National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Antiemesis

Version 1.2021 — December 23, 2020

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Antiemesis

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Discussion

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

Updates in Version 1.2021 of the NCCN Guidelines for Antiemesis from Version 2.2020 include:

AE-1
Principles of Emesis Control for the Cancer Patient
- Other potential causes of emesis in patients with cancer; added:
  - Cannabinoid hyperemesis syndrome
  - Rapid opioid withdrawal
  - Pancreatitis

AE-2
Emetogenic Potential of Parenteral Anticancer Agents
- High emetic risk, added: Melphalan >140 mg/m^2 ~~higher doses~~, sacituzumab govitecan-hziy
- Moderate emetic risk, added: Fam-trastuzumab deruxtecan-nxki, lurbinectedin
- Moderate emetic risk, melphalan edited to <140 mg/m^2
- Removed from Moderate emetic risk: Enfortumab vedotin-ejfv, interferon alfa ≥10 million IU/m^2

AE-3
Emetogenic Potential of Parenteral Anticancer Agents
- Low emetic risk, added: brexucabtagene autoleucel, enfortumab vedotin-ejfv, isatuximab-irfc, mitomycin pyelocalyceal solution, tafasitamab-cxix
- Minimal emetic risk, added: daratumumab and hyaluronidase-fihj, luspatercept-aamt, pertuzumab/trastuzumab and hyaluronidase-zzxf
- Minimal emetic risk, removed: Peginterferon

AE-4
High Emetic Risk Parenteral Anticancer Agents-Acute and Delayed Emesis Prevention
- Footnotes updated

AE-5A
Footnotes for Pages AE-4 and AE-5
- Footnote k edited: With or without lorazepam 0.5–2 mg PO or IV or sublingual every 6 hours as needed days 1–4. With or without H2 blocker or proton pump inhibitor. ~~For olanzapine-containing regimens, only use PO lorazepam if needed.~~ See Principles of Emesis Control for the Cancer Patient (AE-1).
- Footnote m edited: ~~Emerging data from smaller studies and clinical practice~~ *Data* suggest *that* a 5-mg dose *of olanzapine is efficacious.* ~~may be considered, especially for elderly or over sedated patients~~ *Consider this dose especially for elderly or over sedated patients. Hashimoto H, et al. Lancet Oncol 2020;21:242-49.* See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
- Footnote n edited: If not used previously, consider escalating to ~~this option~~ a 4-drug regimen (option A) ~~when~~ if emesis occurred during a previous cycle of ~~chemotherapy~~ *anticancer therapy with a 3-drug regimen* ~~using an olanzapine regimen (B, E) or an NK1 RA-containing regimen (C, D, or F)~~ (olanzapine-containing regimen B or E or NK1 RA-containing regimen C, ~~D,~~ or F). *Olanzapine-containing regimens may be useful for patients with severe nausea.* See Principles for Managing Breakthrough Emesis (AE-C).

AE-7
Emetogenic Potential of Oral Anticancer Agents
- Moderate to high emetic risk, added: azacytidine, bosutinib >400 mg/day ~~higher doses~~, capmatinib, fedratinib, imatinib >400 mg/day ~~higher doses~~.
- Moderate to high emetic risk, levnatinib edited to >12 mg/day
- Minimal to low emetic risk, added: decitabine and cedazuridine, lenvatinib ≤12 mg/day, pemigatinib, pexidartinib, pralsetinib, ripretinib, selpercatinib, tazemetostat, tucatinib.
- Minimal to low emetic risk, bosutinib edited to ≤400 mg/day
- Minimal to low emetic risk, imatinib edited to ≤400 mg/day

AE-7A
Footnotes for Page AE-7
- Footnote aa added: Emerging data and clinical practice suggest adding low-dose olanzapine and/or NK1 RA to 5-HT3 RA for nausea prevention.

Continued

Updates in Version 1.2021 of the NCCN Guidelines for Antiemesis from Version 2.2020 include:

AE-9

Breakthrough Treatment for Anticancer Therapy-Induced Nausea/Vomiting

- **Any nausea/vomiting, 5-HT3 RA, ondansetron edited: ~~16-24 mg~~ *8 mg PO every 8–12 h (16–24 mg total daily dose)* or 8–16 mg IV**
- **Replaced previous footnote gg with Dronabinol oral solution has greater oral bioavailability than dronabinol capsules; 2.1 mg oral solution = 2.5 mg capsules.**

AE-A (1 of 3)

Principles of Managing Multiday Emetogenic Chemotherapy Regimens

- **General principles, corticosteroids, dexamethasone edited: should be administered once daily *in the morning.***

AE-B (1 of 2)

Pharmacologic Considerations for Antiemetic Prescribing

- **Olanzapine, Clinical pearl, removed: Data suggest that sedation is most notable on day 2 and improves over time; from first sub-bullet and created a new bullet.**
- **Olanzapine, Clinical pearl, added new sub-bullet: *Unless given as a premedication prior to anticancer therapy, bedtime administration is recommended when possible due to sedation.***

AE-B (2 of 2)

Pharmacologic Considerations for Antiemetic Prescribing

- **Metoclopramide, added 6th bullet: *The FDA recommends short-term use (<12 weeks) for metoclopramide given risk for tardive dyskinesia with longer use.***

PRINCIPLES OF EMESIS CONTROL FOR THE CANCER PATIENT

- Prevention of nausea/vomiting is the goal.
  - The risk of nausea/vomiting (acute ≤24 hours vs. delayed nausea >24 hours) for persons receiving anticancer agents of high and moderate emetic risk lasts for at least 3 days for high and 2 days for moderate after the last dose of anticancer agents. Patients need to be protected throughout the full period of risk.
- Oral and parenteral serotonin receptor antagonists (5-HT3 RAs) have equivalent efficacy when used at the appropriate doses and intervals.
- Consider the toxicity of the specific antiemetic(s). See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
- Choice of antiemetic(s) used should be based on the emetic risk of the therapy, prior experience with antiemetics, and patient factors.
  - Patient risk factors for anticancer agent-induced nausea/vomiting include:
    - ◊ Younger age
    - ◊ Female sex
    - ◊ Previous history of anticancer agent-induced nausea and vomiting (CINV)
    - ◊ Little or no previous alcohol use
    - ◊ Prone to motion sickness
    - ◊ History of morning sickness during pregnancy
    - ◊ Anxiety / high pretreatment expectation of nausea
- There are other potential causes of emesis in patients with cancer. These may include:
  - Partial or complete bowel obstruction
  - Vestibular dysfunction
  - Brain metastases
  - Electrolyte imbalance: hypercalcemia, hyperglycemia, or hyponatremia
  - Uremia
  - Concomitant drug treatments, including opioids
  - Gastroparesis: tumor or chemotherapy (eg, vincristine) induced or other causes (eg, diabetes)
  - Excessive secretions (eg, seen in patients with head and neck cancers)
  - Malignant ascites
  - Psychophysiologic:
    - ◊ Anxiety
    - ◊ Anticipatory nausea/vomiting
  - Cannabinoid hyperemesis syndrome
  - Rapid opioid withdrawal
  - Pancreatitis
- For use of antiemetics for nausea/vomiting that are not related to radiation and/or anticancer therapy, see NCCN Guidelines for Palliative Care.
- For multi-drug regimens, select antiemetic therapy based on the drug with the highest emetic risk. See Emetogenic Potential of Parenteral Anticancer Agents (AE-2 and AE-3), and see Emetogenic Potential of Oral Anticancer Agents (AE-8).
- Antiemetic regimens added to a patient's anticancer agents may have a potential risk for drug-drug interactions. However, no clinically significant drug-drug interactions have emerged to date in randomized clinical trials of anticancer agents with antiemetics. The panel feels, given a short duration of use (<4 days; not chronic use) of these prophylactic antiemetic regimens, they would not result in clinically relevant interactions with anticancer agents. However, in all situations where medications are prescribed, clinicians must balance the benefit and risk for each patient.
- Consider using an H_2 blocker or proton pump inhibitor to prevent dyspepsia, which can mimic nausea.
- Lifestyle measures may help to alleviate nausea/vomiting, such as eating small frequent meals, choosing healthful foods, controlling the amount of food consumed, and eating food at room temperature. A dietary consult may also be useful. See NCI's "Eating Hints: Before, During, and After Cancer Treatment" (http://www.cancer.gov/cancertopics/coping/eatinghints/page2#4).
- While anticancer agents or radiation therapy-induced nausea and vomiting can significantly impact a patient's quality of life and lead to poor outcomes, providers must be aware of the potential for the overuse of prophylactic antiemetics, especially for anticancer therapy with minimal and low emetic risks, which may expose the patient to potential adverse effects from antiemetic drugs and pose an undue economic burden. Guideline adherence is always encouraged.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS[a]

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[b,c,d]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4 • Carmustine >250 mg/m²	• Cisplatin • Cyclophosphamide >1,500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m² • Epirubicin >90 mg/m² • Ifosfamide ≥2 g/m² per dose	• Mechlorethamine • Melphalan ≥140 mg/m² • Sacituzumab govitecan-hziy • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis)[b,c,d]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC[e] <4 • Carmustine[e] ≤250 mg/m² • Clofarabine • Cyclophosphamide[e] ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin[e]	• Daunorubicin[e] • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Dinutuximab • Doxorubicin[e] <60 mg/m² • Epirubicin[e] ≤90 mg/m² • Fam-trastuzumab deruxtecan-nxki • Idarubicine • Ifosfamide[e] <2 g/m² per dose • Irinotecan[e] • Irinotecan (liposomal)	• Lurbinectedin • Melphalan <140 mg/m² • Methotrexate[e] ≥250 mg/m² • Oxaliplatin[e] • Temozolomide • Trabectedin[e]

Adapted with permission from:
Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. Support Care Cancer 2011;19:S43-S47.

[a] Potential drug interactions between antineoplastic agents/antiemetic agents and various other drugs should always be considered.
[b] Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
[c] Continuous infusion may make an agent less emetogenic.
[d] The emetic risk is expected to be the same for biosimilars as for the parent compound unless otherwise noted.
[e] These agents may be highly emetogenic in certain patients.

Low Emetic Risk (See AE-3)
Minimal Emetic Risk (See AE-3)
Oral Anticancer Therapy (See AE-8)

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EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS[a]

LEVEL	AGENT			
Low emetic risk (10%–30% frequency of emesis)[b,d,f]	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/m² • Amifostine ≤300 mg/m² • Arsenic trioxide • Axicabtagene ciloleucel[g] • Belinostat • Brexucabtagene autoleucel[g] • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Copanlisib • Cytarabine (low dose) 100 mg/m² – 200 mg/m²	• Docetaxel • Doxorubicin (liposomal) • Enfortumab vedotin-ejfv • Eribulin • Etoposide • 5-Fluorouracil (5-FU) • Floxuridine • Gemcitabine • Gemtuzumab ozogamicin • Inotuzumab ozogamicin • Isatuximab-irfc • Ixabepilone • Methotrexate >50 mg/m² – <250 mg/m²	• Mitomycin • Mitomycin pyelocalyceal solution • Mitoxantrone • Mogamulizumab • Moxetumomab • Necitumumab • Olaratumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Polatuzumab vedotin	• Pralatrexate • Romidepsin • Tafasitamab-cxix • Tagraxofusp • Talimogene laherparepvec • Thiotepa • Tisagenlecleucel[g] • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of emesis)[b,d,f]	• Alemtuzumab • Atezolizumab • Avelumab • Asparaginase • Bevacizumab • Bleomycin • Blinatumomab • Bortezomib • Cetuximab • Cemiplimab • Cladribine • Cytarabine <100 mg/m² • Daratumumab	• Daratumumab and hyaluronidase-fihj • Decitabine • Denileukin diftitox • Dexrazoxane • Durvalumab • Elotuzumab • Fludarabine • Ipilimumab • Luspatercept-aamt • Methotrexate ≤50 mg/m² • Nelarabine • Nivolumab	• Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase • Pembrolizumab • Pertuzumab • Pertuzumab/trastuzumab and hyaluronidase-zzxf • Ramucirumab • Rituximab • Rituximab and hyaluronidase human injection for SQ use	• Siltuximab • Temsirolimus • Trastuzumab • Trastuzumab/hyaluronidase • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

Adapted with permission from: Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. Support Care Cancer 2011;19:S43-S47.

[a] Potential drug interactions between antineoplastic agents/antiemetic agents and various other drugs should always be considered.
[b] Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
[d] The emetic risk is expected to be the same for biosimilars as for the parent compound unless otherwise noted.
[f] For some low emetic risk agents, factors related to dosing schedule (particularly continuous dosing) and clinical experience suggest routine premedication is not required. An individualized approach is appropriate for whether to premedicate each dose or prescribe antiemetics as needed.
[g] Corticosteroid antiemetic premedication should be avoided for 3–5 days prior to and 90 days after CAR T-cell therapies. Antiemetic regimens used during lymphodepleting chemotherapy regimens should also employ a corticosteroid-sparing approach to antiemetic prophylaxis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HIGH EMETIC RISK PARENTERAL ANTICANCER AGENTS — ACUTE AND DELAYED EMESIS PREVENTION[h,i,j,k,l]

DAY 1: Select treatment option A[m], B[m], or C
All treatment options are category 1 and should be started before anticancer therapy[j]

DAYS 2, 3, 4:

Treatment option A (preferred), use the following combination:[n]

- Olanzapine 5–10 mg PO once[m]
- NK1 RA (choose one):
  - Aprepitant 125 mg PO once
  - Aprepitant injectable emulsion 130 mg IV once[o]
  - Fosaprepitant 150 mg IV once
  - Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p]
  - Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p]
  - Rolapitant 180 mg PO once[q]
- 5-HT3 RA (choose one):[r,s]
  - Dolasetron 100 mg PO once
  - Granisetron 10 mg SQ once,[t] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy.
  - Ondansetron 16–24 mg PO once, or 8–16 mg IV once
  - Palonosetron 0.25 mg IV once
- Dexamethasone 12 mg PO/IV once[u,v]

Treatment option A:

- Olanzapine 5–10 mg PO daily on days 2, 3, 4[m]
- Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1)
- Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3, 4

Treatment option B, use the following combination:

- Olanzapine 5–10 mg PO once[m]
- Palonosetron 0.25 mg IV once
- Dexamethasone 12 mg PO/IV once[u,v]

Treatment option B:

- Olanzapine 5–10 mg PO daily on days 2, 3, 4[m]

Treatment option C, use the following combination:

- NK1 RA (choose one):
  - Aprepitant 125 mg PO once
  - Aprepitant injectable emulsion 130 mg IV once[o]
  - Fosaprepitant 150 mg IV once
  - Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p]
  - Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p]
  - Rolapitant 180 mg PO once[q]
- 5-HT3 RA (choose one):[r,s]
  - Dolasetron 100 mg PO once
  - Granisetron 10 mg SQ once,[t] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy.
  - Ondansetron 16–24 mg PO once, or 8–16 mg IV once
  - Palonosetron 0.25 mg IV once
- Dexamethasone 12 mg PO/IV once[u,v]

Treatment option C:

- Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1)
- Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3, 4

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See Footnotes on AE-5A

MODERATE EMETIC RISK PARENTERAL ANTICANCER AGENTS — ACUTE AND DELAYED EMESIS PREVENTION[h,i,j,k,l]

DAY 1: Select treatment option D, E, or F. All treatment options are category 1 and should be started before anticancer therapy[j]	DAYS 2, 3:
Treatment option D, use the following combination: • 5-HT3 RA (choose one): ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once[t] (preferred), or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once (preferred) • Dexamethasone 12 mg PO/IV once[u,v]	**Treatment option D:** • Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3 OR • 5-HT3 RA monotherapy[w]: ▸ Granisetron 1–2 mg (total dose) PO daily or 0.01 mg/kg (max 1 mg) IV daily on days 2 and 3 ▸ Ondansetron 8 mg PO twice daily or 16 mg PO daily or 8–16 mg IV daily on days 2, 3 ▸ Dolasetron 100 mg PO daily on days 2, 3
Treatment option E, use the following combination:[x] • Olanzapine 5–10 mg PO once[m] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	**Treatment option E:** • Olanzapine 5–10 mg PO daily on days 2, 3[m]
Treatment option F, use the following combination:[x] • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[o] ▸ Fosaprepitant 150 mg IV once[p] ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p] ▸ Rolapitant 180 mg PO once[q] • 5-HT3 RA (choose one):[r,s] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[t] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	**Treatment option F:** • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • ± Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3

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See Footnotes on AE-5A

Footnotes for pages AE-4 and AE-5

[h] See Emetogenic Potential of Parenteral Anticancer Agents (AE-2).
[i] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[j] See Principles of Managing Multiday Emetogenic Chemotherapy (AE-A).
[k] With or without lorazepam 0.5–2 mg PO or IV or sublingual every 6 hours as needed days 1–4. With or without H2 blocker or proton pump inhibitor. See Principles of Emesis Control for the Cancer Patient (AE-1).
[l] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[m] Data suggest that a 5-mg dose of olanzapine is efficacious. Consider this dose especially for elderly or oversedated patients. Hashimoto H, et al. Lancet Oncol 2020;21:242-49. See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[n] If not used previously, consider escalating to a 4-drug regimen (option A) if emesis occurred during a previous cycle of anticancer therapy with a 3-drug regimen (olanzapine-containing regimen B or E or NK1 RA-containing regimen C or F). Olanzapine-containing regimens may be useful for patients with severe nausea. See Principles for Managing Breakthrough Emesis (AE-C).
[o] Aprepitant injectable emulsion is a unique formulation of aprepitant and is NOT interchangeable with the intravenous formulation of fosaprepitant.
[p] Available as a fixed combination product only.
[q] Rolapitant has an extended half-life and should not be administered at less than 2-week intervals.
[r] If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product used, no further 5-HT3 RA is required.
[s] When used in combination with an NK1 RA, there is no preferred 5-HT3 RA. See Principles of Managing Multiday Emetogenic Chemotherapy (AE-A).
[t] Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the intravenous formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals.
[u] Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable for non-cisplatin regimens based on patient characteristics. If dexamethasone eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (eg, olanzapine). See Discussion.
[v] Use of corticosteroid premedications should be avoided with cellular therapies. See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[w] No further 5-HT3 therapy required if palonosetron or granisetron extended-release injection administered, or if granisetron transdermal patch applied, on day 1.
[x] A 3-drug prophylactic regimen (E or F) is recommended for select patients with additional patient-related risk factors (See AE-1) or previous treatment failure with a corticosteroid + 5-HT3 RA alone.

