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The NCCN

Antiemesis

Clinical Practice Guidelines in Oncology™

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Overview

Chemotherapy-induced vomiting (emesis) and nausea can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy treatment. Nausea and vomiting can also result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of performance 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 undergoing 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 (e.g.,

Antiemesis Clinical Practice Guidelines in Oncology

Key Words
NCCN Clinical Practice Guidelines, antiemesis, nausea and vomiting, chemotherapy-induced, 5-HT3–receptor antagonists, NK-1–receptor antagonists (*JNCCN* 2009;7:572–595)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

Please Note

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Disclosures for the NCCN Antiemesis Guidelines 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 on-line. 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 Guidelines Panel members can be found on page 595. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

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

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age, sex, prior chemotherapy, history of alcohol use). Approximately 70% to 80% of all patients undergoing chemotherapy experience nausea and/or vomiting,[5,6] 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, and is triggered by afferent impulses to the vomiting center (located in the medulla) from the chemoreceptor trigger zone; pharynx and gastrointestinal tract (by way of 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 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. Principal neuroreceptors involved in the emetic response are serotonin (5-hydroxytryptamine [5-HT3]) and dopamine receptors;[13,14] other neuroreceptors 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 dur-

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PRINCIPLES OF EMESIS CONTROL IN 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 at least 4 days for high and 3 days for moderate. Patients must be protected throughout the full period of risk.
- Oral and IV antiemetic formulations have equivalent efficacy.
- 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
  - Psychophysiologic:
    - Anxiety
    - Anticipatory nausea and vomiting
- For use of antiemetics for nausea and vomiting that are not related to radiation and/or chemotherapy, see NCCN Clinical Practice Guidelines in Oncology: Palliative Care.*
- For multidrug regimens, select antiemetic therapy based on drug with the highest emetic risk. See Emetogenic Potential of Antineoplastic Agents (page 580).
- Consider using an H_2 blocker or proton pump inhibitor to prevent dyspepsia, which can mimic nausea.

*To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

HIGH EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION[b,c]

High[a] →

- Start before chemotherapy[b,c]
  - Aprepitant 125 mg PO day 1 or fosaprepitant 115 mg day 1,[d] 80 mg PO daily days 2-3
    and
  - Dexamethasone 12 mg PO or IV days 1-4
    and
  - 5-HT3 antagonist:
    Palonosetron 0.25 mg IV day 1 (preferred, category 2B)[e]
    or
    Dolasetron 100 mg PO or 1.8 mg/kg IV or 100 mg IV day 1[f]
    or
    Granisetron 2 mg PO or 1 mg PO bid or 0.01 mg/kg (maximum 1 mg) IV day 1 or transdermal patch containing 34.3 mg granisetron applied 24-48 h before first dose of chemotherapy[f]
    or
    Ondansetron 16-24 mg PO or 8-12 mg (maximum 32 mg) IV day 1[f]
    and
  - ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h prn days 1-4
  - ± H_2 blocker or proton pump inhibitor

(category 1, for combined regimen)

→ See Breakthrough Treatment (pages 578 and 579)

See Principles of Emesis Control (opposite page)

[a] Data for post-cisplatin (≥ 50 mg/m^2) emesis prevention are category 1, others are category 2A.
[b] Antiemetic regimens should be chosen based on the drug with the highest emetic risk and on patient-specific risk factors.
[c] See Principles for Managing Multi-Day Emetogenic Chemotherapy Regimens (page 583).
[d] Fosaprepitant dimeglumine (115 mg) may be substituted for aprepitant (125 mg) 30 minutes before chemotherapy, on day 1 only of the chemotherapy-induced nausea and vomiting regimen as an infusion administered over 15 minutes.
[e] In a randomized study, a larger dose of palonosetron was used without aprepitant. Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol 2009;10:115-124.
[f] Order of listed antiemetics does not reflect preference.

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MODERATE EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION[b,c]

Moderate[e] →

Day 1

- Start before chemotherapy[b,c]
  - Aprepitant 125 mg PO or fosaprepitant 115 mg IV day 1[d] in select patients[g]
    and
  - Dexamethasone 12 mg PO or IV
    and
  - 5-HT3 antagonist:[f]
    Dolasetron 100 mg PO or 1.8 mg/kg or 100 mg IV (category 1)
    or
    Granisetron 1-2 mg PO or 1 mg PO bid (category 1) or 0.01 mg/kg (maximum 1 mg) IV or transdermal patch containing 34.3 mg granisetron applied 24-48 h before first dose of chemotherapy
    or
    Ondansetron 16-24 mg PO or 8-12 mg (maximum 32 mg/d) IV (category 1)
    or
    Palonosetron 0.25 mg IV (category 1)
    and
  - ± 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 2-3

