2/d) • Dasatinib • Erlotinib • Everolimus • Fludarabine • Gefitinib • Hydroxyurea • Imatinib • Lapatinib • Lenalidomide • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Pazopanib • Sorafenib • Sunitinib • Temozolomide (≤ 75 mg/m^2/d) • Thalidomide • Thioguanine • Topotecan • Tretinoin • Vandetanib • Vorinostat

Adapted with permission from Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Onc 1997;15:103-109; and Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—an update. Support Care Cancer 2011;19(Suppl 1):S43-47.

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

RADIATION-INDUCED EMESIS PREVENTION/TREATMENT



[e]Order of listed antiemetics is alphabetical and does not reflect preference.

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ANTICIPATORY EMESIS PREVENTION/TREATMENT

Anticipatory nausea/vomiting →

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

PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS

- Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea/vomiting based on the emetogenic potential of the individual chemotherapy agents and their sequence. Therefore, 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. 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.

- Examples illustrating the above include BEP (bleomycin, 30 units IV weekly; etoposide, 100 mg/m^2 IV days 1-5; and cisplatin, 20 mg/m^2 IV days 1-5) versus ASHAP (doxorubicin, 25 mg/m^2 IV day 1; methylprednisolone, 500 mg/d IV days 1-5; cisplatin, 25 mg/m^2 IV continuous infusion days 1-4; followed by cytarabine, 2000 mg/m^2 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 because of 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:
A 5-HT3 receptor antagonist should be administered before the first dose of moderately or highly emetogenic chemotherapy (see pages 459-460).

- Dexamethasone should be administered once daily (either orally or intravenously) for moderately or highly emetogenic chemotherapy and for 2-3 days after chemotherapy for regimens that are likely to cause significant delayed emesis (see pages 459-460). Dexamethasone should not be added when the chemotherapy regimen already includes a corticosteroid (as in ASHAP illustrated above).
- 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 (see pages 459-460). Repeat dosing of palonosetron, 0.25 mg IV, is likely to be safe, based on the dose-ranging phase II trial in which 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 with 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 multiday chemotherapy is not yet known.
- Aprepitant may be used for multiday chemotherapy regimens likely to be highly emetogenic and associated with significant risk for delayed nausea and emesis (see page 459). Category 1 evidence is available for single-day chemotherapy regimens only, and aprepitant should be administered at 125 mg orally 1 hour before 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. Based on phase II data, aprepitant, 80 mg, may be safely administered on days 4 and 5 after multiday chemotherapy. Whether dosing aprepitant after day 3 improves control of nausea or emesis in this clinical setting is not yet known. Note that fosaprepitant dimeglumine (115 mg) may be substituted for aprepitant (125 mg) on day 1 only. 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.

PRINCIPLES FOR MANAGING BREAKTHROUGH EMESIS

- Breakthrough emesis presents a difficult situation, because correction of refractory ongoing nausea/vomiting is often challenging to reverse. Nausea/vomiting is generally far easier to prevent than to treat.
- 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 with 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 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 (e.g., 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.
- Before 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
- Before the next cycle of chemotherapy, reassess both the day 1 and postchemotherapy antiemetic regimen that 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, such as dopamine antagonists (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 (e.g., Hesketh method).
  - Possibly switch to a different 5-HT3 receptor antagonist. 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 noncurative, 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 (H_2 blocker or proton pump inhibitor).