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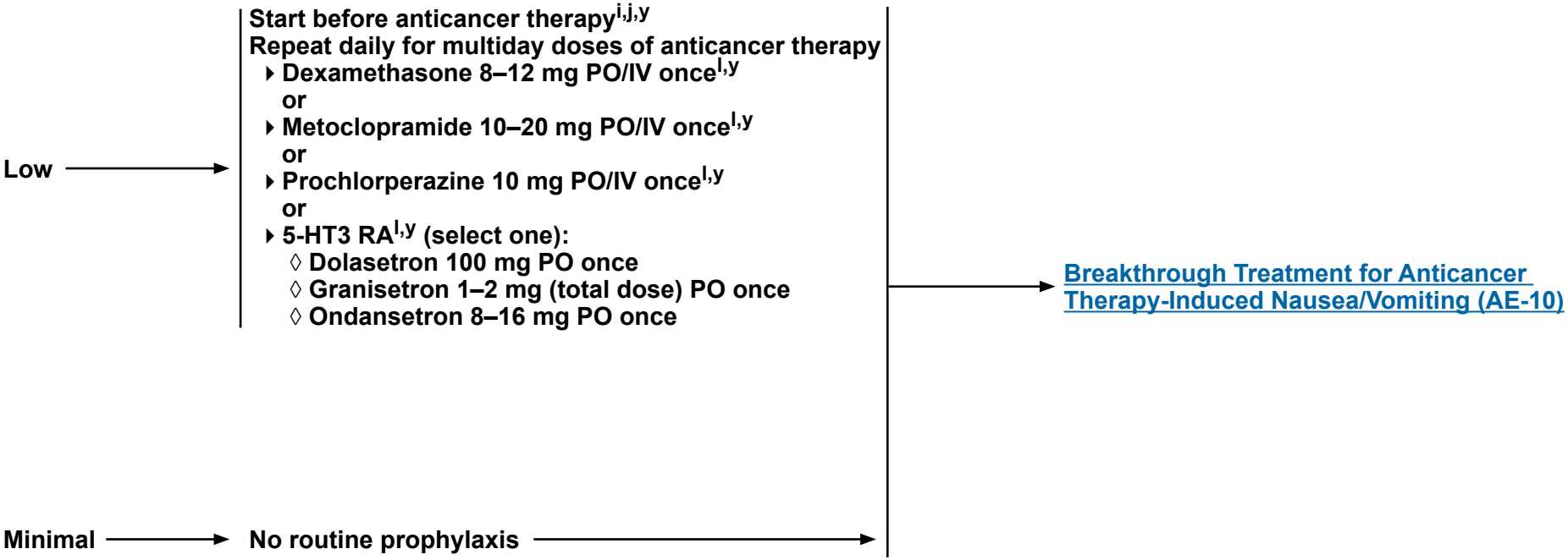
LOW AND MINIMAL EMETIC RISK PARENTERAL ANTICANCER AGENTS - EMESIS PREVENTION[h,i,j,l]



[h] See Emetogenic Potential of Parenteral Anticancer Agents (AE-2).
[i] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[j] See Principles of Managing Multiday Emetogenic Chemotherapy (AE-A).
[l] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[y] With or without lorazepam 0.5–2 mg PO or IV or sublingual every 6 hours as needed days 1–4. With or without H2 blocker or proton pump inhibitor. See Principles of Emesis Control for the Cancer Patient (AE-1).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EMETOGENIC POTENTIAL OF ORAL ANTICANCER AGENTS[a]

LEVEL	AGENT			
Moderate to high emetic risk[b,z] (≥30% frequency of emesis)	• Altretamine • Avapritinib • Azacytidine • Binimetinib • Bosutinib >400 mg/day • Busulfan ≥4 mg/day • Capmatinib • Ceritinib	• Crizotinib • Cyclophosphamide ≥100 mg/m²/day • Dabrafenib • Enasidenib • Encorafenib • Estramustine	• Etoposide • Fedratinib • Imatinib >400 mg/day • Lenvatinib >12 mg/day • Lomustine (single day) • Midostaurin • Mitotane	• Niraparib • Olaparib • Procarbazine • Rucaparib • Selinexor[aa] • Temozolomide >75 mg/m²/day
Minimal to low emetic risk[b] (<30% frequency of emesis)	• Abemaciclib • Acalabrutinib • Afatinib • Alectinib • Alpelisib • Axitinib • Bexarotene • Brigatinib • Bosutinib ≤400 mg/day • Busulfan <4 mg/day • Cabozantinib • Capecitabine • Chlorambucil • Cobimetinib • Cyclophosphamide <100 mg/m²/day • Dacomitinib • Dasatinib • Decitabine and cedazuridine	• Duvelisib • Entrectinib • Erdafitinib • Erlotinib • Everolimus • Fludarabine • Gefitinib • Gilteritinib • Glasdegib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib ≤400 mg/day • Ixazomib • Ivosidenib • Lapatinib • Larotrectinib • Lenalidomide • Lenvatinib ≤12 mg/day	• Lorlatinib • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Neratinib • Osimertinib • Palbociclib • Panobinostat • Pazopanib • Pemigatinib • Pexidartinib • Pomalidomide • Ponatinib • Pralsetinib • Regorafenib • Ribociclib • Ripretinib • Ruxolitinib • Selpercatinib	• Sonidegib • Sorafenib • Sunitinib • Talazoparib tosylate • Tazemetostat • Temozolomide ≤75 mg/m²/day[bb] • Thalidomide • Thioguanine • Topotecan • Trametinib • Tretinoin • Trifluridine/tipiracil • Tucatinib • Vandetanib • Vemurafenib • Venetoclax • Vismodegib • Vorinostat • Zanubrutinib

Adapted with permission from:
Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer 2011;19:S43-S47.

High Emetic Risk (See AE-2)
Moderate Emetic Risk (See AE-2)
Low Emetic Risk (See AE-3)
Minimal Emetic Risk (See AE-3)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See Footnotes on AE-7A

Footnotes for AE-7

[a] Potential drug interactions between antineoplastic agents/antiemetic agents and various other drugs should always be considered.
[b] Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
[z] For some moderate to high emetic risk agents, factors related to dosing schedule (particularly continuous dosing for prolonged periods), and clinical experience suggest routine premedication is not required. An individualized approach is appropriate for whether to premedicate each dose or prescribe antiemetics as needed.
[aa] Emerging data and clinical practice suggest adding low-dose olanzapine and/or NK1 RA or 5-HT3 RA for nausea prevention.
[bb] Temozolomide ≤75 mg/m^2/day should be considered moderately emetogenic with concurrent radiotherapy.

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ORAL ANTICANCER AGENTS - EMESIS PREVENTION[i,j,cc,dd]

High to moderate emetic risk →

Start before anticancer therapy and continue daily (order does not imply preference)[y]
- **5-HT3 RA (choose one):[l]**
  - **Dolasetron 100 mg PO daily**
  - **Granisetron 1–2 mg (total dose) PO daily or 3.1 mg/24-h transdermal patch every 7 days**
  - **Ondansetron 8–16 mg (total dose) PO daily**

→ **Breakthrough Treatment for Anticancer Therapy-Induced Nausea/Vomiting (AE-10)**

Low to minimal emetic risk → **PRN recommended** → **Nausea/ vomiting** →

Start before anticancer therapy and continue daily (order does not imply preference)[y]
- **Metoclopramide 10–20 mg PO and then every 6 h PRN[l]**
  or
- **Prochlorperazine 10 mg PO and then every 6 h PRN (maximum 40 mg/day)[l]**
  or
- **5-HT3 RA (choose one):[l]**
  - ◊ **Dolasetron 100 mg PO daily PRN**
  - ◊ **Granisetron 1–2 mg (total dose) PO daily PRN**
  - ◊ **Ondansetron 8–16 mg (total dose) PO daily PRN**

→ **Breakthrough Treatment for Anticancer Therapy-Induced Nausea/Vomiting (AE-10)**
and
Consider changing antiemetic therapy to higher level primary therapy for the next cycle

[i] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[j] See Principles of Managing Multiday Emetogenic Chemotherapy (AE-A).
[l] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[y] With or without lorazepam 0.5–2 mg PO or IV or sublingual every 6 hours as needed days 1–4. With or without H2 blocker or proton pump inhibitor. See Principles of Emesis Control for the Cancer Patient (AE-1).
[cc] See Emetogenic Potential of Oral Anticancer Agents (AE-7).
[dd] 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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BREAKTHROUGH TREATMENT FOR ANTICANCER THERAPY-INDUCED NAUSEA/VOMITING[j,ee]

Any nausea/ vomiting

The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen.

Atypical antipsychotic:[l]
- **Olanzapine 5–10 mg PO daily (preferred, category 1)[ff]**

• Benzodiazepine:[l]
- **Lorazepam 0.5–2 mg PO/SL/IV every 6 h**

• Cannabinoid:[l]
- **Dronabinol capsules 5–10 mg, or dronabinol oral solution 2.1–4.2 mg/m², PO 3–4 times daily[gg]**
- **Nabilone 1–2 mg PO BID**

• Other:
- **Haloperidol 0.5–2 mg PO/IV every 4–6 h[l]**
- **Metoclopramide 10–20 mg PO/IV every 4–6 h[l]**
- **Scopolamine 1.5 mg transdermal patch 1 patch every 72 h**

• Phenothiazine:[l]
- **Prochlorperazine 25 mg supp PR every 12 h or 10 mg PO/IV every 6 h[l]**
- **Promethazine 25 mg supp PR every 6 h or 12.5–25 mg PO every 4–6 h[j]**

• 5-HT3 RA:[l]
- **Dolasetron 100 mg PO daily**
- **Granisetron 1–2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV daily or 3.1 mg/24-h transdermal patch every 7 days**
- **Ondansetron 8 mg PO every 8–12 h (16–24 mg total daily dose) or 8–16 mg IV**

• Corticosteroid:[l]
- **Dexamethasone 12 mg PO/IV daily**

RESPONSE

Nausea and vomiting controlled → **Continue breakthrough medications, on a schedule, not PRN**

Nausea and/ or vomiting uncontrolled → **Re-evaluate and consider dose adjustments and/ or sequentially add one agent from a different drug class**

SUBSEQUENT CYCLES

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

[j] See Principles of Managing Multiday Emetogenic Chemotherapy (AE-A).
[l] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[ee] See Principles for Managing Breakthrough Emesis (AE-C).

[ff] When not used as part of the acute and delayed emesis prevention regimen.
[gg] Dronabinol oral solution has greater oral bioavailability than dronabinol capsules; 2.1 mg oral solution = 2.5 mg capsules.

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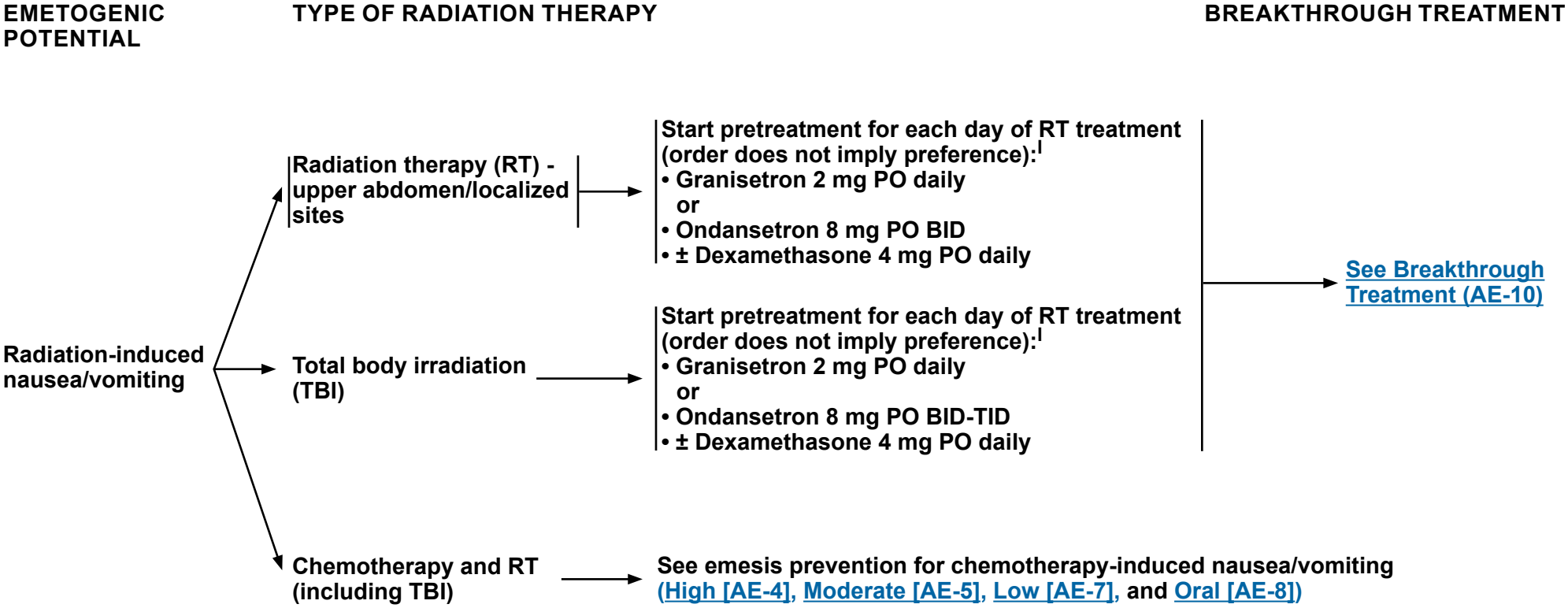
RADIATION-INDUCED EMESIS PREVENTION/TREATMENT



[l] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).

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ANTICIPATORY EMESIS PREVENTION/TREATMENT

Anticipatory nausea/vomiting →

- **Prevention is key:**
  - **Use optimal antiemetic therapy during every cycle of treatment**
  - **Avoid strong smells that may precipitate symptoms**
- **Behavioral therapy:**
  - **Relaxation/systematic desensitization**
  - **Hypnosis**
  - **Relaxation exercises**
    - ◊ **Guided imagery**
    - ◊ **Progressive muscle relaxation (PMR)**
    - ◊ **Biofeedback**
    - ◊ **Music therapy**
  - **Cognitive distraction**
  - **Yoga (if approved by physician)**
- **Acupuncture/acupressure**
- **Consider anxiolytic therapy:**
  - **For example, lorazepam 0.5–2 mg PO beginning on the night before treatment and then repeated the next day 1–2 hours before anticancer therapy begins**

→ **See Emesis Prevention and Breakthrough Treatment for Anticancer Therapy-Induced Nausea and Vomiting (Antiemesis Table of Contents)**

See Principles of Emesis Control for the Cancer Patient (AE-1)

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PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS[a]

Summary:

- **Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea/vomiting based on the emetogenic potential of the individual chemotherapy agents administered on any given day and their sequence. It is therefore difficult to recommend a specific antiemetic regimen for each day, especially since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy.**
- **After chemotherapy administration concludes, the period of risk for delayed emesis also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen.**
- **Practical issues also need to be considered when designing the antiemetic regimen, taking into account the administration setting (eg, inpatient vs. outpatient), preferred route of administration (parenteral, oral, or transdermal), duration of action of the 5-HT3 RA and appropriate associated dosing intervals, tolerability of daily antiemetics (eg, corticosteroids), adherence/compliance issues, and individual risk factors.**

General principles:

Corticosteroids:

- **Dexamethasone should be administered once daily in the morning (either orally or intravenously) for moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC), then continued for 2 to 3 days after chemotherapy for regimens that are likely to cause significant delayed emesis.**
- **Dexamethasone dose may be modified or omitted when the chemotherapy regimen already includes a corticosteroid.**
- **Dexamethasone-sparing strategies**
  - **For patients receiving MEC or non-cisplatin HEC, especially those patients with few identifiable (CINV) risk factors or who are intolerant to corticosteroids, limiting the administration of dexamethasone to day 1 only is an option that may not be associated with a significant reduction in antiemetic control.[1-4]**
  - **If patients cannot tolerate dexamethasone, consider replacing with olanzapine.**

[a] The panel acknowledges that evidence is lacking to support every clinical scenario. Decisions should be individualized for each chemotherapy regimen and each patient. An extensive knowledge of the available clinical data, pharmacology, pharmacodynamics, and pharmacokinetics of the antiemetics and the chemotherapy and experience with patients (regarding tolerability and efficacy) are all paramount to successfully implementing these guidelines into clinical practice.