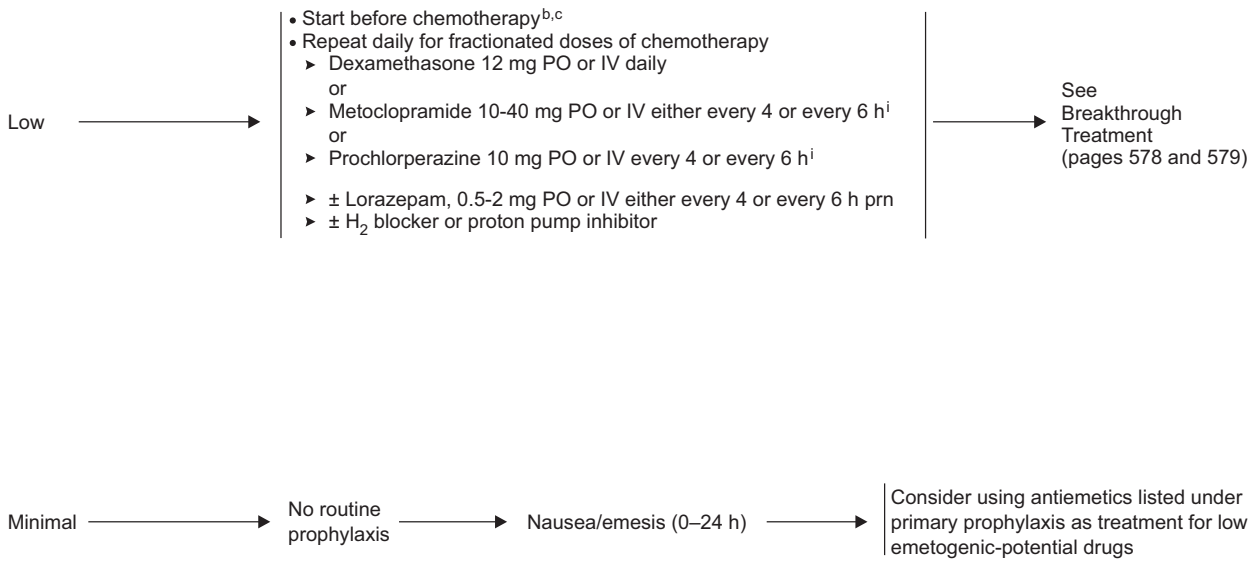
- Aprepitant 80 mg PO days 2-3 if used on day 1
  ± Dexamethasone 12 mg PO or IV daily
  or
- Dexamethasone 12 mg PO or IV daily
  or
- 5-HT3 antagonist:[f,h]
  Dolasetron 100 mg PO daily or 1.8 mg/kg IV
  or
  Granisetron 1-2 mg PO daily or 1 mg PO bid or 0.01 mg/kg (maximum 1 mg) IV
  or
  Ondansetron 8 mg PO bid or 16 mg PO daily or 8 mg (maximum 32 mg/d) IV
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or 6 h prn
- ± H_2 blocker or proton pump inhibitor

See Breakthrough Treatment (pages 578 and 579)

[b]Antiemetic regimens should be chosen based on the drug with the highest emetic risk and on patient-specific risk factors.
[c]See Principles for Managing Multi-Day Emetogenic Chemotherapy Regimens (page 583).
[d]Fosaprepitant dimeglumine (115 mg) may be substituted for aprepitant (125 mg) 30 minutes before chemotherapy, on day 1 only of the chemotherapy-induced nausea and vomiting regimen as an infusion administered over 15 minutes.
[f]Order of listed antiemetics does not reflect preference.
[g]Aprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients undergoing other chemotherapies of moderate emetic risk (e.g., carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, methotrexate).
[h]Data for post-carboplatin (≥ 300 mg/m^2, cyclophosphamide ≥ 600-1000 mg/m^2, doxorubicin ≥ 50 mg/m^2) emesis prevention are category 1.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
All recommendations are category 2A unless otherwise noted.

LOW AND MINIMAL EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION[b,c]



[b]Antiemetic regimens should be chosen based on the drug with the highest emetic risk and on patient-specific risk factors.
[c]See Principles for Managing Multi-Day Emetogenic Chemotherapy Regimens (page 583).
[i]Monitor for dystonic reactions; use diphenhydramine 25-50 mg PO or IV either every 4 or every 6 h for dystonic reactions.