Text continued from p. 457

The chemoreceptor trigger zone, vomiting center, and gastrointestinal 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.[12,13] 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.[14]

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 vomiting.[15–17] 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 are other populations.[10] Delayed nausea is more common than acute nausea, is often more severe, and tends to be resistant to treatment.[17]

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 patient age and gender (with women and patients < 50 years more prone), environment in which chemotherapy is administered, 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.[18,19]

Delayed-onset nausea and/or vomiting develops in patients more than 24 hours after chemotherapy administration.[18,19] 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 occurs 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.[20,21] 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.[22] Breakthrough emesis refers to vomiting that occurs despite prophylactic treatment and/or requires "rescue" with antiemetic agents.[23] 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.[23–25] The gastrointestinal 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.[23,26]

Emetogenicity of Chemotherapy

The frequency of chemotherapy-induced emesis depends primarily on the emetogenic potential of the specific chemotherapeutic agents used. Several clas-

sifications have been developed to define the emetogenicity of chemotherapy; however, none has been universally accepted.[11,27–30]

Hesketh et al.[7] 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 et al.[9,31]; 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 panel to include recently introduced drugs, is used in these NCCN Guidelines. Experts representing the panels of all the published antiemetic treatment guidelines met to prepare a single consensus document. Although this process is ongoing, the consensus guidelines have been published.[8,32] These guidelines currently outline treatment using 4 categories of emetogenic potential for intravenous 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 guidelines attempt to define antiemetic regimens for particular chemotherapy drugs that cover the entire duration 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, these guidelines incorporate a dosing schedule that covers both acute and delayed emesis into a single algorithm. The panel members have also categorized the emetogenic potential of oral antineoplastic agents.[9]

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 (e.g., imatinib, erlotinib). Antiemetic agents can be administered via the oral, rectal, intravenous, intramuscular, or transdermal route. Oral and intravenous 5-HT3 antagonists have equivalent efficacy when used at the appropriate doses.[8,26] For patients unable to swallow or digest tablets because of emesis, intravenous antiemetics are required. 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 experience different responses. 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 (i.e., dolasetron mesylate, granisetron, ondansetron, palonosetron) represents a significant advance in antiemetic therapy.[33–35] All of these agents have been shown to be effective in controlling the acute nausea and/or vomiting associated with cancer chemotherapy.[35–49]

Palonosetron is a 5-HT3 antagonist with an approximately 100-fold higher binding affinity for the 5-HT3 receptor compared with the other serotonin antagonists (i.e., ondansetron, granisetron, and dolasetron). It has a half-life of approximately 40 hours, which is significantly longer than that of other commercially available 5-HT3 antagonists.[35] Data suggest that palonosetron is associated with prolonged inhibition of the 5-HT3 receptor and thus differs from other 5-HT3 antagonists (e.g., ondansetron, granisetron).[50]

Several large, multicenter, double-blind, randomized phase III trials have shown 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.[51–54] 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 intravenously) was comparable to a single dose of dolasetron (100 mg intravenously) for preventing acute chemotherapy-induced nausea and

emesis (CR rate, 63% vs. 53%, respectively); moreover, intravenous palonosetron was superior to dolasetron in preventing delayed emesis (CR rate, 54% vs. 39%; $P = .004$).[52] Approximately 60% of patients in the palonosetron arm and 70% in the dolasetron arm had received anthracycline in combination with cyclophosphamide; only 6% and 5% of patients, respectively, received concomitant corticosteroids.[52] In another study in patients receiving moderately emetogenic chemotherapy (N = 563 evaluable), a single dose of palonosetron (0.25 mg intravenously) was found to be superior to a single dose of ondansetron (32 mg intravenously) in preventing both acute (CR rate, 81% vs. 69%; $P < .01$) and delayed emesis (CR rate, 74% vs. 55%; $P < .01$); no concomitant corticosteroids were given in this study.[53] 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.