Continued

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PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS[a]

Serotonin receptor antagonists (5-HT3 RA):

- A 5-HT3 RA should be administered prior to the first (and subsequent) doses of moderately or highly emetogenic chemotherapy. The frequency or need for repeated administration of the 5-HT3 RA depends on the agent chosen and its mode of administration (parenteral/oral/transdermal).
- Palonosetron:
  - A single intravenous palonosetron dose of 0.25 mg may be sufficient prior to the start of a 3-day chemotherapy regimen instead of multiple daily doses of another oral or intravenous 5-HT3 RA.
  - Repeat dosing of palonosetron 0.25 mg IV is likely to be safe, based on available evidence.
  - In terms of efficacy, limited data are available for multiday dosing.[5]
- Granisetron extended-release injection:
  - Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the intravenous formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals.
  - A single subcutaneous dose of 10 mg was found to be non-inferior to a single intravenous dose of palonosetron 0.25 mg for the prevention of acute and delayed CINV following MEC or HEC when both are used in combination with dexamethasone.[6]
  - A single subcutaneous dose of 10 mg was found to be superior to a single intravenous dose of ondansetron for the prevention of delayed CINV following HEC when both are used in combination with fosaprepitant and dexamethasone.[7]
- When palonosetron or granisetron extended-release injection is used as part of an antiemetic regimen that does NOT contain an NK1 RA, palonosetron or granisetron extended-release injection are the preferred 5-HT3 RA.[6,8]

Neurokinin-1 receptor antagonists (NK1 RA):

- NK1 RAs may be used for multiday chemotherapy regimens likely to be moderately or highly emetogenic and associated with significant risk for delayed nausea and emesis.
- For single-day chemotherapy regimens, category 1 evidence is available for aprepitant, aprepitant injectable emulsion, fosaprepitant, netupitant, fosnetupitant, or rolapitant administered in combination with a 5-HT3 RA and corticosteroid (see AE-5 and AE-6).
- If the oral aprepitant regimen is chosen, limited data exist to support administration of aprepitant on days 4 and 5 after multiday chemotherapy.
- Data from a small phase III randomized study support the use of aprepitant (125 mg day 3, 80 mg days 4–7) with 5-HT3 RA (days 1–5) and dexamethasone (20 mg days 1, 2) in patients with germline cancers treated with a 5-day cisplatin-based chemotherapy.[9]
- Studies investigating repeat dosing of aprepitant injectable emulsion, fosaprepitant, netupitant, fosnetupitant, and rolapitant are not available.
- Fosaprepitant, aprepitant, aprepitant injectable emulsion, netupitant, and fosnetupitant inhibit the metabolism of dexamethasone and may cause higher dexamethasone concentrations. Rolapitant does not inhibit dexamethasone metabolism.
- Rolapitant has an extended half-life and should not be administered at less than 2-week intervals.

[a] The panel acknowledges that evidence is lacking to support every clinical scenario. Decisions should be individualized for each chemotherapy regimen and each patient. An extensive knowledge of the available clinical data, pharmacology, pharmacodynamics, and pharmacokinetics of the antiemetics and the chemotherapy and experience with patients (regarding tolerability and efficacy) are all paramount to successfully implementing these guidelines into clinical practice.

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PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS

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PHARMACOLOGIC CONSIDERATIONS FOR ANTIEMETIC PRESCRIBING (In Order as the Drugs Appear in the Guideline)

To ensure safe and effective treatment with antiemetic therapy, develop a treatment plan with the patient that includes medication access, screening of concomitant medications, goals of therapy, instructions for proper use and side effect management, and adherence assessment. Many of the antiemetic agents contained within this guideline have multiple potential drug-drug or drug-disease interactions. Review patient medical profile and drug package insert for specific interactions and recommendations.

NK1 RAs:
- **Aprepitant, aprepitant injectable emulsion, fosaprepitant, netupitant, and fosnetupitant inhibit the metabolism of dexamethasone, thus increasing dexamethasone serum levels when administered concomitantly. Rolapitant does not share this interaction with dexamethasone.**
- **Rolapitant has an extended half-life and should not be administered at less than 2-week intervals.**
- **Clinical pearl: Place in therapy is for prevention of CINV, not treatment of CINV. Largest benefit seen in delayed CINV setting.**

5-HT3 RAs:
- **The FDA recommends a maximum of 16 mg for a single dose of intravenous ondansetron to prevent prolongation of the QT interval of the ECG. Dolasetron may increase the QT interval in a dose-dependent fashion.**
- **Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the intravenous formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals.**
- **Clinical pearl: After receiving palonosetron, granisetron transdermal patch, or extended-release injection, breakthrough 5-HT3 RAs play a limited role in the delayed infusion period and breakthrough antiemetic should focus on a different mechanism of action.**
- **Clinical pearl: Non-sedating; most common side effects are headache and constipation. Optimal effects seen with scheduled administration, not PRN use. Educate patients regarding constipation and its management.**

Corticosteroids:
- **Side effects associated with prolonged dexamethasone administration should be carefully considered.**
- **Dexamethasone may increase serum glucose; consider monitoring prior to therapy and as clinically indicated.**
- **Use with caution in patients with diabetes mellitus.**
- **Dexamethasone may cause dyspepsia; consider acid-blocking therapy with H_2 antagonist or proton pump inhibitor as clinically indicated.**
- **Clinical pearl: For patients suffering from extended delayed CINV, consider extending the course of delayed dexamethasone as clinically appropriate. Consider AM dosing to minimize insomnia.**
- **Corticosteroid antiemetic premedication should be avoided for 3–5 days prior to and 90 days after CAR T-cell therapies.**

Olanzapine:
- **Monitor for dystonic reactions.[a]**
- **CNS depression; use olanzapine with caution or consider a lower dose in patients at risk for falls (eg, elderly, debilitated, frail) or at risk for orthostatic hypotension.**
- **Clinical pearl:**
  - **Consider a dose of 5 mg if the previously administered 10 mg dose caused excessive sedation.**
  - **Consider 2.5 mg of olanzapine if patients report excessive sedation with 5 mg dose.**
  - **Data suggest that sedation is most notable on day 2 and improves over time.**
  - **Unless given as a premedication prior to anticancer therapy, bedtime administration is recommended when possible due to sedation.**

[a] Use caution and monitor ECG in patients with other risk factors for QT prolongation.

Continued

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PHARMACOLOGIC CONSIDERATIONS FOR ANTIEMETIC PRESCRIBING

Benzodiazepines:
- CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail) or in patients at risk for dependence.
- Clinical pearl: Consider for anticipatory CINV or when breakthrough CINV has an anxiety component.
- Use caution in patients receiving opioids due to increased risk of respiratory depression.

Phenothiazines:
- CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail).
- When administered parenterally, promethazine may cause severe tissue injury.
- Monitor for dystonic reactions.[b]
- Clinical pearl: Promethazine has more histamine blockade than prochlorperazine and is therefore more sedating.

Metoclopramide:
- Use caution in patients at risk for falls (eg, elderly, debilitated, frail).
- May increase the QT interval of the ECG.
- Monitor for dystonic reactions.[b]
- May cause tardive dyskinesia; the risk increases with increasing cumulative dose and duration of treatment.
- Clinical pearl: Metoclopramide increases gut motility and can be utilized to manage gastroparesis.
- The FDA recommends short-term use (<12 weeks) for metoclopramide given risk for tardive dyskinesia with longer use.

Haloperidol:
- CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail).
- May increase the QT interval of the ECG.
- Monitor for dystonic reactions.[b]
- Clinical pearl: Generally, lower doses of haloperidol (see AE-9 and AE-10) are required to produce an antiemetic effect than what is required for an antipsychotic effect.

Scopolamine:
- CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail).
- Clinical pearl: Consider using when positional changes, movement, or excessive secretions are triggering episodes of nausea/vomiting.

Cannabinoid:
- CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail).
- Clinical pearl: May stimulate appetite. To minimize adverse effects, consider starting with lower doses (especially in elderly or marijuana-naïve patients) and titrate to effect.

[b] Use diphenhydramine 25–50 mg PO/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. May consider using amantadine 100 mg BID-TID as treatment of drug-induced dystonic reactions for those patients intolerant of anticholinergic medications.

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PRINCIPLES FOR MANAGING BREAKTHROUGH EMESIS

- Breakthrough emesis presents a difficult situation, as correction of refractory ongoing nausea/vomiting is often challenging to reverse. It is generally far easier to prevent nausea/vomiting than it is to treat it.
- The general principle of breakthrough treatment is to give an additional agent from a different drug class. The choice of agent should be based on assessment of the current prevention strategies used. Some patients may require several agents utilizing differing mechanisms of action.
- One should strongly consider routine, around-the-clock administration rather than PRN dosing.
- The PO route is not likely to be feasible due to ongoing vomiting; therefore, rectal or IV administration is often required.
- Multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary. Dopamine antagonists (eg, phenothiazines, olanzapine, metoclopramide, haloperidol), corticosteroids, and agents such as lorazepam may be required.
- Ensure adequate hydration or fluid repletion, simultaneously checking and correcting any possible electrolyte abnormalities.
- Prior to administering the next cycle of anticancer therapy the patient should be reassessed, with attention given to various possible non-anticancer therapy–related reasons for breakthrough emesis with the current cycle:
  - Brain metastases
  - Electrolyte abnormalities
  - Tumor infiltration of the bowel or other gastrointestinal abnormality
  - Other comorbidities
- Prior to the next cycle of anticancer therapy reassess both the day 1 and post-anticancer therapy antiemetic regimen, which did not protect the patient during the present cycle, and consider alternatives: (Suggestions are not in order of preference)
  - Add an NK1 RA if not previously included.
  - Consider changing from NK1-RA–containing regimens to olanzapine-containing regimen, or vice versa.
  - Consider combining an NK1 RA regimen with olanzapine; see High Emetic Risk Parenteral Anticancer Agents - Acute And Delayed Emesis Prevention, option C (AE-4).
  - Possibly switch to a different NK1 RA with different pharmacokinetic/pharmacodynamic profile. Although no available head-to-head clinical trial data support this, anecdotal evidence suggests it may be helpful.
  - Add other concomitant antiemetics (eg, dopamine antagonists such as metoclopramide or haloperidol), if applicable.
  - Possibly adjust dose(s), either intensity or frequency, of the 5-HT3 RA. Based on the patient's experiences, the anticancer therapy regimen in question may actually be more emetogenic than generally classified (eg, Hesketh method).
  - Possibly switch to a different 5-HT3 RA. Although not necessarily likely to be effective, anecdotal and limited investigational trial data suggest it may sometimes be efficacious. 5-HT3 RAs have different pharmacokinetics/pharmacodynamics and different routes of metabolism that may account for different efficacy in certain populations.
  - If the goal of anticancer therapy is non-curative, consider other appropriate regimens, if any, that might be less emetogenic.
  - It may be beneficial to add an anxiolytic agent in combination with the antiemetic agents.
- Consider antacid therapy if patient has dyspepsia (H2 blocker or proton pump inhibitor).

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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 indicated.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Antiemesis

Discussion

This discussion corresponds to the NCCN Guidelines for Antiemesis. Last updated on December 23, 2020.

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Overview

Vomiting (emesis) and nausea caused by anticancer agents and/or radiation therapy (RT) can significantly affect a patient's quality of life, leading to poor compliance with further anticancer agents and/or RT.[1,2] In addition, nausea and/or vomiting can result in dehydration, metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of the patient's performance status and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment.[3-6] Anticancer agents include chemotherapy, targeted therapy, and immunotherapy, which will all be referred to as *anticancer agents* throughout this Discussion text.

The incidence and severity of nausea and/or vomiting in patients receiving anticancer agents and/or RT is affected by numerous factors, including: 1) the specific therapeutic agents used; 2) dosage of the agents; 3) schedule and route of administration of the agents; 4) target of the RT (eg, whole body, upper abdomen); and 5) individual patient variability (eg, younger age; female sex; prior anticancer agents; history of little or no alcohol use, morning sickness, motion sickness, anxiety).[7,8] More than 90% of patients receiving highly emetogenic chemotherapy (HEC) will have episodes of vomiting. However, if patients receive prophylactic (preventive) antiemetic regimens before treatment with HEC, then only about 30% of these patients will vomit.[7,9,10] Although vomiting can often be prevented or substantially decreased by using prophylactic antiemetic regimens, nausea is harder to control.[11-14]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis are intended to provide an overview of the treatment principles for preventing anticancer agent–induced or RT-induced nausea and/or vomiting, and recommendations for antiemetic prophylaxis according to the emetogenic potential of anticancer agents. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

The NCCN Guidelines also provide specific category designations for all interventions in the guidelines, which are based on evidence from the biomedical literature and consensus among the panel members. In contrast to other NCCN Guidelines in which most of the recommendations are category 2A, many of the recommendations for antiemetic regimens are category 1, reflecting the large number of randomized controlled trials (RCTs) that have focused on antiemetic management.

Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature in antiemesis using the following search terms: chemotherapy-induced nausea vomiting, antiemetics chemotherapy, antiemetic regimens, and antiemesis. The PubMed database was chosen, because it is the most widely used resource for medical literature and indexes peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles selected by the NCCN Panel for review during the NCCN Guidelines update meeting, as well as articles from additional sources deemed as relevant to these guidelines and discussed by the NCCN Panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, recommendations are based on the panel's review of lower-level evidence and expert opinion. The complete details of

the development and update of the NCCN Guidelines are available on the NCCN website (www.nccn.org).

Pathophysiology of Emesis

Vomiting results from stimulation of a multistep reflex pathway controlled by the brain.[1,7,15] Vomiting is triggered by afferent impulses to the vomiting center (located in the medulla) from the chemoreceptor trigger zone, pharynx and gastrointestinal (GI) tract (via vagal afferent fibers), and cerebral cortex. Vomiting occurs when efferent impulses are sent from the vomiting center to the salivation center, abdominal muscles, respiratory center, and cranial nerves.[16]

The chemoreceptor trigger zone, vomiting center, and GI tract have many neurotransmitter receptors. Activation of these receptors by chemotherapeutic agents or their metabolites may be responsible for anticancer agent–induced emesis. The principal neuroreceptors involved in the emetic response are the serotonin (5-hydroxytryptamine [5-HT3]) and dopamine receptors; 5-HT3 receptors are associated with acute emesis via a peripheral pathway.[1,17,18] Other neuroreceptors involved in emesis include acetylcholine, corticosteroid, histamine, cannabinoid, opioid, and neurokinin-1 (NK1) receptors, which are located in the vomiting and vestibular centers of the brain.[19] NK1 receptors are associated with delayed emesis via a central pathway.[1]

Antiemetics can block different neuronal pathways, exert their effects at different points during the course of emesis, or behave synergistically with other antiemetics to potentiate an antiemetic effect. When used at a certain concentration, each antiemetic agent predominantly blocks one receptor type. Olanzapine is the exception in that it acts on multiple receptors involved in the emetic pathway.[20] A final common pathway for emesis has yet to be identified. No single agent can be expected to provide complete protection from the various emetic phases of anticancer agents. Therefore, prophylactic antiemetic regimens for HEC and moderately emetogenic chemotherapy (MEC) include two to four antiemetics that block different receptors.

Nausea

With use of effective antiemetic regimens, patients receiving emetogenic anticancer agents often experience more nausea than vomiting.[11,12,21-24] Vomiting and nausea are related; however, they may occur via different mechanisms.[25,26] In general, younger patients are more likely to have nausea than older patients. Younger women receiving anticancer agents for breast cancer are more prone to nausea than other populations.[14] Delayed nausea is more common than acute nausea, is often more severe, and tends to be resistant to treatment (see *Delayed Nausea* in this Discussion).[24]

Types of Nausea and/or Vomiting

Chemotherapy-Induced Nausea and/or Vomiting

Nausea and/or vomiting induced by anticancer agents has traditionally been referred to as chemotherapy-induced nausea and/or vomiting (CINV); it 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 administration of certain anticancer agents and commonly resolves within the first 24 hours. The intensity of acute-onset emesis generally peaks after 5 to 6 hours. Factors that influence acute emesis include type and dosage of the emetogenic agent, history of nausea and/or vomiting, environment in which anticancer agents are administered, and efficacy of the antiemetic regimen.[27] The occurrence of acute emesis is increased in younger (<50 years) women with a history of no or low ethanol use, motion sickness, or morning sickness.

Delayed-onset CINV develops in patients more than 24 hours after anticancer agent administration.[28,29] It occurs commonly with the administration of HEC, such as cisplatin, carboplatin, cyclophosphamide, and/or anthracyclines. For cisplatin, emesis reaches its maximal intensity 48 to 72 hours after administration and can last 6 to 7 days.