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BREAKTHROUGH TREATMENT FOR CHEMOTHERAPY INDUCED NAUSEA/VOMITING[c,j]

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 6 h[i]
    or
  - Metoclopramide 10-40 mg PO or IV either every 4 or 6 h[i]
    or
  - Lorazepam 0.5-2 mg PO either every 4 or 6 h
    or
  - Dolasetron 100 mg PO daily or 1.8 mg/kg IV or 100 mg IV
    or
  - Ondansetron 16 mg PO or 8 mg IV daily
    or
  - Granisetron 1-2 mg PO daily or 1 mg PO bid or 0.01 mg/kg (maximum 1 mg) IV or transdermal patch containing 34.3 mg granisetron
    or
  - Haloperidol 1-2 mg PO every 4-6 h prn
    or
  - Dronabinol 5-10 mg PO either every 3 or 6 h
    or
  - Nabilone 1-2 mg PO bid
    or
  - Dexamethasone 12 mg PO or IV daily
    or
  - Olanzapine 2.5-5 mg PO bid (category 2B)[k]
    or
  - Promethazine 12.5-25 mg PO or IV every 4 h

[c]See Principles for Managing Multi-Day Emetogenic Chemotherapy Regimens (page 583).
[i]Monitor for dystonic reactions; use diphenhydramine 25-50 mg PO or IV either every 4 or 6 h for dystonic reactions.
[j]See Principles of Managing Breakthrough Emesis (page 584).
[k]See blackbox warning/label indication regarding type II diabetes, hyperglycemia, and death in elderly dementia patients.

RESPONSE TO BREAKTHROUGH ANTIEMETIC TREATMENT	SUBSEQUENT CYCLES
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
	See Principles of Emesis Control (page 574)

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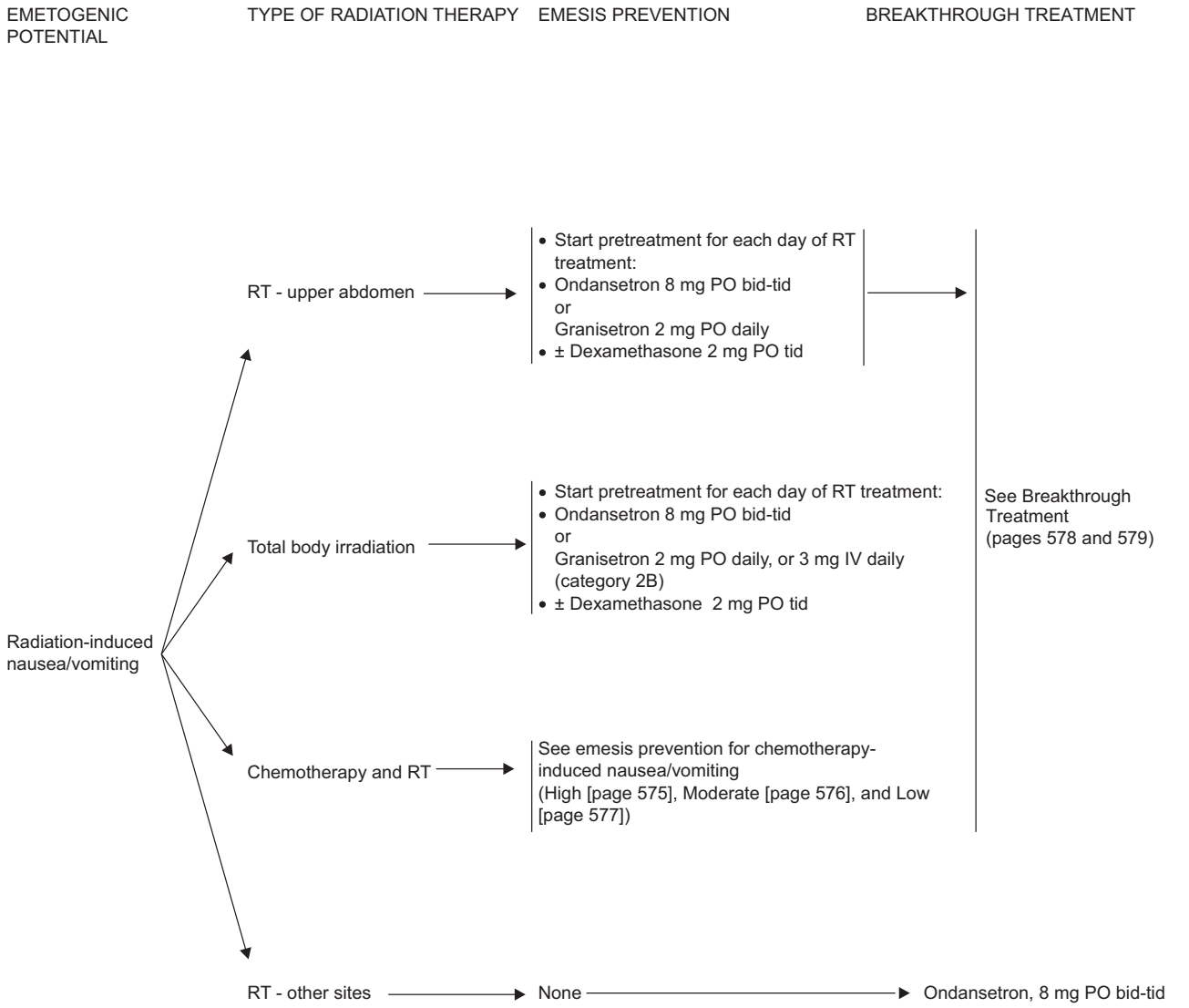
EMETOGENIC POTENTIAL OF ANTINEOPLASTIC AGENTS