In a phase III randomized trial that compared palonosetron with ondansetron in patients receiving highly emetogenic chemotherapy (N = 667), most (67%) had received dexamethasone on day 1 of antiemetic therapy.[51] Among this subgroup of patients who received concomitant dexamethasone (n = 447), palonosetron (0.25 mg intravenously) was similar to ondansetron (32 mg intravenously) in preventing acute emesis (CR rate, 65% vs. 56%), but significantly more effective in preventing delayed emesis (CR rate, 41% vs. 25%; $P = .021$). In a more recent phase III randomized trial that compared palonosetron (at a higher dose of 0.75 mg intravenously) with granisetron (40 mcg/kg intravenously), 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%; $P < .0001$).[54]

Intravenous palonosetron 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 intravenous chemotherapy and is also recommended (category 1) for emesis prevention when using moderate emetic risk intravenous chemotherapy (see High Emetic Risk Intravenous Chemotherapy: Acute and Delayed Emesis Prevention, and Moderate Emetic Risk Intravenous Chemotherapy: Emesis Prevention, on pages 459 and 460, respectively, and Prevention of Acute and Delayed Emesis, page 475). The recommendation for palonosetron as the preferred 5-HT3 antagonist for antiemetic prophylaxis in the setting of high emetic risk chemotherapy is based on data from randomized studies (discussed earlier) with the 2-drug combination of palonosetron and dexamethasone.

Intravenous palonosetron is superior to other 5-HT3 antagonists for preventing delayed nausea.[15,51–54] Repeat dosing of palonosetron in the days after chemotherapy (i.e., days 2 or 3) is likely to be safe. However, in the setting of multiday chemotherapy, the need for repeat dosing with palonosetron is not yet known (see Managing Multiday Emetogenic Chemotherapy Regimens, page 478).

Many 5-HT3 antagonists can be delivered orally or intravenously. Although oral palonosetron has been approved by the FDA for moderate emetic risk chemotherapy, it is not available in the United States.[55] Note that intravenous dolasetron is no longer recommended for the prevention of nausea and vomiting in the algorithm, because it has been associated with an increased risk for cardiac arrhythmias.[56] Oral dolasetron is still recommended.

In addition, the FDA has approved the use of a granisetron transdermal system for chemotherapy-induced nausea and vomiting.[57] The patch containing 34.3 mg of granisetron is applied approximately 24 to 48 hours before the first dose of chemotherapy, and is worn for a maximum duration of 7 days. A phase III randomized study comparing the patch with oral granisetron in patients receiving either highly or moderately emetogenic chemotherapy found the patch to be noninferior to repeat dosing of the oral antiemetic granisetron over 3 to 5 days.[58,59]

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.[51–54,60–73] A meta-analysis found no difference in efficacy among ondansetron, granisetron, and dolasetron mesylate.[74] A recent meta-analysis of studies comparing ondansetron with granisetron has also confirmed the similar efficacy of these 5-HT3 antag-

onists in controlling acute and delayed nausea and vomiting, with similar safety profiles among these agents.[75] The most recent meta-analysis of randomized controlled trials comparing palonosetron with other available 5-HT3 antagonists showed that palonosetron was significantly more effective in preventing acute and delayed nausea and vomiting for both moderately and highly emetogenic chemotherapy agents.[76]

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 to 3 when used with palonosetron for moderately emetic chemotherapy.[77]

Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis but seem to be less effective for delayed emesis. A 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.[78] Another study found that 5-HT3 antagonists (except palonosetron, which was not studied) were not more effective than prochlorperazine for preventing delayed emesis.[17] Intravenous palonosetron seems to be effective for preventing both delayed and acute emesis.

NK-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 all other commercially available antiemetics. Aprepitant has been shown to augment the antiemetic activity of the 5-HT3 receptor antagonists and the corticosteroid dexamethasone for preventing both acute and delayed cisplatin-induced emesis.[79–81] In a randomized phase III trial comparing a standard antiemetic regimen (32 mg of intravenous ondansetron 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 alone in controlling both acute (CR rate, 89% vs. 78%; $P < .001$) and delayed emesis (CR rate, 75% vs. 56%; $P < .001$).[80] Another similarly designed randomized phase III study (N = 523 evaluable) also showed a significant benefit for adding aprepitant to ondansetron and dexamethasone compared with the 2-drug regimen alone for controlling both acute (CR rate, 83% vs. 68%; $P < .001$) and delayed emesis (CR rate, 68% vs. 47%; $P < .001$).[81] A pooled analysis of data combined from these 2 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.[79]

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 were associated with significantly increased protection compared with control.[82]

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%; $P = .015$). However, approximately 40% of patients (receiving either regimen) still experienced significant nausea.[83] The aprepitant regimen included aprepitant, ondansetron, and dexamethasone, whereas the standard regimen included ondansetron and dexamethasone.