Anticipatory CINV occurs before patients receive their next treatment with anticancer agents. Because it is primarily considered a conditioned response, anticipatory emesis typically occurs after a previous negative experience with anticancer agents. The incidence of anticipatory CINV ranges from 18% to 57%, and nausea is more common than vomiting.[30,31] Younger patients may be more susceptible to anticipatory nausea and/or vomiting, because they generally receive more aggressive anticancer agents and, overall, have poorer emesis control than older patients.[32]

Breakthrough CINV refers to nausea and/or vomiting that occurs despite prophylactic antiemesis treatment and/or requires rescue with antiemetics.[33]

Refractory CINV refers to nausea and/or vomiting that occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue has not been effective in earlier cycles.[34]

Causes of Nausea and/or Vomiting

As enumerated in the guideline, aside from CINV, the differential diagnoses of nausea and/or vomiting in patients with cancer include: partial or complete bowel obstruction, vestibular dysfunction, brain metastases, electrolyte imbalances (ie, hypercalcemia, hyperglycemia, or hyponatremia), uremia, gastroparesis, excess secretions (ie, such as those seen in patients with head and neck cancer), malignant ascites, cannabinoid hyperemesis syndrome,[35] rapid opioid withdrawal,[36] and pancreatitis, as well as psychophysiologic causes. A thorough evaluation of the patient is thus necessary to rule out alternative causes of nausea and/or vomiting and decide upon the most appropriate intervention.

Radiation-Induced Nausea and/or Vomiting

Patients receiving total body RT have the greatest likelihood of developing nausea and/or vomiting (>90% emesis); those receiving upper abdominal RT are at moderate risk of emesis (30%–90%).[33,37-39] The GI tract (specifically, the small intestine) contains rapidly dividing cells that are particularly sensitive to RT. In addition, the potential for nausea and/or vomiting increases with larger daily fractional doses of RT, larger total doses, and larger amounts of irradiated tissue. Total body irradiation, when given before bone marrow transplantation, commonly induces nausea and/or vomiting.[33,40,41]

Emetogenicity of Anticancer Agents

The frequency of anticancer agent–induced emesis depends primarily on the emetogenic potential of the specific chemotherapeutic agents used. Several classifications have been developed to define the emetogenicity of anticancer agents; however, none has been universally accepted.[16,42-45]

Hesketh and colleagues developed a classification of the acute emetogenicity of anticancer chemotherapeutic agents and developed an algorithm to define the emetogenicity of combination chemotherapeutic regimens.[9] The classification was updated by Grunberg and colleagues; it divides chemotherapeutic agents into four levels according to the percentage of patients who experience acute emesis when they do not receive antiemetic prophylaxis.[46] This classification is used in these NCCN Guidelines and is updated each year by the NCCN Panel with recently introduced drugs.

The NCCN Guidelines currently outline antiemetic treatment using four categories of emetogenic potential for parenteral agents, which correspond to the Hesketh/Grunberg classification as follows:

- High emetic risk—more than 90% of patients experience acute emesis;
- Moderate emetic risk—more than 30% to 90% of patients experience acute emesis;
- Low emetic risk—10% to 30% of patients experience acute emesis;
- Minimal emetic risk—fewer than 10% of patients experience acute emesis.

In addition, the NCCN Guidelines attempt to define antiemetic regimens for particular anticancer agents that cover the entire duration of time a patient is at risk for nausea and/or vomiting. Panel members were concerned that some patients may not receive adequate prophylaxis for delayed emesis; therefore, the NCCN Guidelines incorporate a dosing schedule that covers both acute and delayed emesis into single algorithms for HEC and MEC. The NCCN Panel has also categorized the emetogenic potential of oral anticancer agents.[46]

Clinicians should avoid overuse of antiemetics, especially in settings where the anticancer agents are of minimal or low emetic risk, to avoid exposing patients to adverse effects from antiemetics, to decrease possible drug-drug interactions, and to prevent unnecessary expense (see *Principles of Emesis Control for the Cancer Patient* in the NCCN Guidelines for Antiemesis).[37,47,48] Routine antiemetic premedication may not be required for continuous dosing of some low emetic risk parenteral agents or some moderate to high emetic risk oral agents; an individualized approach is appropriate in these settings. If clinicians use the emetogenic classification of anticancer agents in the NCCN Guidelines, this will decrease unnecessary prescribing of antiemetics.

Types of Antiemetic Therapies

In general, to provide maximal protection against anticancer agent–induced emesis, antiemetic therapy should be initiated before treatment with anticancer agents. The antiemetic therapy should also be continued for the same length of time as the duration of the anticancer agents being used. However, daily use of certain antiemetics, such as dexamethasone, may not be recommended for some anticancer agents that are taken long-term on a regular basis, such as the oral anticancer agents of moderate/high emetic risk (see the NCCN Guidelines for Antiemesis). Antiemetics can be administered by the oral, sublingual, rectal, IV, intramuscular, subcutaneous, or transdermal route. Oral and parenteral 5-HT3 antagonists have equivalent efficacy when used at the appropriate doses.[10,41] However, subcutaneous granisetron extended-release injection and IV granisetron are not interchangeable; the subcutaneous formulation should not be given intravenously and vice versa. Aprepitant injectable emulsion and IV fosaprepitant are also not interchangeable. The dosing is different for all of these formulations. For patients at risk for CINV or unable to swallow or digest tablets because of emesis, non-oral antiemetics are recommended.

Although studies may show antiemetics to be equally effective on a population basis, individual patients may respond differently. Therefore, some antiemetic options may be based on a patient's individual experience. Patients may be at risk for drug-drug interactions if they are receiving anticancer agents along with antiemetic regimens; clinicians should balance benefit and risk for each patient. Many drug-drug interactions between antiemetics and anticancer agents occur with chronic dosing and are often not clinically relevant with short-term use of prophylactic antiemetic regimens, as shown by the lack of clinically significant drug-drug interactions in randomized trials of anticancer agents along with antiemetic regimens.[49] Corticosteroid antiemetics should be avoided for 3 to 5 days before and 90 days after chimeric antigen receptor

(CAR) T-cell therapies. Replacing dexamethasone with olanzapine is an option for patients who cannot tolerate or take steroids.

Serotonin (5-HT3) Antagonists

Ondansetron, Granisetron, and Dolasetron

All of the 5-HT3 antagonists—dolasetron mesylate, granisetron, ondansetron, and palonosetron—have been shown to be effective in controlling the acute nausea and/or vomiting associated with anticancer agents.[50-66] Ondansetron, granisetron, and dolasetron mesylate are first-generation 5-HT3 antagonists. Many clinical trials have compared ondansetron, granisetron, dolasetron mesylate, and palonosetron. These trials have used various doses, routes, and schedules of administration.[67-84] A meta-analysis found no difference in efficacy between the first-generation 5-HT3 antagonists.[85] Another meta-analysis of studies comparing ondansetron with granisetron has also confirmed the similar efficacy of these first-generation 5-HT3 antagonists in controlling acute and delayed nausea and vomiting, with similar safety profiles between these agents.[86]

A meta-analysis of RCTs comparing palonosetron with the first-generation 5-HT3 antagonists reported that palonosetron was significantly more effective in preventing acute and delayed nausea and vomiting for both HEC and MEC; most patients receiving MEC actually received anthracycline and cyclophosphamide (AC regimens).[87] AC regimens are classified as HEC, although they were previously classified as MEC.[37,88] Palonosetron is preferred for MEC if the regimen does not contain an NK1 receptor antagonist (RA) (see *Palonosetron* in this Discussion).[68] Similar to palonosetron, the panel also recommends subcutaneous granisetron extended-release injection as a preferred 5-HT3 antagonist option when used with dexamethasone in antiemetic regimens that do not contain an NK1 RA (see *Principles of Managing Multiday Emetogenic Chemotherapy Regimens* in the NCCN Guidelines for Antiemesis).[89]

Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis but appear to be less effective for delayed emesis. A meta-analysis of RCTs found that adding a 5-HT3 antagonist to dexamethasone did not improve the antiemetic effect of dexamethasone for preventing delayed emesis.[90] Another study found that 5-HT3 antagonists (except palonosetron, which was not studied) were not more effective than prochlorperazine in preventing delayed emesis.[24] A single dose of IV palonosetron appears to be effective for preventing both delayed and acute emesis.

The NCCN Guidelines recommend IV palonosetron as a preferred 5-HT3 antagonist for MEC when used with dexamethasone but without an NK1 RA (see *Principles of Managing Multiday Emetogenic Chemotherapy Regimens* in the NCCN Guidelines for Antiemesis).[68] Several studies[91-94] have evaluated the efficacy of a three-drug combination regimen with palonosetron, dexamethasone, and NK1 RAs as prophylaxis in patients receiving MEC (see *Neurokinin-1-Receptor Antagonists* in this Discussion). However, these studies do not provide evidence that a single dose of palonosetron is better than a single dose of a first-generation 5-HT3 antagonist when using an NK1-antagonist–containing regimen for MEC.

A phase 3 trial assessed subcutaneous granisetron extended-release injection versus IV palonosetron in a two-drug regimen with dexamethasone for patients receiving HEC or MEC.[89] Two doses of subcutaneous granisetron extended-release injection were assessed: 5 mg and 10 mg. The data showed that subcutaneous granisetron extended-release injection is not inferior to IV palonosetron for preventing acute and delayed CINV after either HEC or MEC. For patients receiving HEC, acute complete responses (CRs) for the 5- or 10-mg granisetron doses were 77.7% (−12.1, 6.1) and 81.3% (−8.2, 9.3), respectively, compared with 80.7% for those receiving a 0.25-mg dose of IV

palonosetron. For patients receiving MEC, acute CRs for 5 mg or 10 mg of subcutaneous granisetron were 74.8% (−9.8, 9.3) and 76.9% (−7.5, 11.4), respectively, compared with 75.0% for palonosetron. The FDA approved the use of a 10-mg dose of subcutaneous granisetron extended-release injection when used in antiemetic regimens for MEC or AC combination anticancer agent regimens. Based on this trial and the FDA approval, the NCCN Panel recommends IV palonosetron or subcutaneous granisetron extended-release injection as preferred 5-HT3 antagonists for MEC when used with dexamethasone in two-drug antiemetic regimens that do not contain an NK1 RA. The panel does not recommend these two-drug antiemetic regimens for HEC. The panel recommends for HEC either a four-drug preferred regimen (which includes olanzapine and an NK1 RA) or three-drug antiemetic regimens, which include an NK1 RA or olanzapine.

MAGIC, a phase 3 randomized trial, assessed a single dose of subcutaneous granisetron extended-release injection compared with a single dose of IV ondansetron in a three-drug regimen with dexamethasone and fosaprepitant for patients receiving HEC.[95,96] The data show that the regimen containing granisetron extended-release injection improved the CR rate (no emesis or rescue medication) for delayed-phase CINV (24–120 hours) compared with the ondansetron regimen (P = .014). This was the first published trial that compared a single dose of two different 5-HT3 antagonists when used in combination with dexamethasone and an NK1 RA. As a result, granisetron extended-release injection was the first FDA-approved 5-HT3 antagonist indicated for the prevention of delayed CINV associated with AC anticancer agents. When administered subcutaneously, granisetron extended-release injection is effective for 5 or more days.

The NCCN Panel recommends a 10-mg dose of subcutaneous granisetron extended-release injection on day 1 only for patients receiving either HEC or MEC when used in the antiemetic regimens based on the MAGIC trial, the trial comparing dexamethasone with either palonosetron or subcutaneous granisetron, and the FDA approval.[89,95,96] It is important to note that granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the IV formulation; the subcutaneous formulation should not be injected and vice versa. Subcutaneous granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals.

Ondansetron and granisetron can be delivered orally or intravenously; granisetron extended-release injection is administered subcutaneously. Note that IV dolasetron or 32 mg of ondansetron is no longer recommended for the prevention of nausea and/or vomiting, because they have been associated with an increased risk for cardiac arrhythmias (see *Cardiac Side Effects* in this Discussion).[97-100] Oral administration of ondansetron poses less of a risk for cardiac arrhythmias than IV administration.[99] Oral dolasetron is still recommended.

A phase 3 randomized trial compared the granisetron transdermal patch to oral granisetron in patients receiving either HEC or MEC. The patch contains 3.1 mg of granisetron/24 hours and is applied approximately 24 to 48 hours before the first dose of anticancer agents; the maximum duration of the patch is 7 days. The patch proved non-inferior to repeat dosing of the oral antiemetic granisetron over 3 to 5 days.[13,22,101] A phase 4 trial assessed an antiemetic regimen containing the transdermal granisetron patch versus a palonosetron regimen for patients receiving MEC; transdermal granisetron was not inferior to palonosetron in preventing nausea and vomiting in the acute stage.[102] The NCCN Panel recommends the granisetron transdermal patch as a 5-HT3 option when used as part of recommended antiemetic regimens for patients receiving

either HEC or MEC based on clinical trial data and the FDA approval.[22,101,102] No further 5-HT3 therapy is required on days 2 and 3 if a granisetron transdermal patch is applied on day 1 or if palonosetron or granisetron extended-release injection is given on day 1.

The addition of dexamethasone improves the efficacy of antiemetic regimens containing 5-HT3 antagonists (see *Dexamethasone* in this Discussion). However, dexamethasone is associated with side effects, such as insomnia. When dexamethasone is used with palonosetron for MEC, a 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.[103]

Cardiac Side Effects

Ondansetron, granisetron, and dolasetron have been associated with an increased risk for developing abnormal electrical activity of the heart that is detectable on ECG, including prolongation of electrocardiographic intervals, such as PR or QT intervals.[99,100,104-111] Although the ECG changes can be reversible and asymptomatic, abnormal activity can also result in potentially fatal cardiac arrhythmias (including torsade de pointes) in some cases.[99] Patients who may be particularly at risk for developing torsade de pointes include those with congenital long QT syndrome or other underlying cardiac diseases, congestive heart failure, bradycardia, those with electrolyte abnormalities (eg, hypokalemia, hypomagnesemia), and those taking other medications that can lead to QT prolongation.[100,108,112] A single IV dose of 32 mg of ondansetron is no longer recommended based on FDA review of clinical data suggesting prolongation of the QT interval of the ECG at this dose.[97-99] The FDA recommends a maximum single IV dose of 16 mg of ondansetron given once on the first day; the dose recommendations for oral administration of ondansetron are 16 to 24 mg given once on the first day.[98] IV dolasetron is no longer recommended for the prevention of nausea and vomiting, because it has been associated with an increased risk for cardiac arrhythmias.[99,100]

Palonosetron

Palonosetron is a 5-HT3 antagonist with an approximately 100-fold higher binding affinity for the 5-HT3 receptor compared to ondansetron, granisetron, and dolasetron. Palonosetron has a half-life of approximately 40 hours, which is significantly longer than other commercially available 5-HT3 antagonists.[52] Data suggest that palonosetron is associated with prolonged inhibition of the 5-HT3 receptor and thus differs from ondansetron, granisetron, and dolasetron.[113,114] By suppressing cross talk between 5-HT3 and NK1 signaling pathways, palonosetron may indirectly inhibit substance P.

Several randomized phase 3 trials have assessed the efficacy of palonosetron compared with other 5-HT3 antagonists in preventing emesis associated with both MEC and HEC regimens, particularly for delayed emesis.[67-70] In these studies, the primary efficacy endpoint was CR, defined as having no emesis and no rescue treatments. In a study in patients receiving MEC (N = 563 evaluable), a single dose of palonosetron (0.25 mg IV) was found to be superior to a single dose of ondansetron (32 mg IV) in preventing both acute (CR rate, 81% vs. 69%; $P < .01$) and delayed emesis (CR rate, 74% vs. 55%; $P < .01$); no concomitant corticosteroids were given in this study.[70] The safety and side-effect profiles of palonosetron were indistinguishable from the control 5-HT3 antagonists (ondansetron and dolasetron). Note that the FDA recommends a maximum of 16 mg for a single dose of IV ondansetron.[99]

A phase 3 randomized trial compared palonosetron with ondansetron in patients receiving HEC (N = 667), and most patients (67%) received dexamethasone on day 1 of antiemetic therapy; NK1 RAs were not used in this trial.[67] Among this subgroup of patients who received concomitant dexamethasone (n = 447), palonosetron (0.25 mg IV) was similar to ondansetron (32 mg IV) in preventing acute emesis (CR rate, 65% vs.

56%); however, palonosetron was significantly more effective in preventing delayed emesis (CR rate, 41% vs. 25%; *P* = .021).

Another phase 3 randomized trial in patients treated with HEC (N = 1114 evaluable) compared a single dose of palonosetron (at a higher dose of 0.75 mg IV) with a single dose of granisetron (40 mcg/kg IV), both in combination with dexamethasone; NK1 RAs were not used in this trial. Palonosetron showed similar activity to granisetron in preventing acute emesis (CR rate, 75% vs. 73%) and superior activity in preventing delayed emesis (CR rate, 57% vs. 44.5%; *P* < .0001).[68] A meta-analysis of 24 RCTs assessed whether palonosetron was more efficacious than the other 5-HT3 antagonists. Although palonosetron seems to be more efficacious and safe than other 5-HT3 RAs and was statistically superior in 10 of 19 endpoints, overall the authors suggest that palonosetron should generally not be the preferred 5-HT3 antagonist.[115] The NCCN Panel does not recommend palonosetron as the preferred 5-HT3 antagonist in regimens for HEC, because an NK1 RA was not used in these studies and it is unknown if a single dose of palonosetron would be superior to a single dose of granisetron in the presence of an NK1 RA.[67,68,70,115,116]

As previously mentioned, the NCCN Panel recommends either palonosetron or subcutaneous granisetron extended-release injection as preferred 5-HT3 antagonists for MEC when used with dexamethasone in two-drug antiemetic regimens that do not contain an NK1 RA (see *Ondansetron, Granisetron, and Dolasetron* in this Discussion and *Principles of Managing Multiday Emetogenic Chemotherapy Regimens* in the NCCN Guidelines for Antiemesis).[89] Palonosetron (0.25 mg IV) is FDA approved as a single dose on day 1 for the prevention of acute and delayed nausea and vomiting associated with MEC and for the prevention of acute nausea and vomiting associated with HEC. No further 5-HT3 therapy is required for MEC on days 2 and 3 if palonosetron or granisetron extended-release injection is given on day 1 or if granisetron transdermal patch is applied on day 1.