LEVEL	AGENT	
High emetic risk (> 90% frequency of emesis)[l]	• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide • Altretamine • Carmustine > 250 mg/m^2 • Cisplatin ≥ 50 mg/m^2	• Cyclophosphamide > 1500 mg/m^2 • Dacarbazine • Mechlorethamine • Procarbazine (oral) • Streptozocin
Moderate emetic risk (30%-90% frequency of emesis[l]	• Aldesleukin > 12-15 million units/m^2 • Amifostine > 300 mg/m^2 • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan > 4 mg/d • Carboplatin • Carmustine ≤ 250 mg/m^2 • Cisplatin < 50 mg/m^2 • Cyclophosphamide ≤ 1500 mg/m^2 • Cyclophosphamide (oral) • Cytarabine > 1 g/m^2 • Dactinomycin • Daunorubicin	• Doxorubicin • Epirubicin • Etoposide (oral) • Idarubicin • Ifosfamide • Imatinib (oral)[m] • Irinotecan • Lomustine • Melphalan > 50 mg/m^2 • Methotrexate 250 to > 1000 mg/m^2 • Oxaliplatin > 75 mg/m^2 • Temozolomide (oral) • Vinorelbine (oral)
Low emetic risk (10%-30% frequency of emesis)[l]	• Amifostine ≤ 300 mg • Bexarotene • Capecitabine • Cytarabine (low dose) 100-200 mg/m^2 • Docetaxel • Doxorubicin (liposomal) • Etoposide • Fludarabine (oral) • 5-Fluorouracil • Gemcitabine	• Ixabepilone • Methotrexate > 50 mg/m^2 < 250 mg/m^2 • Mitomycin • Mitoxantrone • Nilotinib • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Topotecan • Vorinostat
Minimal emetic risk (< 10% frequency of emesis)[l]	• Alemtuzumab • Alpha Interferon • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Busulfan • Cetuximab • Chlorambucil (oral) • Cladribine (2-chlorodeoxyadenosine) • Decitabine • Denileukin diftitox • Desatinib • Dexrazoxane • Erlotinib • Fludarabine • Gefitinib • Gemtuzumab ozogamicin	• Hydroxyurea (oral) • Lapatinib • Lenalidomide • Melphalan (oral low-dose) • Methotrexate ≤ 50 mg/m^2 • Nelarabine • Panitumumab • Pentostatin • Rituximab • Sorafenib • Sunitinib • Temsirolimus • Thalidomide • Thioguanine (oral) • 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 2005;13:80–84.

[l]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis
[m]Daily use of antiemetics is not recommended based on clinical experience.



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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

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

See Principles of Emesis Control (page 574)

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
All recommendations are category 2A unless otherwise noted.

PRINCIPLES OF MANAGING MULTI-DAY EMETOGENIC CHEMOTHERAPY REGIMENS

- Patients undergoing multi-day chemotherapy are at risk for both acute and delayed nausea and emesis based on the emetogenic potential of the individual chemotherapy agents and their sequence. Therefore, recommending a specific antiemetic regimen for each day is difficult, 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 conclusion of chemotherapy administration 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/day IV days 1-5, cisplatin 25 mg/m^2 IV continuous infusion days 1-4 followed by cytarabine 2000 mg/m^2 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 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 (category 2B):

- A 5-HT3 receptor antagonist should be administered before each day's first 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).
- Intravenous palonosetron may be used before the start of a 3-day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT3 receptor antagonists. Repeat dosing of palonosetron, 0.25 mg IV, is likely to be safe, based on the dose-ranging phase II trial 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 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 as 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 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