A phase II study (N = 58) found that combining palonosetron, aprepitant, and dexamethasone was effective for preventing both acute and delayed emesis and nausea when using various chemotherapeutic regimens (moderate to moderate–highly emetogenic); 78% of patients experienced a CR (no emetic episodes and no rescue medication) during the overall time frame (from 0 to 120 hours after initiation of emetogenic therapy).[84] 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 intravenously), aprepitant (285 mg orally), and dexamethasone (20 mg) was effective; 76% and 66% of patients experienced a CR during the acute and delayed phases, respectively.[85]

Oral aprepitant is approved by the FDA for the prevention of nausea and vomiting in patients receiving highly (e.g., cisplatin-containing) and mod-

erately emetogenic chemotherapy.[86] The oral doses of aprepitant are 125 mg on day 1 (before chemotherapy) and then 80 mg on days 2 and 3 (after chemotherapy).[86,87] An intravenous version of aprepitant (fosaprepitant dimeglumine), which can be given on day 1 only, is also approved by the FDA. Intravenous fosaprepitant is given 30 minutes before chemotherapy on day 1 only, per the package insert.[88] If a higher dose of fosaprepitant is used (150 mg intravenously) on day 1, then oral aprepitant does not need to be given on days 2 to 3.[89,90] Note that the dexamethasone dosing is slightly different on days 3 and 4 (8 mg orally twice daily) when using the higher dose of fosaprepitant (150 mg intravenously) per the package insert.[88] A recent randomized study showed that a single dose of 150 mg of intravenous fosaprepitant was noninferior to the standard regimen with 3-day oral aprepitant.[91] No studies show 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.[92] Thus, aprepitant can alter the metabolism of certain drugs and change their plasma concentrations (i.e., area under the curve [AUC]). These interactions are more significant with orally administered forms of these drugs than with intravenous 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," according to the aprepitant package insert.[86] 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). Again, these interactions are more significant with orally administered forms of these drugs than with intravenous forms because of first-pass metabolism.

Induction of warfarin metabolism by aprepitant may lead to clinically significant reductions in international normalized ratio values, particularly for patients on therapeutic (compared with prophylactic) warfarin regimens. These changes, although brief in duration, may require increased patient monitoring.[86] 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.[86] Additionally, certain drugs can affect the AUCs of aprepitant. Concomitant administration with CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin) may lead to increased aprepitant AUCs, whereas concomitant administration with CYP3A4 inducers (e.g., 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,[93] substituted benzamides,[94,95] antihistamines,[96] butyrophenones,[97] corticosteroids,[98–100] benzodiazepines,[101,102] and cannabinoids.[103,104] 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.

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[105]; other studies have also shown the value of olanzapine for preventing delayed and refractory emesis and nausea.[106–109] 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).[110,111]

Treatment Issues

Clinicians should consider the new data on the use of antiemetics in patients receiving chemotherapy as it becomes available, even if the information has not been included in the guidelines. In contrast to

other NCCN Clinical Practice Guidelines in Oncology (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 described in the algorithm and are summarized here (see Principles of Emesis Control for the Cancer Patient, page 458). 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.[9] Patients must be protected throughout the entire period of risk, which lasts 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).[112] 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 should cover the first 24 hours after treatment. These guidelines describe the specific antiemetic regimens for highly, moderately, low, and minimally emetogenic intravenous drugs. Emesis prevention for oral chemotherapeutic agents is also described in these guidelines. This section discusses prechemotherapy and postchemotherapy emesis prevention rather than primary treatment.