IV palonosetron is superior to other first-generation 5-HT3 antagonists in preventing delayed nausea.[23,67-70] Repeat dosing of palonosetron on days 2 or 3 after anticancer agents is likely to be safe. However, in the setting of multiday anticancer agents, limited data are available to recommend multiday dosing with palonosetron (see *Principles of Managing Multiday Emetogenic Chemotherapy Regimens* in the NCCN Guidelines for Antiemesis).[117]

Neurokinin-1-Receptor Antagonists

For patients receiving HEC and MEC, the NCCN Panel recommends several options for prophylactic antiemetic regimens based on clinical trial data and FDA approvals, including: 1) NK1 RA-containing regimens, which are discussed in this section; and 2) olanzapine-containing regimens. NK1 RA regimens include oral aprepitant, IV fosaprepitant, oral rolapitant, oral netupitant, or IV fosnetupitant. It is important to note that oral netupitant (or IV fosnetupitant) is only available in combination with palonosetron (NEPA); netupitant is not available as a single agent.

A prophylactic two-drug regimen of one of the 5-HT3 antagonists plus dexamethasone is recommended for MEC but not HEC. However, a prophylactic three-drug antiemetic regimen that includes either an NK1 RA or olanzapine is recommended for select patients receiving MEC who have additional risk factors or previous treatment failure with the two-drug regimen. These additional risk factors include younger age; female sex; anxiety and/or high pretreatment expectation of nausea and/or vomiting; and history of CINV, motion sickness, morning sickness during pregnancy, and little or no alcohol use.[118] Patients receiving anticancer agents that are classified as moderate emetic risk but are at the higher end of the risk spectrum (eg, carboplatin, carmustine, cyclophosphamide, dactinomycin,

daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, methotrexate, oxaliplatin, trabectedin) are at greater risk for emesis and may also need a three-drug prophylactic antiemetic regimen.

Aprepitant

Aprepitant selectively blocks the binding of substance P at the NK1 receptor in the central nervous system. Thus, it provides a different and complementary mechanism of action compared with other commercially available antiemetics. Aprepitant has been shown to augment the antiemetic activity of the 5-HT3 antagonists and the corticosteroid dexamethasone to prevent both acute and delayed cisplatin-induced emesis.[119-121] Most of the clinical trial data described in this Discussion are based on studies with oral aprepitant. Aprepitant injectable emulsion is a formulation of aprepitant that is approved by the FDA for HEC and MEC when used in combination with other antiemetic regimens.[122]

Oral Aprepitant

A randomized phase 3 trial compared ondansetron 32 mg IV and oral dexamethasone with or without the addition of oral aprepitant in patients receiving emetogenic systemic therapy with high-dose cisplatin (N = 521 evaluable). The addition of oral aprepitant was significantly more effective than the 2-drug regimen in controlling both acute (CR rate, 89% vs. 78%; $P < .001$) and delayed emesis (CR rate, 75% vs. 56%; $P < .001$).[120] Another similarly designed randomized phase 3 study (N = 523 evaluable) also showed a significant benefit of adding oral 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%; $P < .001$).[121] A pooled analysis of data combined from these two phase 3 trials found that the oral aprepitant regimen was particularly beneficial in improving CR rates for patients receiving concomitant emetogenic therapy with doxorubicin and cyclophosphamide (AC regimen) or cyclophosphamide, along with high-dose cisplatin therapy.[119]

A large meta-analysis (of 17 RCTs) evaluated outcomes with typical antiemetic therapy with or without oral aprepitant in patients receiving MEC or HEC. The addition of oral aprepitant was associated with significantly improved CR (no emetic episodes and no rescue medication) rate compared with control antiemetic therapy (72% vs. 54%; $P < .001$) during the overall timeframe from 0 to 120 hours after starting anticancer agents.[123] The significant increase in CR rate associated with oral aprepitant was observed for both the acute and delayed periods. A smaller meta-analysis (of seven RCTs) of patients receiving HEC found that oral aprepitant used alone or with control antiemetic therapy did not significantly increase protection from acute emesis or nausea; however, for delayed emesis and nausea, oral aprepitant was associated with significantly increased protection compared with control.[124] Based on data from three trials that reported on infectious complications, both oral aprepitant regimens and other antiemetic regimens were associated with a low rate of severe infections (6% vs. 2%; $P < .001$); the risk of febrile neutropenia or other hematologic toxicities was not increased.[123] A randomized phase 3 trial (N = 866) showed that an oral aprepitant regimen was more effective than a control antiemetic regimen in preventing vomiting in patients receiving HEC during 120 hours after initiation of anticancer agents (CR rate, 51% vs. 43%; $P = .015$); no delayed dexamethasone was used in this trial. However, approximately 40% of patients receiving either regimen still experienced significant nausea.[125] The oral aprepitant regimen included ondansetron and dexamethasone; the control antiemetic regimen included ondansetron and dexamethasone.

A 3-drug antiemetic regimen with palonosetron, dexamethasone, and oral aprepitant has also been investigated in patients undergoing treatment

with HEC. A phase 2 study in patients receiving HEC with cisplatin-containing regimens (N = 222) showed that the three-drug combination of palonosetron (0.25 mg IV day 1), oral aprepitant (125 mg day 1; 80 mg days 2, 3), and dexamethasone (20 mg IV day 1; 4 mg oral days 2, 3) resulted in a CR rate (no emetic episodes and no rescue medication) of 70% during the overall study period (0–120 hours).[93] In addition, 93% of patients had no emesis and 60% had no nausea during the study period. Constipation was the most commonly reported adverse event (39%).[93] A phase 2 study evaluated a higher dose of palonosetron (0.75 mg IV day 1) with oral aprepitant (125 mg day 1; 80 mg days 2, 3) and dexamethasone (10 mg oral day 1; 8 mg oral days 2–4) in patients with lung cancer undergoing HEC (N = 63); the CR rate was 81% during the overall study period (0–120 hours).[94] The CR rates during the acute and delayed phases were 97% and 81%, respectively. In addition, 54% of patients had no nausea during the overall study period. Grade 1 or 2 constipation was the most commonly reported adverse event.[94]

A phase 3 trial added oral aprepitant to a control antiemetic regimen of oral granisetron and oral dexamethasone in patients receiving MEC. The addition of oral aprepitant improved control of nausea, vomiting, and quality of life compared with granisetron and dexamethasone.[126] A phase 2 study (N = 58) found that combining palonosetron (0.25 mg IV day 1), oral aprepitant (125 mg day 1; 80 mg days 2, 3), and dexamethasone (12 mg day 1; 8 mg days 2, 3) was effective in preventing both acute and delayed emesis and nausea when using various chemotherapeutic regimens (moderate to moderately highly emetogenic); 78% of patients had a CR (no emetic episodes and no rescue medication) during the overall timeframe, from 0 to 120 hours after initiation of emetogenic therapy.[91] A phase 2 study in patients with breast cancer (N = 41) receiving MEC also found that a single-day regimen of palonosetron (0.25 mg IV), oral aprepitant (285 mg oral), and dexamethasone (20 mg) was effective; 76% and 66% of patients had a CR during the acute and delayed phases, respectively.[92]

A randomized double-blind phase 3 trial compared the effectiveness of combining ondansetron (8 mg oral twice daily [BID] day 1), oral aprepitant (125 mg day 1; 80 mg days 2, 3), and dexamethasone (12 mg day 1) versus control antiemetic therapy with ondansetron (8 mg oral BID days 1–3) and dexamethasone (20 mg day 1) in patients receiving MEC (N = 585).[127] Dexamethasone was only given on day 1 for both treatment groups. A significantly higher proportion of patients in the three-drug regimen with oral aprepitant had no vomiting compared with the control antiemetic regimen (76% vs. 62%; $P < .001$) during the overall timeframe from 0 to 120 hours after starting anticancer agents. In addition, the CR (no emetic episodes, no rescue medications) rate was significantly increased in the oral aprepitant group (69% vs. 56%; $P < .001$) during the overall time period. The significant improvement in antiemetic activity (with regard to no emesis as well as CR rate) in the oral aprepitant group was observed for both the acute and delayed phases. The three-drug regimen was well tolerated, and the incidence of adverse events was similar between treatment groups.[127] Oral aprepitant is FDA approved for the prevention of nausea and vomiting in patients receiving HEC (eg, cisplatin-containing) and MEC. The oral doses of aprepitant are 125 mg on day 1 (before anticancer agents) and then 80 mg on days 2 and 3 (after anticancer agents).[128]

The NCCN Panel recommends prophylactic oral aprepitant in combination with dexamethasone, a 5-HT3 RA, and with or without olanzapine (category 1) for acute and delayed emesis prevention for HEC and MEC based on clinical trial data and on FDA approvals.[119,120,129]

Fosaprepitant

Fosaprepitant dimeglumine is an IV version of aprepitant, which can be given on day 1 only; it is also FDA approved. A single dose of 150 mg IV

fosaprepitant was shown to be non-inferior to the control antiemetic regimen with 3-day oral aprepitant in a randomized study.[130] As previously mentioned, IV fosaprepitant is NOT interchangeable with aprepitant injectable emulsion. IV fosaprepitant is given 30 minutes before anticancer agents on day 1 only, per the package insert. If a higher dose of fosaprepitant is used (150 mg IV) on day 1, then it is not necessary to give oral aprepitant on days 2 to 3.[131,132] Note that the dexamethasone dosing is slightly different on days 3 and 4 (8 mg PO/IV BID) when using the higher dose of fosaprepitant (150 mg IV) per the package insert. There are no studies showing efficacy or safety of chronic dosing with oral aprepitant. It is possible that the drug-drug interaction profile may change with chronic dosing.

The NCCN Panel recommends prophylactic fosaprepitant in combination with dexamethasone, a 5-HT3 RA, and with or without olanzapine (category 1) for acute and delayed emesis prevention for HEC and MEC based on clinical trial data and on FDA approvals.[130]

Aprepitant Injectable Emulsion

IV fosaprepitant contains polysorbate 80 and other surfactants that may cause infusion-site reactions including pain, erythema, and swelling.[122,133,134] Aprepitant injectable emulsion is a formulation of aprepitant that does not contain polysorbate 80 and other surfactants. A phase 1 bioequivalence study (n = 100) compared IV fosaprepitant with aprepitant injectable emulsion.[122] Patients receiving aprepitant injectable emulsion had fewer treatment-emergent adverse effects compared with those receiving IV fosaprepitant (1% vs. 20%); all these adverse events resolved. Three patients receiving IV fosaprepitant had dyspnea. None of the patients had severe treatment-emergent adverse effects, serious adverse events, or resultant death. Aprepitant injectable emulsion was bioequivalent to IV fosaprepitant (bioequivalence bounds, 80%–125%).

The NCCN Panel recommends prophylactic aprepitant injectable emulsion in combination with dexamethasone, a 5-HT3 RA, and with or without olanzapine (category 1) for acute and delayed emesis prevention for HEC and MEC based on clinical trial data and on FDA approvals.[122] As previously mentioned, aprepitant injectable emulsion is not interchangeable with IV fosaprepitant.

Drug Interactions

Aprepitant is simultaneously a substrate, moderate inducer, and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4); aprepitant also induces CYP2C9.[135] Thus, aprepitant can alter the metabolism of certain drugs and change their plasma concentrations (ie, areas under the curve [AUCs]). However, these interactions are more significant with orally administered forms of these drugs than with IV forms because of first-pass metabolism. Patients should not take oral aprepitant or aprepitant injectable emulsion with pimozide or astemizole; these combinations are contraindicated because they may cause serious or life-threatening reactions (see the aprepitant package inserts). Chemotherapeutic agents known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. In clinical trials, oral aprepitant was used concurrently with etoposide, vinorelbine, or paclitaxel; although anticancer agent doses were not adjusted for potential drug interactions in phase 3 trials, no observed adverse effect or decreased efficacy was observed; caution is urged when using any chemotherapeutic agent that is metabolized by CYP3A4. A systematic review also describes potential drug-drug interactions with aprepitant and fosaprepitant.[136] However, short-term use of antiemetics may not result in clinically relevant drug interactions.[49]

Aprepitant has been shown to interact with several non-chemotherapeutic drugs, including warfarin, dexamethasone, methylprednisolone, and oral contraceptives. Induction of warfarin metabolism by aprepitant may lead to

clinically significant reductions in INR (international normalized ratio) values, particularly for patients on therapeutic (as compared to prophylactic) warfarin regimens. These changes, although brief in duration, may require increased patient monitoring. 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. Additionally, certain drugs can affect the AUCs of aprepitant. Concomitant administration with CYP3A4 inhibitors (eg, ketoconazole, itraconazole, erythromycin) may lead to increased aprepitant AUCs, whereas concomitant administration with CYP3A4 inducers (eg, carbamazepine, rifampin, phenytoin) may lead to decreased levels of aprepitant.

Netupitant (or Fosnetupitant) and Palonosetron (NEPA)

Netupitant is a highly selective NK1 RA that targets serotonin and substance P–mediated pathways involved in CINV. Oral netupitant is combined with oral palonosetron (NEPA) in a single tablet, and netupitant is not available as a single agent; oral NEPA is approved by the FDA for the prevention of nausea and vomiting in patients receiving HEC and MEC based on several randomized trials.[137-140] IV fosnetupitant is combined with IV palonosetron (IV NEPA), and fosnetupitant is also not available as a single agent; IV NEPA is approved by the FDA for the prevention of nausea and vomiting in patients receiving HEC and other types of anticancer agents.

A randomized trial in patients receiving HEC assessed dexamethasone plus three dose levels of prophylactic oral NEPA compared with oral palonosetron plus dexamethasone.[137] The oral NEPA fixed-dose combination of 300 mg of netupitant decreased nausea and vomiting in the acute, delayed, and overall phases versus palonosetron alone. The CR for the NEPA300 arm was 89.6% versus 76.5% for the palonosetron arm ($P < .050$). A randomized phase 3 trial in patients receiving AC regimens assessed oral NEPA plus dexamethasone compared with palonosetron plus dexamethasone.[139] More patients in the oral NEPA arm had CR during the delayed phase compared with the control arm (76.9% vs. 69.5%; $P = .001$). In addition, patients in the oral NEPA arm also had more CRs in the overall phases (0–120 h) (74.3% vs. 66.6%; $P = .001$) and acute phases (0–24 h) (88.4% vs. 85.0%; $P = .047$).

A phase 3 randomized trial assessed a single dose of oral NEPA compared with a three-day aprepitant/granisetron regimen in patients (n = 828) receiving HEC; all patients received oral dexamethasone on days 1 through 4.[141] The oral NEPA regimen was non-inferior to the aprepitant regimen (overall CR: oral NEPA, 73.8% vs. aprepitant/granisetron, 72.4%; 95% CI, -4.5%–7.5%). Similar rates were observed for both groups for no emesis (oral NEPA, 75.0% vs. aprepitant/granisetron, 74.0%; 95% CI, -4.8%–6.9%) and no significant nausea (oral NEPA, 75.7% vs. aprepitant/granisetron, 70.4%; 95% CI, -0.6%–11.4%).

The NCCN Panel recommends prophylactic oral or IV NEPA in combination with dexamethasone and with or without olanzapine (category 1) for acute and delayed emesis prevention for HEC and MEC based on randomized trials, FDA approvals, and clinical experience.[137,139,141,142] Currently, IV NEPA is only FDA approved for HEC. However, the NCCN Panel recommends IV NEPA regimens for MEC based on clinical experience.

Similar to the other NK1 RAs (ie, oral aprepitant, IV fosaprepitant, oral rolapitant), netupitant and fosnetupitant improve control for delayed emesis compared with traditional antiemetic regimens. Netupitant and fosnetupitant inhibit CYP3A4; therefore, caution should be used with drugs that are metabolized by CYP3A4 to avoid drug interactions (see prescribing information). Concomitant use with certain agents that are strong inducers (eg, rifampin) of CYP3A4 is contraindicated. However,

short-term use of antiemetics may not result in clinically relevant drug interactions.