- Breakthrough emesis presents a difficult situation as correction of refractory ongoing nausea and vomiting is often challenging to reverse. Generally, nausea and vomiting are 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 treatment is better than another for managing breakthrough emesis.
- Clinicians should strongly consider routine around-the-clock, administration rather than PRN dosing.
- 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 (e.g., metoclopramide), haloperidol, corticosteroids, and agents such as lorazepam may be required.
- Adequate hydration or fluid repletion should be ensured, with simultaneous checking and correcting of any possible electrolyte abnormalities.
- Before the next cycle of chemotherapy is administered, patients 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 gastrointestinal abnormality
  - Other comorbidities
- Before the next cycle of chemotherapy, clinicians should reassess both the day 1 and postchemotherapy antiemetic regimen that did not protect the patient during the present cycle, and consider alternatives, such as (suggestions are not in order of preference):
  - Addition of aprepitant
  - Addition of other concomitant antiemetics (e.g., dopamine antagonists [metoclopramide], 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 (e.g., Hesketh method)
  - Possibly switching to a different 5-HT3; although not necessarily likely to be effective, anecdotal and limited investigational trial data suggest this may sometimes be efficacious
  - If the goal of chemotherapy is palliative or adjuvant, consider other appropriate regimens, if any, that might be less emetogenic
  - Adding an anxiolytic agent in combination with the antiemetic agents
- If patient has dyspepsia, antacid therapy (H_2 blocker or proton pump inhibitor) should be considered.

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ing 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 not been 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 emesis generally peaks after 5 to 6 hours, and its occurrence is influenced by patient age and gender (women and patients < 50 years are more prone), environment in which chemotherapy is administered, whether the patient has a history of chronic alcoholism (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.[16,17]

Delayed-onset nausea and/or vomiting develops in patients more than 24 hours after chemotherapy is administered[16,17] and commonly occurs when cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin are used. 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 occurs before patients undergo 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%, with nausea being more common than vomiting.[18,19] Younger patients may be more susceptible, because they are generally treated with more aggressive chemotherapy and, overall, have poorer emesis control than older patients.[20] *Breakthrough* emesis refers to vomiting that occurs despite prophylactic treatment and/or requires rescue with antiemetic agents. *Refractory* emesis refers to emesis that occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles.

Radiation-Induced Nausea and/or Vomiting

Patients undergoing whole body or upper abdominal radiation therapy have the greatest likelihood of developing nausea and/or vomiting.[21,22] The gastrointestinal 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.[22,23]

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 have been universally accepted.[12,24–27]

Hesketh et al.[28] developed a classification of acute emetogenicity for anticancer chemotherapeutic agents and an algorithm to define the emetogenicity of combination chemotherapeutic regimens. The classification, which was updated by Grunberg et al.,[29] divides chemotherapeutic agents into 4 levels according to the percentage of patients not receiving antiemetic prophylaxis who experience acute emesis. This classification, which was updated with recently introduced drugs, is used in these 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.[30] These guidelines currently outline treatment using 4 categories of emetogenic potential (see page 580), 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

These guidelines also attempt to define antiemetic regimens for particular chemotherapy drugs that cover the entire period a patient is at risk for

nausea and vomiting. Panel members were concerned that some patients may not receive adequate prophylaxis for delayed emesis, and 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 and continued for the duration of the emetic activity according to the chemotherapeutic agent being used. However, daily use of antiemetics is not recommended for some therapeutic agents that are taken long-term (i.e., imatinib; see page 580). Antiemetic agents can be administered orally, rectally, intravenously, intramuscularly, or transdermally. Compared with other routes of administration, oral formulations of antiemetic agents are equally effective and safe, while being more convenient and less costly. For patients unable to swallow or digest tablets because of emesis, intravenous antiemetics are required. In selected patients unable to swallow, transdermal antiemetics may be of value. Although studies may show drugs to be equally effective on a population basis, individual patients may respond differently. Therefore, some drug options may be based on a patient's individual experience.

Serotonin (5-HT3) Receptor Antagonists

The development of the 5-HT3–receptor antagonists (i.e., ondansetron, granisetron, dolasetron mesylate, palonosetron) represent a significant advance in antiemetic therapy.[31–33] All agents have been shown to be effective in controlling acute chemotherapy-induced nausea and/or vomiting.[33–47]

Palonosetron is a 5-HT3 antagonist with approximately a 100-fold higher binding affinity for the 5-HT3 receptor compared with other serotonin antagonists (e.g., ondansetron, granisetron, 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 undergoing moderately emetogenic chemotherapy showed that a single intravenous dose of palonosetron was comparable to the same dose of dolasetron for preventing acute chemotherapy-induced nausea and emesis. However, intravenous palonosetron was superior in preventing delayed emesis.[48] The safety and side-effect profiles of palonosetron were indistinguishable from the control 5-HT3 antagonists (ondansetron and dolasetron) according to data submitted to the FDA.

Intravenous palonosetron is FDA-approved as a single dose on day 1. It is recommended (category 1) for preventing acute and delayed emesis associated with moderately emetogenic chemotherapy[48] and is superior to other 5-HT3 antagonists in preventing delayed nausea.[49] However, repeat dosing of palonosetron in the days after chemotherapy (days 2 or 3) is not supported by scientific literature. Repeat dosing of palonosetron in the setting of multi-day chemotherapy regimens has not been studied.