Prechemotherapy Emesis Prevention: These guidelines specify different prophylactic antiemetic regimens for patients receiving chemotherapy of different emetogenic potential (i.e., 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, showing their effectiveness in a range of doses. Unless indicated, the order of listed antiemetics in these guidelines does not reflect preference.

Highly emetogenic intravenous drugs in the guidelines include carmustine at a dose greater than 250 mg/m^2; cisplatin at a dose of 50 mg/m^2 or greater; cyclophosphamide at a dose greater than 1500 mg/m^2; dacarbazine, doxorubicin at a dose greater than 60 mg/m^2; epirubicin at a dose greater than 90 mg/m^2; ifosfamide at a dose of 10 g/m^2 or greater; mechlorethamine; streptozocin; or anthracycline plus cyclophosphamide (AC) combinations (e.g., 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,[8] 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 with or without lorazepam and with or without either an H_2 blocker or a proton pump inhibitor (category 1 for the combined regimen)[23,26,80]; note that the regimen and doses are often modified on days 2 to 4 after chemotherapy. Although it is not recommended as a single agent, lorazepam is a useful adjuvant because it decreases anxiety.[26,102] Lorazepam is also recommended for patients who are at risk for anticipatory nausea and/or vomiting (see Anticipatory Emesis Prevention/Treatment, page 467). Antacid therapy (e.g., proton pump inhibitors, H_2 blockers) should be considered in patients who have dyspepsia, because sometimes they have difficulty discriminating heartburn from nausea.

For intravenous 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 dose of 12 mg on day 1, and it can be oral or intravenous. Note that intravenous fosaprepitant may be substituted for oral aprepitant on day 1 only. If appropriate, lorazepam (0.5–2.0 mg either every 4 or every 6 hours on days 1–4; either oral, intravenous, or sublingual) may be used

with each of these regimens (i.e., high, moderate, or low emetic risk). A recent phase III randomized trial suggested that palonosetron is preferred over granisetron for high emetic risk chemotherapy in combination with dexamethasone.[54] This trial has been criticized because 1) the control arm was not adequately dosed, and thus the trial "stacked the deck" in favor of palonosetron; 2) a larger non–FDA-approved dose of palonosetron was used (i.e., 0.75 mg intravenous); and 3) aprepitant was not used in this study. The superiority of palonosetron over other available 5-HT3 antagonists in preventing acute and delayed nausea and vomiting in the setting of high emetogenic chemotherapy was shown in a recent meta-analysis of randomized controlled trials.[76] Therefore, the panel recommends palonosetron as the preferred 5-HT3 antagonist for high emetic risk chemotherapy. As previously noted, the recommendation for palonosetron as the preferred 5-HT3 antagonist for antiemetic prophylaxis in this setting is based on data from randomized studies (discussed earlier) with the 2-drug combination of palonosetron and dexamethasone.

A Canadian meta-analysis suggested that the use of 5-HT3 antagonists (i.e., ondansetron) on days 2 to 4 to prevent delayed emesis was not cost-effective; however, ondansetron (when used alone) did protect against delayed emesis in this meta-analysis.[113] Palonosetron was not assessed in these studies. The panel recommends the use of 5-HT3 antagonists as one of several options to prevent delayed emesis for moderately emetogenic agents.

The antiemetic regimen for moderately emetogenic intravenous drugs on day 1 includes dexamethasone and a 5-HT3 antagonist with or without lorazepam and with or without either an H_2 blocker or a proton pump inhibitor.[5] Aprepitant (or fosaprepitant) should be added (to dexamethasone and a 5-HT3 antagonist) for select patients receiving certain moderate emetic risk chemotherapy (e.g., carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, methotrexate),[83] because these agents are more emetogenic than the other moderately emetogenic agents.[7,26] Intravenous 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 highly and moderately emetogenic chemotherapy agents[76]; hence, the panel recommends palonosetron as the preferred 5-HT3 antagonist in the setting of moderately emetogenic chemotherapy.