Rolapitant

Oral rolapitant is another NK1 RA that is approved by the FDA for the prevention of nausea and vomiting in patients receiving HEC and other types of anticancer agents based on several phase 3 randomized trials.[143,144] In a phase 3 randomized trial assessing a prophylactic oral rolapitant-containing regimen for HEC, patients received 180 mg of oral rolapitant on day 1 only; all patients received granisetron (10 mcg/kg intravenously) and dexamethasone (20 mg orally) on day 1, and dexamethasone (8 mg orally) BID on days 2 to 4.[144] More patients receiving the oral rolapitant-containing regimen had CRs for prevention of delayed emesis compared with those receiving granisetron/dexamethasone alone (pooled studies: 382 [71%] vs. 322 [60%]; odds ratio [OR], 1.6; 95% CI, 1.3–2.1; *P* = .0001). For patients receiving HEC, the NCCN Panel recommends several prophylactic antiemetic regimens (category 1); a 5-HT3 antagonist, dexamethasone, and oral rolapitant regimen with or without olanzapine is recommended for acute and delayed emesis prevention based on the FDA approval and the phase 3 randomized trial.[144]

A randomized phase 3 trial assessed a prophylactic oral rolapitant-containing regimen for anticancer regimens previously considered to be MEC, which are now categorized as HEC by the NCCN Panel (ie, AC regimens and regimens containing carboplatin with an AUC ≥4). With the revised definition of HEC regimens, this trial actually contained mostly HEC and only some MEC regimens (18% and 14% of patients had non-AC regimens and non-carboplatin regimens).[88,143] Most patients also received granisetron (2 mg orally) and dexamethasone (20 mg orally) on day 1 followed by granisetron (2 mg orally) on days 2 to 3.[143] Significantly more patients receiving the oral rolapitant-containing regimen had CRs in the delayed phase than did those receiving granisetron/dexamethasone alone (475 [71%] vs. 410 [62%]; OR, 1.6; 95% CI, 1.2–2.0; *P* = .0002). For patients receiving MEC, the NCCN Panel recommends several prophylactic antiemetic regimens (category 1); a 5-HT3 antagonist/dexamethasone (category 1) with (or without) oral rolapitant is recommended for acute and delayed emesis prevention based on the FDA approval and the phase 3 randomized trial.[143] Although most of the clinical trial data for rolapitant are in patients receiving HEC, the NCCN Panel feels that prophylactic antiemetic regimens with oral rolapitant are appropriate for patients receiving MEC based on the FDA approval and clinical experience.

Oral rolapitant has an extended half-life and should not be administered at less than 2-week intervals. If oral rolapitant is given on day 1 for either HEC or MEC, no further NK1 RA is needed on days 2 and 3. Similar to the other NK1 RAs, oral rolapitant improves control for delayed emesis compared with traditional antiemetic regimens. Rolapitant does not inhibit or induce CYP3A4; therefore, the dexamethasone dose does not need to be adjusted (see *Dexamethasone* in this Discussion). Rolapitant does, however, inhibit CYP2D6, P-glycoprotein, and breast cancer resistance protein (BCRP); therefore, caution is required when rolapitant is used concomitantly with drugs that are substrates of these enzymes, including thioridazine, pimozide, digoxin, irinotecan, topotecan, methotrexate, and rosuvastatin. The IV formulation of rolapitant was removed because of infusion-related hypersensitivity/anaphylaxis.

Other Antiemetics

Before the advent of the 5-HT3 antagonists and NK1 RAs, the available antiemetics included phenothiazines,[145] substituted benzamides,[146,147] antihistamines,[148] butyrophenones,[149] corticosteroids,[150-152] benzodiazepines,[153,154] and cannabinoids.[155,156] Based on clinical trial data, the NCCN Panel includes olanzapine-containing regimens as another

antiemetic option. Combination antiemetic therapy is generally more effective than single-agent therapy. Other agents such as gabapentin have also been evaluated as part of antiemetic regimens.

Dexamethasone

Dexamethasone has been used for many years in combination with other antiemetics. The antiemetic effects of dexamethasone may be due to interactions with the neurotransmitter serotonin and receptor proteins tachykinin NK1 and NK2; it may also act directly at the solitary tract nucleus in the medulla.[157] Before the mid-1990s, studies assessing dexamethasone as an antiemetic agent were characterized by small sample size and variations in efficacy outcomes between the studies. A meta-analysis of 32 studies (published from 1966–1999) was done in 5613 patients; the dose range was 8 to 100 mg of dexamethasone on day 1, and the mean total dose (acute and delayed) was 56 mg.[158] The authors concluded that dexamethasone offered a clear advantage over placebo for protection against anticancer agent–induced emesis in both the acute and delayed phases. There was incremental benefit when adding dexamethasone to both 5-HT3 antagonist-containing regimens and non–5-HT3 antagonist regimens. Although data *suggested* that dexamethasone was superior to 5-HT3 antagonists for protection against delayed emesis, there was a lack of a strong dose/response relationship. The authors could not rule out a subtle dose/response relationship for total doses less than 20 mg of dexamethasone, but even low doses showed clear efficacy.

The Italian Group for Antiemetic Research conducted two randomized, phase 3 multicenter trials to determine the dose of dexamethasone to be given on day 1 of an antiemetic regimen.[159,160] The first trial was conducted in chemo-naive patients receiving 50 mg/m^2 or more of cisplatin, which is considered HEC.[159] IV dexamethasone day 1 doses were 4, 8, 12, and 20 mg (approximately 130 patients/arm). All patients received the following: 1) ondansetron 8 mg IV on day 1; 2) metoclopramide 20 mg oral every 6 hours on days 2 to 4; and 3) dexamethasone 8 mg oral BID on days 2 and 3, followed by 4 mg oral BID on day 4. Complete protection from emesis and nausea was 69.2% and 60.9%; 69.1% and 61.0%; 78.5% and 66.9%; and 83.2% and 71.0% for the 4-, 8-, 12-, and 20-mg dexamethasone doses, respectively. For protection against acute emesis, the 20-mg dose of dexamethasone was statistically significant compared to the 4- and 8-mg doses. However, the 20-mg and the 12-mg doses of dexamethasone were equivalent for protection against acute emesis. The 20-mg dose of dexamethasone was not significantly different from the other doses for protection against acute nausea. Adverse effects and control of delayed emesis and nausea were similar among the four groups.

The second Italian study compared three dosing regimens of dexamethasone on day 1 in patients receiving anthracyclines, cyclophosphamide, or carboplatin, either alone or in combination with other anticancer agents, which previously were considered to be MEC.[160] Note that AC regimens are now considered to be HEC by the NCCN Panel; likewise, carboplatin with an AUC of 4 or more is now considered to be HEC. For the prevention of acute emesis, during the first 24 hours, one of the following dexamethasone regimens was used in combination with 8 mg of IV ondansetron: 1) for arm A, 8 mg of IV dexamethasone before anticancer agents plus 4 mg oral dexamethasone every 6 hours for 4 doses, starting at the same time as the anticancer agents; 2) for arm B, 24 mg of IV single-dose dexamethasone before anticancer agents; or 3) for arm C, 8 mg of IV single-dose dexamethasone before anticancer agents. All patients received oral dexamethasone 4 mg BID on days 2 to 5. Complete protection from acute vomiting and nausea was 84.6% and 66.7%, 83.6% and 56.9%, and 89.2% and 61.0% for arms A, B, and C, respectively. Side effects and control of delayed vomiting and nausea were not significantly different among the three groups. The authors concluded that 8 mg of IV dexamethasone is the best dose when using dexamethasone in antiemetic regimens for patients receiving anticancer

agents with these agents. Of note, 95% of the patients were being treated for breast cancer; thus, most patients were women.

Information from early studies with oral aprepitant-containing regimens suggested that the dose of dexamethasone should be decreased from 20 mg to 12 mg because of a near doubling in the AUC of dexamethasone, presumably due to CYP3A4 inhibition (see *Drug Interactions* in this Discussion). The studies by the Italian Group were done before the NK1 RAs were available, and dose-finding studies for dexamethasone on day 1 in combination with NK1 RAs and 5-HT3 antagonists have not been done.[159,160] This information, along with the previous data showing a lack of a dose/response correlation, was the basis of the NCCN Panel's recommendation of 12 mg of dexamethasone as the day 1 dose for all emetic categories when using any of the recommended antiemetic regimens to simplify the recommendations as described in the next paragraph.

The doses and schedules for dexamethasone in the NCCN Guidelines are mainly based on the doses and schedules used in the clinical trials for each regimen. However, the NCCN Panel feels that dexamethasone doses may be individualized; lower doses, frequency, or even elimination of dexamethasone on subsequent days may be acceptable based on patient characteristics. Dexamethasone-sparing strategies may be appropriate for patients receiving MEC or non-cisplatin HEC; limiting dexamethasone to day 1 only in these patients may be especially appropriate for patients with few identifiable risk factors for CINV or for those intolerant to corticosteroids (see the NCCN Guidelines for Antiemesis).[103,161-167] Dexamethasone is associated with side effects, such as insomnia.

The dosing for dexamethasone for the IV HEC and MEC regimens has been simplified. For the three-drug prophylactic olanzapine regimen—olanzapine plus palonosetron plus dexamethasone—for HEC and MEC, the dose of dexamethasone was decreased to 12 mg orally (or intravenously) for day 1, because all the other antiemetic regimens use this dexamethasone dose on day 1. Previously, the panel had recommended a dexamethasone dose of 20 mg orally (or intravenously) on day 1 in the three-drug olanzapine regimen. For all the HEC regimens, the panel also simplified the dosing for delayed dexamethasone to 8 mg orally (or intravenously) daily on days 2 to 4 (previously, some of the HEC regimens had used twice-daily dosing of dexamethasone). The NCCN Panel recommends that if patients cannot tolerate dexamethasone, it can be replaced with olanzapine.

When dexamethasone is used with palonosetron for MEC, a 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.[103] A similar phase 3 trial assessed palonosetron with dexamethasone on day 1 only versus palonosetron (day 1) with dexamethasone on days 1 to 3 in women receiving MEC regimens.[165] For women receiving dexamethasone on day 1 only (n = 166), the overall CR rates were 67.5% versus 71.1% for those receiving dexamethasone on days 1 to 3 (n = 166; difference -3.6% [95% CI, -13.5–6.3]). There was no difference in CR rates between the two regimens during the acute (0–24 hours post-chemotherapy; 88.6% vs. 84.3%; $P = .262$) and delayed phases (days 2–5; 68.7% vs. 77.7%; $P = .116$).[165]

Olanzapine

Olanzapine is an atypical antipsychotic agent that is also useful as an antiemetic agent; it is an antagonist of multiple receptors involved in CINV, including dopamine, serotonin, histamine, and acetylcholine-muscarine.[20] A three-drug antiemetic regimen with olanzapine, dexamethasone, and palonosetron is effective for preventing acute and delayed emesis as described in the following sections.[20,168-176] An olanzapine-containing four-drug antiemetic regimen is also effective for preventing acute and

delayed emesis.[177] A Cochrane analysis also reported that olanzapine regimens are effective.[178] The NCCN Panel recommends (category 1) olanzapine-containing three-drug or four-drug antiemetic regimens for both HEC and MEC based on the clinical trial data as described in the following sections.[37] Olanzapine can be substituted for dexamethasone if patients cannot tolerate dexamethasone (eg, diabetics).

Common side effects with olanzapine include postural hypotension, anticholinergic side effects, fatigue, and sedation.[179] 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).[180] Data suggest that a 5-mg dose of olanzapine may be considered, especially for elderly or oversedated patients.[181-185] Sedation is most notable on day 2 and improves over time. For this reason, bedtime administration is recommended unless olanzapine is administered as a premedication prior to anticancer therapy.

A single-arm, multi-center, phase 2 study, evaluating the efficacy and safety of the 5 mg dose of olanzapine in combination with an NK1 RA, a 5-HT3 RA, and dexamethasone in gynecological cancer patients scheduled to be administered AUC ≥4 mg/ml/min carboplatin combination therapy (CBDCA), reported the combination to be an effective prophylactic antiemetic regimen.[186] Similarly, in a multi-center, randomized, double-blind, placebo-controlled phase 3 trial (J-FORCE) evaluating the efficacy of the 5 mg dose of olanzapine with a three-drug regimen for the prevention of CINV, patients received either olanzapine 5 mg PO or an oral placebo once daily on days 1 through 4 combined with aprepitant, palonosetron, and dexamethasone. The primary endpoint of the study (ie, the proportion of individuals who achieved a CR [the absence of vomiting and lack of rescue medication use in the delayed phase]) was met, as 79% of patients (95% CI 75-83) in the olanzapine group and 66% of those in the placebo group (95% CI 61-71) exhibited a CR. It was concluded that to avoid unwanted sedation in select individuals, a 5mg dose of olanzapine may be suitable for combination with HEC antiemetic prophylaxis.[187] Finally, a dose of 2.5 mg of olanzapine may be considered if patients have excessive sedation with the 5-mg dose.

Three-Drug Regimen

Several studies have reported favorable results following the addition of olanzapine to the antiemetic prophylaxis regimen for HEC agents.[188-190] A three-drug antiemetic regimen with olanzapine, dexamethasone, and palonosetron is effective for preventing acute and delayed emesis based on phase 3 trials, phase 2 trials, and meta-analyses.[20,168-176] A randomized phase 3 trial evaluated the effectiveness of an olanzapine (10 mg oral days 1–4) regimen versus an oral aprepitant (125 mg oral day 1, 80 mg oral days 2, 3) regimen with dexamethasone 8 mg on days 2 to 4 for preventing acute and delayed emesis in patients (N = 251) receiving HEC (cisplatin, or AC regimens); both treatment arms included palonosetron (0.25 mg IV) and dexamethasone administered on day 1.[175] The CR (no emesis, no rescue) rate was similar between the olanzapine and oral aprepitant regimens, both during the acute (97% vs. 87%) and delayed (77% vs. 73%) periods. The proportion of patients without nausea was similar for the acute period (87% in each study arm), but the olanzapine regimen was associated with a higher rate of nausea control during the delayed period (69% vs. 38%) compared with the oral aprepitant regimen.[175] A systematic review summarized the phase 1 and 2 studies of olanzapine for preventing acute and delayed emesis.[20] Across four studies (201 patients), the CR rate was 97.2%, 83.1%, and 82.8 % for the acute, delayed, and overall phases, respectively. Other studies have also shown the value of olanzapine for delayed, refractory, and breakthrough emesis and nausea.[170-173,184]

In a randomized, double-blind, placebo-controlled study conducted by Jeon and colleagues, to evaluate the efficacy of olanzapine in patients receiving MEC regimens, patients were randomized to receive either olanzapine or placebo in combination with palonosetron and dexamethasone. The primary endpoint of the study was CR during the acute phase, while the secondary endpoints included CR during the delayed and overall (0—120 hours) phases, proportion of significant nausea, use of rescue therapy, and impact on quality of life (PQOL). It was found that although the CRs were relatively similar across both treatment arms, the percentage of patients with significant nausea (17.2% vs. 44%; P=0.032) and the use of rescue therapy was lower in the olanzapine group associated with an overall better QOL.[191]

Finally, in a systematic review and meta-analysis of 27 RCTs evaluating 12 antiemetic regimens, Yokoe and colleagues found that olanzapine-containing regimens were both efficacious and cost-effective for CINV associated with HEC regimens. Although, the combination of an NK1RA, palonosetron, and dexamethasone was found to be the most efficacious of the three-drug regimens, olanzapine, when substituted for an NK1RA, was reported to be a more cost-effective alternative. Overall, however, it was concluded that the four-drug olanzapine-containing regimen was the most effective to control CINV associated with HEC.[192] The NCCN Panel recommends (category 1) a prophylactic olanzapine-containing three-drug antiemetic regimen for both HEC and MEC based on the phase 3 and phase 2 trials.[20,168-176] As previously mentioned, the NCCN Panel recommends a dose of dexamethasone 12 mg orally (or intravenously) on day 1 for the three-drug antiemetic regimen with olanzapine/palonosetron/dexamethasone. The panel also agrees that palonosetron should be used in the three-drug olanzapine regimen; no data are available to support substituting any of the other 5-HT3 antagonists.

Four-Drug Regimen

A phase 3 randomized trial assessed adding olanzapine or placebo to an antiemetic regimen of oral aprepitant or fosaprepitant, a 5-HT3 antagonist, and dexamethasone for patients receiving HEC.[177] The four-drug regimen with olanzapine increased the CR rate (no emesis, no rescue) compared with placebo during three time periods (<24 hours after chemotherapy, 25–120 hours, and the overall 120 hours: 86% vs. 65% [*P* < .001], 67% vs. 52% [*P* = .007], and 64% vs. 41% [*P* < .001], respectively). In addition, more patients receiving the four-drug olanzapine regimen had no chemotherapy-induced nausea compared with placebo during the three time periods (<24 hours after chemotherapy, 25–120 hours, and 120 hours: 74% vs. 45% [*P* = .002], 42% vs. 25% [*P* = .002], and 37% vs. 22% [*P* = .002], respectively). FOND-O, a phase 3 randomized trial, assessed adding olanzapine to fosaprepitant, ondansetron, and dexamethasone in patients receiving HEC and hematopoietic transplantation.[40] The CR was 55% in patients receiving the four-drug olanzapine regimen versus 26% in those receiving the 3-drug regimen in the overall phase (*P* = .03); the CR was 60.8% versus 30%, respectively, in the delayed phase (*P* = .001).

Based on the trial by Navari and colleagues, the NCCN Panel recommends (category 1) the four-drug olanzapine antiemetic regimen for HEC.[177] A four-drug olanzapine regimen is also preferred (category 1) for patients with HEC based on trial data and clinical experience.[177] In addition, clinicians can consider switching patients to the four-drug olanzapine regimen if patients have significant emesis after the first cycle of HEC when receiving other antiemetic regimens such as: 1) NK1 RA-containing regimens; or 2) the three-drug olanzapine regimen (olanzapine/dexamethasone/palonosetron).[37] The panel agreed that any NK1 RA (ie, not just fosaprepitant or oral aprepitant) could be used in the four-drug HEC regimen on day 1 (olanzapine/NK1 RA/5-HT3/dexamethasone), because all of the NK1 RAs are effective if the appropriate dose is used. Thus, aprepitant injectable emulsion, oral

rolapitant, or NEPA may be used in the four-drug olanzapine regimen on day 1; however, none of these agents is continued on days 2 to 4.