Many 5-HT3 antagonists can be delivered orally or intravenously. In addition, the FDA recently approved the use of a granisetron transdermal system for chemotherapy-induced nausea and vomiting (http://www.fda.gov/cder/foi/label/2008/022198lbl.pdf). The patch, containing 34.3 mg of granisetron, is applied 24 to 48 hours before the first dose of chemotherapy. A phase III randomized study compared the patch with oral granisetron in patients undergoing either highly or moderately emetogenic chemotherapy, and it proved to be noninferior to repeat dosing of the oral antiemetic granisetron over 3 to 5 days.[50]

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,[48,51–70] and have shown that 5-HT3 antagonists are equally effective and have mild infrequent side effects. A recent meta-analysis found no difference in efficacy.[71] Adding dexamethasone improves the efficacy of antiemetic regimens containing 5-HT3 antagonists.

Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis, but seem to be less effective in preventing delayed emesis. However, intravenous palonosetron is effective for preventing both delayed and acute emesis. A meta-analysis of randomized controlled trials found that adding a 5-HT3 antagonist to dexamethasone did not improve its ability to prevent delayed emesis.[72] Another study found that 5-HT3 antagonists (except palonosetron, which was not studied) were not more effective than prochlorperazine in preventing delayed emesis.[11]

NK-1–Receptor Antagonist

Aprepitant selectively blocks the binding of substance P at the NK-1 receptor in the central nervous system, providing a different and complementary mechanism of action to all other commercially available antiemetics. Aprepitant has been shown to augment the antiemetic activity of 5-HT3–receptor antagonists and corticosteroid dexamethasone, inhibiting both acute and delayed cisplatin-induced emesis. The FDA has approved the use of aprepitant for preventing emesis in patients undergoing moderately emetogenic chemotherapy. An intravenous version of aprepitant (fosaprepitant dimeglumine), which can be given on day 1 only, was recently approved by the FDA (http://www.fda.gov/cder/foi/label/2008/022023lbl.pdf).

When combined with 5-HT3 antagonists and dexamethasone on day 1 (125 mg)[73] before cisplatin-based highly emetogenic chemotherapy, and continued orally with dexamethasone on days 2 and 3 (80 mg)[73] after chemotherapy, aprepitant significantly improved control of acute and delayed chemotherapy-induced nausea and emesis.[74,75] No studies show efficacy or safety of chronic dosing with aprepitant; the drug–drug interaction profile may change with chronic dosing.

A randomized phase III study (866 patients) showed that an aprepitant regimen (aprepitant, ondansetron, and dexamethasone) is better than a standard regimen (ondansetron and dexamethasone) for preventing vomiting in patients undergoing moderately emetogenic chemotherapy (non–cisplatin-based) within 120 hours after initiation of chemotherapy (complete response, 50.8% vs. 42.5%; P = .015); however, 40% of patients (undergoing either regimen) still experienced significant nausea.[76,77] An analysis of 2 phase III randomized trials found that an aprepitant regimen is useful for treating patients undergoing moderately emetogenic chemotherapy plus high-dose cisplatin.[78]

A meta-analysis of 7 randomized controlled trials of patients undergoing 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.[79] A phase II study of 58 patients found that combining palonosetron, aprepitant, and dexamethasone was useful for various chemotherapeutic regimens (moderate to moderate-to-highly emetogenic); 78% experienced a complete response (no emetic episodes or rescue medication).[80]

Drug Interactions: Aprepitant is simultaneously a substrate, moderate inducer, and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4); aprepitant also induces CYP2C9.[81] Therefore, aprepitant can alter the metabolism of certain drugs and change their plasma concentrations (area under the curve [AUC]). These interactions are more significant with orally administered forms 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."[82]

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 metabolized by CYP3A4.

Aprepitant has been shown to interact with several non-chemotherapeutic drugs (including warfarin, dexamethasone, methylprednisolone, oral contraceptives). Again, these interactions are more significant with orally administered forms of these drugs than with 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 (vs. prophylactic) warfarin regimens. These changes, although brief in duration, may require increased patient monitoring (http://www.fda.gov/cder/foi/label/2008/021549s015lbl.pdf).

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 (i.e., ketoconazole, itraconazole, erythromycin) may lead to increased aprepitant AUCs, whereas concomitant administration with CYP3A4 inducers (i.e., 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, available antiemetic agents included phenothiazines,[83] substituted benzamides,[84,85] antihistamines,[86] butyrophenones,[87] corticosteroids,[88–90] benzodiazepines,[91,92] and cannabinoids.[93,94] 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 acute and delayed emesis in a phase II trial in patients (n = 30) treated with cyclophosphamide, doxorubicin, and/or cisplatin;[95,96] other studies have also shown the value of olanzapine for delayed and refractory emesis and nausea.[97–100] However, olanzapine should be used with caution in elderly patients (see boxed warning/label indication regarding death, type II diabetes, and hyperglycemia [http://www.fda.gov/cder/foi/label/2007/020592s042s043,021086s022s023,021253s026lbl.pdf]).[101]

Treatment Issues

Selected issues that arose in the panel deliberations are discussed in the following sections. When caring for patients undergoing chemotherapy, clinicians should consider new data that may become available on the use of antiemetics, even if the information was not included in the guidelines. In contrast to other NCCN guidelines in which most of the recommendations are category 2A, many 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 page 574).