The antiemetic regimen for low emetogenic intravenous drugs includes agents such as dexamethasone, prochlorperazine, or metoclopramide, with or without lorazepam, and with or without either an H_2 blocker or a proton pump inhibitor. When using prochlorperazine or metoclopramide, patients should be monitored for dystonic reactions.[114–116] Diphenhydramine can be used for dystonic reactions.[117,118] Benztropine may be used in patients who are allergic to diphenhydramine.[115] If appropriate, lorazepam (0.5–2.0 mg either every 4 or every 6 hours on days 1–4; either oral, intravenous, or sublingual) may be used with each of these regimens (i.e., high, moderate, or low).

The emetogenic potential of oral chemotherapeutic agents is shown in the guidelines. Antiemetic prophylaxis is recommended for the following oral agents: altretamine, busulfan (≥ 4 mg/d), cyclophosphamide (≥ 100 mg/m^2/d), estramustine, etoposide, lomustine (single-day), procarbazine, and temozolomide (> 75 mg/m^2/d). 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 H_2 blocker or a proton pump inhibitor. For low or minimal emetic risk oral agents, recommended prophylaxis includes metoclopramide, prochlorperazine, or haloperidol with or without lorazepam and with or without either an H_2 blocker or a proton pump inhibitor; prophylaxis is given before chemotherapy is started, and then on an as-needed basis only (i.e., PRN).

Postchemotherapy/Delayed Emesis Prevention: The best management for delayed emesis is prevention.[119] For chemotherapeutic agents with high emetogenic potential, the prophylactic treatment (i.e., 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 exam-

ple, palonosetron (category 1) is only administered on day 1.[53] If either aprepitant or fosaprepitant was used on day 1, then aprepitant is continued on days 2 and 3.

The antiemetic regimens in these NCCN Guidelines include different options on days 2 to 3 for moderate emetic risk agents.[23,26,119] Three possible regimens can be used on days 2 to 3, including: 1) aprepitant, 2) dexamethasone, or 3) a 5-HT3 antagonist, such as ondansetron, granisetron, or dolasetron.[119] Each of these regimens may also include the following: ± lorazepam and ± either an H_2 blocker or a proton pump inhibitor. Importantly, the doses of both aprepitant (80 mg orally) and dexamethasone (8 mg orally or intravenously) 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.

The NCCN, MASCC, and ASCO guidelines all recommend using aprepitant to prevent delayed nausea and/or vomiting when giving AC regimens.[8,26,120] Note that the MASCC guidelines are updated on a biannual basis after 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 Principles for Managing Breakthrough Emesis, on page 469). Generally, preventing nausea and/or vomiting is much easier than treating it. Thus, routine around-the-clock administration of antiemetics should be strongly considered to prevent emesis, rather than PRN dosing. The general principle of breakthrough treatment is to give an additional agent as-needed from a different drug class.[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 intravenous therapy is often required. Nasal sprays might be useful for treatment of breakthrough emesis, because they provide acute delivery of agents.[121,122] Multiple concurrent agents, perhaps given at alternating schedules or through alternating routes, may be necessary.

Miscellaneous agents (e.g., haloperidol, metoclopramide, olanzapine, scopolamine transdermal patch), corticosteroids, and agents such as lorazepam may be incorporated for breakthrough treatment. Dronabinol and nabilone (which are cannabinoids) are approved by the FDA in patients whose nausea and vomiting 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 (e.g., brain metastases, electrolyte abnormalities, tumor infiltration of the bowel or other gastrointestinal abnormality, other comorbidities; see Principles for Managing Breakthrough Emesis, on page 469).