Treatment Issues

These NCCN Guidelines include a section on pharmacologic considerations for the different antiemetics describing: 1) the major classes of antiemetics; 2) clinical pearls associated with the different types of agents; and 3) possible drug-drug or drug-disease interactions among the different antiemetics, although these drug interactions are less likely to occur with short-term use of antiemetic agents (see *Pharmacologic Considerations for Antiemetic Prescribing* in the NCCN Guidelines for Antiemesis*)*.

Principles of Emesis Control

The goal of emesis control is to prevent nausea and/or vomiting (see *Principles of Emesis Control for the Cancer Patient* in the NCCN Guidelines for Antiemesis). Prophylactic antiemetic regimens should be chosen based on the drug with the highest emetic risk in the anticancer agent regimen, previous experience with antiemetics, and patient-specific risk factors.[46] Patients need to be protected throughout the entire period of risk, which lasts for at least 3 days for HEC and 2 days for MEC after the last dose of an anticancer agent. In addition to using antiemetic regimens, patients can adjust their eating habits and adopt other lifestyle measures that may alleviate nausea and/or vomiting (see *Eating Hints: Before, During, and After Cancer Treatment* from the National Cancer Institute).[193] 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 nauseated.

Prevention of Acute and Delayed Emesis

To prevent acute emesis, antiemetic therapy should start before the administration of anticancer agents and then should cover the first 24 hours. In the NCCN Guidelines for Antiemesis, the specific prophylactic antiemetic regimens are described for patients receiving highly emetogenic parenteral drugs, moderately emetogenic parenteral drugs, low emetogenic parenteral drugs, and minimally emetogenic parenteral drugs. Prophylactic antiemetic regimens for oral chemotherapeutic agents are also described in the NCCN Guidelines. This section discusses emesis prevention before and after anticancer agent administration rather than primary treatment for ongoing emesis.

Decreasing Acute Emesis

The NCCN Guidelines specify different prophylactic antiemetic regimens for cancer patients receiving anticancer agents of different emetogenic potential (ie, high, moderate, low, minimal). Prophylactic antiemetics should be administered before anticancer agents. The recommendations for prophylactic antiemetic treatment include drug dosages. The guidelines reflect accumulating experience with the different antiemetic agents, demonstrating their effectiveness in a range of doses. As previously mentioned, if patients receive prophylactic antiemetic regimens, emesis will be decreased but not completely prevented. More than 90% of patients receiving HEC without antiemetic prophylaxis will have episodes of vomiting. However, if patients receive prophylactic (preventive) antiemetic regimens before treatment with HEC, then only about 30% of these patients will vomit.[7,9,10]

Highly emetogenic parenteral drugs in the NCCN Guidelines include carboplatin (AUC ≥ 4), carmustine (>250 mg/m^2), cisplatin (any dose), cyclophosphamide (>1500 mg/m^2), dacarbazine (any dose), doxorubicin (≥60 mg/m^2), epirubicin (>90 mg/m^2), ifosfamide (≥2 g/m^2 per dose), mechlorethamine (any dose), streptozocin (any dose), melphalan (≥140mg/m^2), sacituzumab govitecan-hziy, or AC combination regimens at any dose (eg, cyclophosphamide plus either doxorubicin or epirubicin).

With reference to carboplatin, when dosed at an AUC of 4 or more, it is considered highly emetogenic; carboplatin at an AUC of less than 4, however, is considered moderately emetogenic. [194] Data show it is beneficial to add an NK1 RA to the two-drug regimen of 5-HT3 antagonist and dexamethasone for the prevention of CINV associated with carboplatin-based regimens.[143,194-198] All of the commercially available NK1 RAs have an FDA-approved indication for MEC, but older versions of NCCN Guidelines supported the addition of an NK1 RA only for select patients receiving MEC with additional CINV risk factors or for those who had failed previous therapy with a corticosteroid and 5-HT3 antagonist alone.

Several drugs listed as moderately emetogenic in the NCCN Guidelines may be highly emetogenic in certain patients (eg, carboplatin [AUC < 4], carmustine [≤250 mg/m^2], cyclophosphamide [≤1500 mg/m^2], dactinomycin, daunorubicin, doxorubicin [<60 mg/m^2], epirubicin [≤90 mg/m^2], idarubicin, ifosfamide [<2 g/m^2], irinotecan, methotrexate [≥250 mg/m^2], oxaliplatin, trabectedin). AC-based regimens were reclassified in 2011 as highly emetogenic in the ASCO antiemetic guidelines.[88]

Antiemetic Regimens for Parenteral HEC

The NCCN Guidelines recommend three-drug and four-drug antiemetic regimen options (all are category 1) for patients receiving HEC, including 1) NK1 RA, a 5-HT3 RA, and dexamethasone; 2) olanzapine, palonosetron, and dexamethasone; or 3) olanzapine, an NK1 RA, a 5-HT3 RA, and dexamethasone.[175,177] The four-drug olanzapine regimen (olanzapine, NK1 RA, 5-HT3 RA, dexamethasone) is the preferred regimen for patients at high risk for emesis from parenteral anticancer agents (see *Olanzapine* in this Discussion). If needed, lorazepam, an H2 blocker, or a proton pump inhibitor may also be added (alone or in any combination) to all of these regimens.[33,41,120] Note that the regimens and doses are often modified on days 2 to 4 after anticancer agents.

Although it is not recommended as a single agent, lorazepam is a useful adjuvant because it decreases anxiety.[41,154] Lorazepam is also recommended for patients who are at risk for anticipatory nausea and/or vomiting (see *Anticipatory Emesis Prevention/Treatment* in the NCCN Guidelines for Antiemesis). Antacid therapy (eg, proton pump inhibitors, H2 blockers) should be considered if patients have dyspepsia, because patients sometimes have difficulty discriminating heartburn from nausea. If appropriate, lorazepam (0.5–2 mg every 6 hours on days 1–4; either oral, IV, or sublingual) may be used with each of these regimens.

For parenteral HEC, aprepitant is used at an oral dosage of 125 mg on day 1 and then 80 mg on days 2 and 3. When given with aprepitant, dexamethasone is used at a dosage of 12 mg on day 1; the dexamethasone dose can be oral or IV. Note that aprepitant injectable emulsion or IV fosaprepitant may be used instead of oral aprepitant on day 1 only. As previously discussed, a phase 3 randomized trial suggested that palonosetron is preferred over granisetron in combination with dexamethasone for HEC.[68] This trial has been criticized because: 1) the control arm was not adequately dosed; thus, the trial “stacked the deck” in favor of palonosetron; 2) a larger non–FDA-approved dose of palonosetron was used (ie, 0.75 mg IV); and 3) aprepitant was not used in this study. Therefore, the NCCN Guidelines do not recommend palonosetron as the preferred 5-HT3 antagonist for HEC. As previously noted, an alternative antiemetic regimen in the setting of parenteral HEC includes olanzapine (5–10 mg oral days 1–4), palonosetron (0.25 mg IV day 1 only), and dexamethasone (12 mg IV day 1 only).[175]

A Canadian meta-analysis suggested that the use of 5-HT3 antagonists (ie, 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.[199] Palonosetron was not assessed in

these studies. The NCCN Guidelines do not recommend a 5-HT3 antagonist for the prevention of CINV on days 2 to 4 for HEC.

Antiemetic Regimens for Parenteral MEC

Agents that have been newly added under MEC include fam-trastuzumab deruxtecan-nxki, lurbinectedin, and melphalan at a dose less than 140 mg/m^2. Interferon alfa was removed due to its lack of availability and sacituzumab govitecan-hziy was classified as HEC.

The NCCN Guidelines recommend two-drug and three-drug antiemetic regimens for parenteral MEC, including: 1) dexamethasone and a 5-HT3 antagonist with NK1 RAs, such as aprepitant (oral or injectable emulsion), fosaprepitant, netupitant, fosnetupitant, or oral rolapitant; 2) olanzapine, palonosetron, and dexamethasone; or 3) dexamethasone and a 5-HT3 antagonist (palonosetron or subcutaneous granisetron extended-release injection are preferred). If needed, lorazepam, an H2 blocker, or a proton pump inhibitor may be added (alone or in any combination) to these regimens.[7] Netupitant (or fosnetupitant) is only available combined with palonosetron (NEPA) and not as a single agent. As previously mentioned, an NK1 RA or olanzapine should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients with additional risk factors or failure of previous therapy with a corticosteroid and 5-HT3 antagonist alone. These additional risk factors include younger age; female sex; anxiety and/or high pretreatment expectation of nausea and/or vomiting; and history of CINV, motion sickness, morning sickness during pregnancy, and little or no alcohol use.[118] IV fosaprepitant or aprepitant injectable emulsion may be substituted for oral aprepitant on day 1 only. The NCCN Guidelines recommend the use of 5-HT3 antagonists as one of several options to prevent delayed emesis for MEC. Any one of the 5-HT3 antagonists can be used in the first regimen for day 1; however, preferred 5-HT3s include palonosetron or subcutaneous granisetron extended-release injection when an NK1 RA is not included, as previously mentioned.[68,89]

Antiemetic Regimens for Parenteral Low Emetic Risk Anticancer Agents

Newly added agents under low emetic risk include brexucabtagene autoleucel, enfortumab vedotin ejfv (moved from MEC), mitomycin pyelocalyceal solution, and finally tafasitamab-cxix. Similarly, new agents under minimal emetic risk include daratumumab and hyaluronidase fihj, luspatercept-aamt, pertuzumab/trastuzumab and hyaluronidase-zzxf. Peginterferon was removed due to lack of availability.

The single-agent antiemetic regimens for low emetogenic risk parenteral anticancer agents include dexamethasone, prochlorperazine, metoclopramide, or orally administered 5-HT3 antagonists, such as granisetron, ondansetron, or dolasetron (see the NCCN Guidelines for Antiemesis). Lorazepam, an H2 blocker, or a proton pump inhibitor may also be added (alone or in any combination) to all of these agents.[7] When using prochlorperazine or metoclopramide, patients should be monitored for dystonic reactions.[200-202] Diphenhydramine can be used for the treatment of dystonic reactions.[203,204] Benztropine may be used in patients who are allergic to diphenhydramine.[201] Amantadine is also an option for drug-induced dystonic reactions in patients who are intolerant of anticholinergic agents.[205-208]

Antiemetic Regimens for Oral Anticancer Agents

The emetogenic potential of oral anticancer agents is shown in the NCCN Guidelines, which is updated every year with the new agents. Oral antiemetic prophylaxis is recommended for the following oral agents, which are of high or moderate emetic risk: altretamine, avapritinib, azacytidine, binimetinib, bosutinib (>400 mg/day), busulfan (≥4 mg/day), capmatinib, ceritinib, crizotinib, cyclophosphamide (≥100 mg/m^2/day), dabrafenib, enasidenib, encorafenib, estramustine, etoposide, fedratinib,

imatinib (>400 mg/day), lenvatinib (>12 mg/day), lomustine (single day), midostaurin, mitotane, niraparib, olaparib, procarbazine, rucaparib, selinexor, and temozolomide (>75 mg/m^2/day or ≤75 mg/m^2/day with concurrent radiotherapy). Newly added agents under minimal to low emetic risk agents include: bosutinib (≤400 mg/day), decitabine and cedazuridine, imatinib (≤400 mg/day), lenvatinib (≤12 mg/day), pemigatinib, pexidartinib, pralsetinib, ripretinib, selpercatinib, tazemetostat, and tucatinib. PRN management of nausea/vomiting is recommended following the administration of minimal to low emetic risk oral anticancer agents.

For high or moderate emetic risk oral anticancer agents, recommended prophylaxis includes single-agent antiemetic therapy with granisetron, ondansetron, or dolasetron. For low or minimal emetic risk oral anticancer agents, recommended oral agents are given on an as-needed basis only (ie, PRN) and include granisetron, ondansetron, dolasetron, metoclopramide, or prochlorperazine; the NCCN Panel previously deleted haloperidol. Lorazepam, an H2 blocker, or a proton pump inhibitor may also be added (alone or in any combination) if needed to all of these high/moderate or low/minimal emetic risk regimens.[7] Some patients receiving oral anticancer agents of low/minimal emetogenicity may experience nausea and/or vomiting; these patients should be escalated to the next higher level of antiemetic therapy in future cycles of anticancer agents.

Decreasing Delayed Nausea and/or Emesis

Delayed Nausea

Many antiemetic regimens are very useful for decreasing vomiting but are less useful for decreasing delayed nausea that many patients experience when taking emetogenic anticancer agents.[12,21,25,46] Patients rank nausea as more of a problem than vomiting.[12] Data suggest that oral rolapitant and netupitant are effective at decreasing delayed nausea.[137,139,143,144] Palonosetron and subcutaneous granisetron extended-release injection are the preferred 5-HT3 antagonists for preventing delayed nausea associated with MEC.

A phase 3 randomized trial assessed adding olanzapine or placebo to an antiemetic regimen of fosaprepitant or oral aprepitant, a 5-HT3 antagonist, and dexamethasone for patients receiving HEC.[177] More patients receiving the 4-drug regimen with olanzapine had no anticancer agent–induced nausea compared with placebo during the delayed time period (ie, 25–120 hours, 42% vs. 25% [*P* = .002]). Nausea was also reduced with the 4-drug regimen with olanzapine during the acute phase and the overall time period compared with placebo. The 4-drug regimen with olanzapine increased the CR rate (no emesis, no rescue) during the delayed time period compared with placebo (67% vs. 52%; *P* = .007). The 3-drug olanzapine/dexamethasone/palonosetron regimen was associated with a higher rate of nausea control during the delayed period (69% vs. 38%) compared with the 3-drug oral aprepitant regimen (with palonosetron and dexamethasone).[175] However, the proportion of patients without nausea was similar for the acute period (87% in each study arm).[175] Therefore, olanzapine seems especially effective for decreasing nausea.

Delayed Emesis

The best management for delayed emesis is prevention.[209] A survey among oncology nurses found that there is low adherence (only 25%) to antiemetic guidelines for preventing delayed emesis.[210] For HEC, the prophylactic antiemetic treatment on days 2 to 4 depends on which antiemetics were used on day 1. Fosaprepitant, aprepitant injectable emulsion, oral rolapitant, granisetron extended-release injection, granisetron transdermal patch, palonosetron, or NEPA are used on day 1 only, because they are effective for an extended period of time. If oral olanzapine was used on day 1 for HEC, then oral olanzapine is continued on days 2 to 4. If oral aprepitant was used on day 1 for HEC, then oral

aprepitant is continued on days 2 and 3. Dexamethasone may be continued on days 2 to 4 for HEC, depending on the regimen. However, 5-HT3 antagonists are given on day 1 only for HEC. There are several possible HEC antiemetic regimens on days 2 to 4, including: 1) oral aprepitant (if used on day 1) with dexamethasone and with or without olanzapine; or 2) olanzapine only. If needed, each of these regimens may also include lorazepam, an H2 blocker, or a proton pump inhibitor (alone or in any combination).[7]

The antiemetic regimens in the NCCN Guidelines include different options on days 2 to 3 for MEC, including single-agent therapy.[33,41,209] Antiemetic treatment on days 2 to 3 depends on which antiemetic regimens were used on day 1. If oral aprepitant or olanzapine was used on day 1, then oral aprepitant or olanzapine is continued on days 2 and 3. However, granisetron extended-release injection, granisetron transdermal patch, palonosetron, aprepitant injectable emulsion, fosaprepitant, oral rolapitant, or NEPA are not given on days 2 and 3.[70] There are several possible MEC antiemetic regimens for days 2 to 3, including: 1) oral aprepitant (if used on day 1) with or without dexamethasone; 2) dexamethasone only; 3) ondansetron, granisetron, or dolasetron only (if no NK1 RA, granisetron extended-release injection, granisetron transdermal patch, or palonosetron was given on day 1); or 4) olanzapine only.[209] If needed, each of these regimens may also include lorazepam, an H2 blocker, or a proton pump inhibitor (alone or in any combination).[7] The doses are decreased when used on days 2 to 3 for oral aprepitant (80 mg oral) and dexamethasone (8 mg oral or IV) compared with the doses given on day 1. However, the dose of olanzapine is not decreased on days 2 and 3.

Breakthrough Nausea and/or Vomiting Treatment

Breakthrough nausea or emesis presents a difficult situation because refractory ongoing nausea and/or vomiting is often challenging to reverse (see *Principles for Managing Breakthrough Emesis* in the NCCN Guidelines for Antiemesis). Generally, it is much easier to prevent nausea and/or vomiting than to treat it, which is why the NCCN Guidelines recommend prophylactic antiemesis regimens. Routine around-the-clock administration of antiemetics is recommended to prevent emesis, rather than PRN (as needed) dosing. The general principle of breakthrough treatment is to add an additional agent as needed from a different drug class.[33] Some patients may require several agents each with a different mechanism of action. The oral route may not be feasible because of ongoing vomiting; therefore, rectal, topical, subcutaneous, or IV therapy is often required. Multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary. Another option is to consider changing from the current NK1-containing regimen to an olanzapine-containing regimen, or vice versa, prior to the next cycle of anticancer agents. Olanzapine is possibly more effective than NK1-antagonist–containing regimens for preventing nausea.[20,175,176] Switching to a different 5-HT3 RA and/or NK1 RA with a different pharmacokinetic/pharmacodynamic profile is another option, although there is only anecdotal evidence that this may be helpful.