- The goal is to prevent nausea and/or vomiting.
- The risk for emesis and nausea for persons undergoing chemotherapy of high and moderate emetogenic potential lasts at least 4 days for high and 3 days for moderate. Patients must be protected throughout the full period of risk.
- Oral and intravenous antiemetic formulations have equivalent efficacy.
- The toxicity of the specific antiemetic(s) should be considered.
- 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.

In addition to emesis induced by chemotherapy, emesis in patients with cancer 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 (e.g., vincristine)
- Psychophysiologic factors, including anxiety, anticipatory nausea, and vomiting
- For the use of antiemetics for nausea and vomiting that is not related to radiation and/or chemotherapy, see the NCCN Clinical Practice Guidelines in Oncology: 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 page 580).[28,29]

Prevention of Acute Emesis

To prevent acute emesis, antiemetic therapy should start before the administration of chemotherapy and cover the first 24 hours. For highly emetogenic drugs, the regimens are described on page 575. For moderately emetogenic drugs, the regimens are described on page 576. For low and minimally emetogenic drugs, the regimens are described on page 577. This section discusses prechemotherapy and postchemotherapy emesis prevention rather than primary treatment.

Prechemotherapy Emesis Prevention: The guidelines specify different prophylactic antiemetic regimens for patients with cancer undergoing chemotherapy of different emetogenic potential (e.g., high, moderate, low, minimal). Prophylactic antiemetics should be administered before chemotherapy, and recommendations for treatment include drug dosages. The guidelines reflect accumulating experience with 5HT3–serotonin antagonists, showing 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/m^2), cisplatin (≥ 50 mg/m^2), cyclophosphamide (> 1500 mg/m^2), dacarbazine, mechlorethamine, procarbazine (oral), streptozocin, or anthracycline and cyclophosphamide (AC) combinations (doxorubicin or epirubicin with cyclophosphamide). 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 proton pump inhibitor (category 1 for combined regimen [see page 575]);[22,23,74] note that the regimen and doses are often modified on days 2 to 4 after chemotherapy. Although any 5-HT3 antagonist can be used, palonosetron is preferred (category 2B) in combination with dexamethasone and aprepitant for patients undergoing chemotherapy of high emetic risk based on results from a recent randomized study.[102] However, this study used a larger dose of palonosetron and did not use aprepitant.

A Canadian meta-analysis suggests that using 5-HT3 antagonists (e.g., ondansetron) on days 2 to 4 to prevent delayed emesis is not cost-effective; however, ondansetron (when used alone) protected against delayed emesis.[103] Palonosetron was not assessed in these studies. The NCCN Antiemesis Panel recommends using 5-HT3 antagonists as one of several options to prevent delayed emesis associated with moderately emetogenic agents (see page 576).

The antiemetic regimen for moderately emetogenic drugs (see page 580) on day 1 includes dexamethasone and a 5-HT3 antagonist with or without lorazepam and/or either an H_2 blocker or proton pump inhibitor (see page 576).[77] Aprepitant should be added (to dexamethasone and a 5-HT3 antagonist) for select patients undergoing other chemotherapies of moderate emetic risk (i.e., carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate; see page 576), because these agents are more emetogenic than the other moderately emetogenic agents.[23,28] Any of the 5HT3 antagonists can be used because they are all category 1. Note that the regimens differ on days 2 to 3 because 3 possible regimens are available (lorazepam and/or either an H_2 blocker or a proton pump inhibitor may be added to each of these regimens), including 1) aprepitant with or without dexamethasone, 2) dexamethasone, or 3) 5HT3 antagonist, such as ondansetron, granisetron, or dolasetron. Note that palonosetron is not given on days 2 to 3.

The antiemetic regimen for low emetogenic drugs (see page 580) includes non–5-HT3 antagonists, such as dexamethasone, prochlorperazine, or metoclopramide, with or without lorazepam and/or either an H_2 blocker or proton pump inhibitor (see page 577). When using prochlorperazine or metoclopramide, patients should be monitored for dystonic reactions; diphenhydramine (25–50 mg orally or intravenously either every 4 or 6 hours) can be used for dystonic reaction.