In addition, before the next cycle of chemotherapy, the antiemetic regimen (both the day 1 and post-chemotherapeutic) that did not protect the patient during the current cycle should be assessed and alternatives should be considered (see Principles for Managing Breakthrough Emesis, on page 469). Because patients sometimes have difficulty discriminating heartburn from nausea, antacid therapy (e.g., proton pump inhibitors, H_2 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.[24,123,124] 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.[125]

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 experienced complete control of emesis compared with 45% of patients who received placebo ($P < .05$).[126] 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.[127] Another randomized study in patients receiving radiotherapy to the upper abdomen found that oral granisetron decreased emesis and nausea compared with placebo.[128]

Patients undergoing total body irradiation may receive antiemetic prophylaxis with either ondansetron or granisetron; either agent can be given with or without oral dexamethasone.[8,24,129] 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

Approximately 20% of patients develop anticipatory nausea and/or vomiting. However, the rate of anticipatory nausea and/or vomiting seems to be decreasing (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 using optimal antiemetic therapy during every cycle of treatment.[23,130,131] Behavioral therapy has been used in patients with anticipatory nausea and/or vomiting.[132–137] Systematic desensitization may also be helpful.[133] Hypnosis with guided imagery is another behavioral technique that has shown some success in treating this condition.[134]

The antianxiety agents lorazepam and alprazolam have been combined with antiemetics for anticipatory nausea and/or vomiting.[131,138,139] 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 those with advanced liver disease, the usual starting dose of alprazolam is 0.25 mg orally 2 or 3 times daily for treatment of anxiety.[140] 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 and/or vomiting based on the emetogenic potential of the individual chemotherapy agents and their sequence.[23,141–145] 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 completion of chemotherapy also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. For multidrug 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 page 468).

For antiemetic prophylaxis of multiday emetogenic chemotherapy regimens (e.g., cisplatin-containing regimens), the combination of a 5-HT3 antagonist with dexamethasone remains the standard treatment.[8,23,120] 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 (aldesleukin) and interferon.[146]

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.[147,148] Repeat dosing of palonosetron (0.25 mg intravenously) 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 intravenously).[51–53,149] Compared with the approved dose of palonosetron of 0.25 mg intravenously, 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 intravenously on days 1, 3, and 5) and

dexamethasone, which prevented nausea and emesis in most patients on days 1 through 5 (51%) and on days 6 through 9 (83%); the most common adverse events were mild headache and constipation.[150] A recent study assessed palonosetron given for 1, 2, or 3 days in combination with dexamethasone for patients receiving multiday high-dose chemotherapy before stem cell transplantation for multiple myeloma (N = 73). During the 7-day emesis prevention period, 40% to 45% of patients experienced no emesis (with no differences observed among 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% experienced a CR (i.e., emesis-free without rescue medication).[151] Another study found that a palonosetron/dexamethasone regimen seemed 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.[147] 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 remains to be defined. 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 were given for an additional 2 days after chemotherapy.[152] CR (during the period from day 1 until 5 days after chemotherapy) was observed in 58% and 73% of patients who received high and moderate emetogenic regimens, respectively.[152] Aprepitant may be used for multiday chemotherapy regimens that are likely to be highly emetogenic and are associated with significant risk for delayed nausea and emesis. As per the labeled indication, aprepitant should be administered at 125 mg orally 1 hour before chemotherapy on day 1, along with a 5-HT3 receptor antagonist and dexamethasone. Aprepitant at 80 mg should be administered daily on days 2 and 3 after the start of chemotherapy, along with dexamethasone.[141] 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.[86,141] Based on phase II data, aprepitant at 80 mg may be safely administered on days 4 and 5 after chemotherapy.[87] Whether dosing aprepitant after day 3 improves control of nausea or emesis in this clinical setting is not yet known. Fosaprepitant dimeglumine (115 mg) may be substituted for aprepitant (125 mg) on day 1 only. Alternatively, for highly emetogenic chemotherapy regimens, 150 mg of intravenous fosaprepitant 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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Individual Disclosures of the NCCN Antiemesis Panel					
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