In a randomized phase 3 trial, the effectiveness of olanzapine (10 mg/day oral for 3 days) as treatment for breakthrough emesis was compared with metoclopramide in patients treated with HEC who developed breakthrough emesis or nausea despite antiemetic prophylaxis with palonosetron, dexamethasone, and fosaprepitant (n = 108 evaluable).[211] Patients were observed for emesis and nausea during the 72 hours after treatment with olanzapine or metoclopramide. During this observation period, more patients had no emesis (70% vs. 31%; $P < .01$) and no nausea (68% vs. 23%; $P < .01$) with olanzapine than with metoclopramide.[211] Thus, olanzapine was more effective in controlling breakthrough emesis and nausea compared with metoclopramide in this patient population. The MASCC/ESMO and ASCO Guidelines recommend olanzapine for breakthrough emesis.[34,212] The NCCN Panel recommends olanzapine

(category 1; preferred) for breakthrough emesis if olanzapine was not used on days 1 to 4 as part of a prophylactic regimen. This category 1 recommendation is based on the magnitude of superiority of olanzapine over metoclopramide in the randomized phase 3 trial.[211] Other recommended treatment options for breakthrough emesis may be added to the current antiemetic regimen such as metoclopramide, haloperidol, scopolamine transdermal patch, corticosteroids, cannabinoids, and lorazepam. It should be noted that haloperidol may prolong the QT interval on the ECG.

Dronabinol and nabilone are cannabinoids that are approved by the FDA for refractory nausea and vomiting when patients have not responded to conventional antiemetics. Note that dronabinol oral solution (5 mg/mL) and dronabinol capsules are not bioequivalent. Dronabinol oral solution has greater oral bioavailability than dronabinol capsules (2.1 mg oral solution = 2.5 mg capsules).[213] Recommended starting doses are dronabinol oral solution (4.2 mg/m^2) or dronabinol capsules (5 mg/m^2) both given three to four times daily. Lower doses are recommended in elderly patients.

Before administering the next cycle of anticancer agents, the patient should be reassessed for other possible reasons for breakthrough emesis with the current cycle that are not related to anticancer agents, including brain metastases, electrolyte abnormalities, tumor infiltration of the bowel or other GI abnormality, and other comorbidities (see *Principles for Managing Breakthrough Emesis* and *Principles of Emesis Control for the Cancer Patient* in the NCCN Guidelines for Antiemesis). Adequate hydration or fluid repletion should be ensured, and any possible electrolyte abnormalities should be assessed and corrected. If the antiemetic regimen (both on day 1 and days 2–4) did not protect the patient during the present cycle, the antiemetic regimen should be assessed and alternatives should be considered before the next cycle of anticancer agents (see *Principles for Managing Breakthrough Emesis* in the NCCN Guidelines for Antiemesis). Because patients sometimes have difficulty discriminating heartburn from nausea, addition of antacid therapy should be considered, such as proton pump inhibitors and H2 blockers.

Radiation-Induced Nausea and/or Vomiting

Antiemetic prophylaxis for RT-induced nausea and/or vomiting is based on the site of RT and whether it is combined with anticancer agents.[37,38,214,215] When RT is combined with anticancer agents, prophylaxis is dictated by the emetogenic potential of the anticancer agent regimen.[216] ASCO and MASCC/ESMO guidelines state that total body irradiation is associated with the highest risk for emesis and that upper abdominal RT is associated with moderate risk.[37,38,217] A meta-analysis suggests that 5-HT3 antagonists are the preferred agents for preventing RT-induced vomiting.[218]

Patients undergoing RT to the upper abdomen may receive antiemetic prophylaxis with oral ondansetron or oral granisetron, with or without oral dexamethasone.[10,38] A randomized trial compared oral ondansetron with placebo in patients receiving daily fractionated radiotherapy including the abdomen. In this study, 67% of patients given ondansetron had complete control of emesis compared with 45% of patients who received placebo ($P < .05$).[219] A randomized trial showed that the addition of oral dexamethasone (4 mg daily) to the ondansetron regimen decreases emesis and nausea, although the effect was modest.[220] Patients receiving ondansetron/dexamethasone had better complete control of emesis (23% vs. 12%; $P = .02$) and a lower average nausea score (0.28 vs. 0.39; $P = .03$) compared with those receiving ondansetron alone. Another randomized trial in patients receiving radiotherapy to the upper abdomen found that oral granisetron decreased emesis and nausea compared with placebo.[221]

The NCCN Panel recommends that patients undergoing total body irradiation or upper abdomen RT receive antiemetic prophylaxis with either

oral ondansetron or oral granisetron; either agent can be given with or without oral dexamethasone.[10,38,222] Treatment of breakthrough RT-induced emesis is similar to anticancer agent–induced emesis. Patients who experience breakthrough nausea and/or vomiting may be treated with a different class of agent, or with ondansetron or granisetron if they did not receive primary prophylaxis (see *Breakthrough Treatment for Anticancer Therapy-Induced Nausea/Vomiting* in the NCCN Guidelines for Antiemesis).

Anticipatory Nausea and/or Vomiting

About 20% of patients develop anticipatory nausea and/or vomiting.[223] However, the rate of anticipatory nausea and/or vomiting appears to be decreasing with current use of more effective antiemetic regimens compared with older studies.[10] 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.[33,37,224,225] Behavioral therapy has been used in patients with anticipatory nausea and/or vomiting.[37,226-231] Systematic desensitization may also be helpful.[227] Hypnosis with guided imagery is another behavioral technique that has shown some success in treating this condition.[228]

The antianxiety agent lorazepam has been combined with antiemetics for anticipatory nausea and/or vomiting.[225,232,233] The usual starting dose of lorazepam for anxiety is 0.5 to 2 mg orally, beginning on the night before treatment and then repeated the next day 1 to 2 hours before treatment begins with anticancer agents. The usual starting dose of lorazepam is 0.5 mg orally for treatment of anxiety in patients who are elderly, those with debilitating disease, and those with advanced liver disease (see prescribing information). 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 lorazepam therapy.

The NCCN Panel recommends behavioral therapy options for anticipatory nausea and/or vomiting including yoga, cognitive distraction, relaxation exercises (eg, music therapy), and biofeedback (see the NCCN Guidelines for Antiemesis). The panel also recommends lorazepam and acupuncture. Lorazepam should be used with caution in patients receiving scheduled opioids because of the increased risk of respiratory depression. The NCCN Guidelines also recommend that patients avoid strong smells that may precipitate symptoms.

Multiday Emetogenic Anticancer Agent Regimens

Patients receiving multiday anticancer agents are at risk for both acute and delayed nausea and/or vomiting based on the emetogenic potential of the individual anticancer agents and their sequence.[33,234-238] 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 the anticancer therapy until the last day. The period of risk for delayed emesis following completion of the anticancer agents also depends on the specific regimen and the emetogenic potential of the last anticancer agent administered in the regimen. For multidrug regimens, antiemetic therapy should be selected based on the drug with the highest emetic risk.[37] General principles for managing multiday emetogenic chemotherapy regimens recommended by the NCCN Panel are described in the algorithm (see *Principles of Managing Multiday Emetogenic Chemotherapy Regimens* in the NCCN Guidelines for Antiemesis).

A meta-analysis reported that a three-drug regimen with 5-HT3 RA, oral aprepitant, and dexamethasone was useful for decreasing emesis with multiday cisplatin regimens.[239] For antiemetic prophylaxis of multiday emetogenic anticancer agent regimens (eg, cisplatin-containing regimens), the combination of a 5-HT3 antagonist with dexamethasone was previously recommended in the 2011 MASCC/ESMO guidelines.[10,33] The NCCN Guidelines and 2017 MASCC/ESMO guidelines currently

recommend a three-drug regimen. For single-day systemic therapy regimens, category 1 evidence is available for aprepitant, aprepitant injectable emulsion, fosaprepitant, netupitant, fosnetupitant, or rolapitant administered in combination with a 5-HT3 RA and corticosteroid. The clinical trial data to support these recommendations are described in the following sections.

Dexamethasone

Dexamethasone should be administered once daily in the morning either orally or intravenously for every day of MEC or HEC and continued for 2 to 3 days for anticancer agent regimens that are likely to cause significant delayed emesis. However, dexamethasone should not be added when the anticancer regimen already includes a corticosteroid. The NCCN Panel does not recommend the use of corticosteroids in antiemetic regimens for 3 to 5 days before and 90 days after CAR T-cell therapies, because corticosteroids may decrease the persistence of the CAR T-cell population.[240,241] All of the immune checkpoint inhibitors are of minimal emetic risk. Dexamethasone-sparing strategies or replacing dexamethasone with olanzapine are options for patients who cannot tolerate corticosteroids.[162,163]

5-HT3 Antagonists

For multiday anticancer regimens, a 5-HT3 antagonist should be administered each day before the first dose of MEC or HEC. IV palonosetron, subcutaneous granisetron, or transdermal granisetron may be used before the start of a three-day anticancer regimen instead of multiple daily doses of oral or IV 5-HT3 antagonists.[242,243] It is not known whether repeat dosing with subcutaneous granisetron for multiday regimens would be effective. Repeat dosing of palonosetron (0.25 mg IV) is likely to be safe, based on the dose-ranging phase 2 trial and the three phase 3 trials using palonosetron as a single fixed dose (0.75 mg IV).[67,69,70,244] Compared to the approved dose of palonosetron of 0.25 mg IV, these higher doses were not associated with significantly different adverse events.

The need for repeat dosing with palonosetron, either daily or less frequently, in the setting of multiday anticancer regimens is not yet known. In one study, patients receiving highly emetogenic multiday cisplatin-based therapy for testicular cancer (N = 41) received multiday dosing of palonosetron (0.25 mg IV on days 1, 3, and 5) and dexamethasone, which prevented nausea and emesis in most patients on days 1 to 5 (51%) and on days 6 to 9 (83%); the most common adverse events were mild headache and constipation.[245] A study assessed palonosetron given for 1, 2, or 3 days in combination with dexamethasone for patients receiving multiday high-dose anticancer regimens prior to hematopoietic cell transplantation for multiple myeloma (N = 73); during the 7-day emesis prevention period, about 40% to 45% of patients had no emesis (with no differences observed between palonosetron treatment groups), and no serious adverse events were reported. However, even among the patients who received either 2 or 3 days of palonosetron, only 20% had a CR (ie, emesis free without rescue medication).[117] Another study found that a palonosetron/dexamethasone regimen appeared to be more effective for multiday anticancer therapy 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.[242] A review also cited the value of palonosetron for patients receiving multiday anticancer therapy.[246] Further studies are needed to define whether a need exists for repeat dosing of palonosetron in the setting of multiday anticancer therapy.

NK1 RAs

The potential role of NK1 RAs in the antiemetic management of multiday anticancer therapy has been investigated in several studies.[144,212,247-249] In a randomized phase 3 trial, the efficacy of adding oral aprepitant (vs.

placebo) to an antiemetic regimen with a 5-HT3 antagonist and dexamethasone was evaluated in patients with testicular cancer undergoing two cycles of a five-day cisplatin combination therapy regimen (n = 69 evaluable).[247] Patients were randomized to receive oral aprepitant (125 mg oral day 3, 80 mg oral days 4–7) or placebo, combined with a 5-HT3 antagonist (days 1–5) and dexamethasone (20 mg days 1, 2) during the first cycle, and then crossed over to the opposite antiemetic regimen during the second cycle of anticancer therapy. Thus, patients served as their own controls after receiving either oral aprepitant or placebo for cycle 1. Palonosetron was excluded from the options for 5-HT3 antagonists due to its longer half-life.[247] The primary endpoint of the study was CR (no emetic episodes and no rescue medication) during the overall study period (days 1–8). The CR rate for the overall study period was significantly higher with oral aprepitant compared with placebo (42% vs. 13%; $P < .001$). The CR rates were also higher with oral aprepitant during the acute phase (days 1–5; 47% vs. 15%; $P < .001$) and delayed phase (days 6–8; 63% vs. 35%; $P < .001$).[247] No statistically significant differences were observed between treatment regimens in terms of nausea (based on patient-reported visual analog scale). Importantly, no increase in toxicity with oral aprepitant compared with placebo was reported.[247]

The addition of oral aprepitant to granisetron and dexamethasone was evaluated in patients receiving multiday HEC and MEC (N = 78). In this study, the three-drug antiemetic regimen was given during anticancer therapy; oral aprepitant and dexamethasone were given for an additional 2 days following anticancer therapy.[249] A CR (during the time period from day 1 until 5 days after anticancer therapy) was observed in 58% and 73% of patients who received antiemetic regimens for HEC and MEC, respectively.[249] In a multicenter phase 2 study, an extended 7-day regimen with oral aprepitant (125 mg oral day 1, 80 mg oral days 2–7) combined with a 5-HT3 antagonist (days 1–5) and dexamethasone (8 mg oral days 1–8) was evaluated in patients with germ cell tumors undergoing anticancer therapy cycles with 5-day cisplatin-based regimens (N = 50).[248] During cycle 1 of anticancer therapy, 96% of patients had no emesis on day 1 and 82% had no emesis during days 1 to 7. In addition, 71% had no nausea on day 1 of cycle 1, and 27% had no nausea during days 1 to 7. More than 80% of patients had no emesis on any given day of any given anticancer therapy cycle. No unexpected or serious adverse events were reported.[248]

NK1 antagonists may be used for multiday anticancer therapy likely to be moderately or highly emetogenic and associated with significant risk for delayed nausea and emesis. As per the labeled indication, 125 mg of oral aprepitant should be administered 1 hour prior to anticancer therapy on day 1, along with a 5-HT3 antagonist and dexamethasone. Oral aprepitant 80 mg should be administered daily on days 2 and 3 after the start of anticancer therapy along with dexamethasone.[234] Repeated dosing of oral aprepitant over multiple cycles of cisplatin-based therapy appears to be feasible and well tolerated; importantly, protection from emesis and from significant nausea was maintained during the subsequent cycles of emetogenic anticancer therapy.[234,247] Based on smaller studies, oral aprepitant 80 mg may be safely administered beyond day 3 of initiating anticancer therapy.[128,248] Alternatively, for HEC regimens, aprepitant injectable emulsion 130 mg IV or fosaprepitant 150 mg IV with dexamethasone may be given on day 1, with no need for oral aprepitant on days 2 and 3, with recommended dosing of dexamethasone on days 2 to 4. Data are not available for repeat dosing of fosaprepitant, aprepitant injectable emulsion, NEPA, or oral rolapitant.

Summary

The NCCN Guidelines for Antiemesis provide an overview of the principles for preventing or substantially decreasing anticancer agent–induced or RT-induced nausea and/or vomiting, and provide recommendations for

prophylactic antiemetic regimens based on the emetogenic potential of anticancer agents. Prophylactic antiemetic regimens are recommended for patients who will receive emetogenic anticancer agents, because it is harder to control nausea and/or vomiting once it has started. Although vomiting can often be prevented or substantially decreased by using prophylactic antiemetic regimens, nausea is harder to control. This Discussion text for antiemesis describes the recent updates in greater detail, in particular the clinical trial data and references that support the NCCN Panel's recommendations in the algorithm.

For the 2021 update, the major additions and revisions to the guideline are detailed as follows. The NCCN Panel added other potential causes of nausea and/or vomiting in patients with cancer, including cannabinoid hyperemesis syndrome, rapid opioid withdrawal, and pancreatitis. New anticancer agents were added to the various emetogenic categories and existing regimens were re-classified based on clinical experience. Under parenteral HEC regimens, sacituzumab govitecan-hziy and melphalan (≥140 mg/m^2) were added. Fam-trastuzumab deruxtecan-nxki was classified under parenteral MEC and lurbinectedin and melphalan <140 mg/m^2 were also added under this category. Enfortumab vedotin ejfv was moved under parenteral low emetic risk regimens and brexucabtagene autoleucel, isatuximab-irfc, mitomycin pyelocalyceal solution, and tafasitamab-cxix were also added under this category. Under parenteral minimal emetic risk agents, daratumumab and hyaluronidase-fihj, luspatercept-aamt, pertuzumab/trastuzumab and hyaluronidase-zzxf were added. Interferon alfa and peginterferon were removed due to lack of availability. For patients with severe nausea, the NCCN Panel clarified that olanzapine-containing regimens may be useful. Under oral anticancer agents with moderate to high emetic risk, azacytidine, bosutinib (>400 mg/day), capmatinib, fedratinib, imatinib (>400 mg/day), and lenvatinib (>12 mg/day) were added. Bosutinib (≤400 mg/day), decitabine and cedazuridine, imatinib (≤400 mg/day), lenvatinib (≤12 mg/day), pemigatinib, pexidartinib, pralsetinib, ripretinib, selpercatinib, tazemetostat, and tucatinib were added under oral anticancer agents with minimal to low emetic risk. Finally, phase 3 data was added to support the use of a 5 mg dose of olanzapine for antiemetic prophylaxis prior to HEC and MEC, especially for elderly and oversedated patients. The NCCN Panel recommends administration of olanzapine at bedtime due to the effect of sedation.

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