For regimens with high emetogenic potential, aprepitant is used at an oral dosage of 125 mg on day 1, and 80 mg on days 2 and 3 (see page 575). When given with aprepitant, dexamethasone is used at an oral or intravenous dosage of 12 mg. All of the 5-HT3–receptor antagonists (i.e., ondansetron, granisetron, dolasetron, palonosetron) are considered to have similar effectiveness for controlling acute emesis. If appropriate, lorazepam (0.5–2 mg either every 4 or 6 hours on days 1–4; either oral, intravenous, or sublingual) may be used with each of these regimens (e.g., high, moderate, or low).

Postchemotherapy/Delayed Emesis Prevention: The best management for delayed emesis is prevention. For chemotherapy involving agents with high emetogenic potential, prophylactic 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 page 576).[51] If aprepitant was used on day 1, then it is continued on days 2 and 3 and is given with or without dexamethasone, lorazepam, and/or either an H_2 blocker or proton pump inhibitor. Alternatively, either dexamethasone or a 5-HT3 antagonist can be used; lorazepam and/or either an H_2 blocker or proton pump inhibitor 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 page 584). 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. However, no one treatment is better than another for managing this condition.[104] The oral route is not likely to be feasible because of ongoing vomiting; therefore, rectal or intravenous therapy is often required.

Multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary. Dopamine antagonists (i.e., metoclopramide), haloperidol, corticosteroids, and agents such as lorazepam may be required. Nabilone (cannabinoid) is 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 assessed and corrected. Before the next cycle of chemotherapy is administered, patients should be reassessed with attention to various possible non–chemotherapy-related reasons for breakthrough emesis with the current cycle, such as brain metastases, electrolyte abnormalities, tumor infiltration of the bowel, other gastrointestinal abnormalities, and other comorbidities (see page 584). In addition, before the next cycle of chemotherapy, the antiemetic regimen (both day 1 and postchemotherapeutic) that failed during the present cycle should be assessed and alternatives considered (see page 584). Antacid therapy (i.e., proton pump inhibitors, H_2 blockers) should be considered if patients have dyspepsia, because patients sometimes have difficulty discriminating heartburn from nausea.

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 (see page 581). 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, 2–3 times daily), with or without oral dexamethasone, based on the results of a randomized study comparing oral ondansetron with placebo in patients undergoing daily fractionated radiotherapy that included the abdomen. In this study, 67% of patients given ondansetron experienced complete control of emesis compared with 45% of patients who received placebo.[105] 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.[106] Another option is oral granisetron (2 mg daily) with or without oral dexamethasone.

Total body irradiation may be treated with either ondansetron (8 mg, 2–3 times daily) or granisetron; either agent can be given with or without oral dexamethasone (2 mg, 3 times daily).[106] The dose of granisetron is either 2 mg orally every day or 3 mg intravenously every day[107,108] (category 2B, because this dose of granisetron is higher than the dose typically used). No prophylaxis is recommended for patients undergoing 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 page 582). Behavioral therapy has been used in patients with anticipatory nausea and/or vomiting.[109–111] Systematic desensitization may also be helpful.[110] Hypnosis with guided imagery is another behavioral technique that has shown some success in treating this condition.[111] The antianxiety agents lorazepam and alprazolam have been combined with antiemetics for anticipatory nausea and/or vomiting with mixed results.[112] The usual starting dose of alprazolam is 0.25 to 0.5 mg orally 3 times daily, beginning the night before treatment. In elderly patients or those with debilitating or advanced liver disease, the usual starting dose of alprazolam is 0.25 mg orally 2 or 3 times daily for treatment of anxiety.[113] This dose may be gradually increased if needed. 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 undergoing multiday chemotherapy are at risk for both acute and delayed nausea and vomiting

based on the emetogenic potential of the individual chemotherapy agents and their sequence.[75,114–117] A specific antiemetic regimen for each day is difficult to recommend, 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 the conclusion of chemotherapy also depends on the specific regimen and emetogenic potential of the last chemotherapy agent administered in the regimen. The algorithm describes general principles recommended by the panel for managing multiday emetogenic chemotherapy regimens (category 2B; see page 583).

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Individual Disclosures of the NCCN Antiemesis Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Debra K. Armstrong, RN	Morphotek Inc.; and Agensys	Agiotech Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Fresenius Medical Care AG; Genentech, Inc.; Morphotek Inc.; Agensys; OCI; and Oncotech	None	None	11/19/08
Sally Barbour, PharmD, BCOP	None	None	None	None	7/15/08
Michael J. Berger, PharmD, BCOP	None	None	None	None	7/11/08
Philip J. Bierman, MD	None	None	None	None	6/20/08
Bob Bradbury, BCPS	None	None	None	None	4/22/08
Georgiana Ellis, MD	MGI PHARMA, INC.	None	None	None	11/16/08
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Steve Kirkegaard, PharmD	None	Eisai Inc.	None	None	7/23/08
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The NCCN guidelines staff have no conflicts to disclose.