National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Antiemesis

Version 1.2019 — February 28, 2019

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NCCN Guidelines Panel Disclosures

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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/clinicians.aspx.

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2019 of the NCCN Guidelines for Antiemesis from Version 2.2018 include:

General:
- Changed Intravenous to *Parenteral* in several places.
- Changed Steroid to *Corticosteroid* throughout.

AE-1
- Removed reference from the last bullet.

AE-2
- Added irinotecan (liposomal) to Moderate emetic risk.

AE-3
- Added the following to Low emetic risk:
  - Axicabtagene ciloleucel
  - Copanlisib
  - Gemtuzumab ozogamicin
  - Inotuzumab ozogamicin
  - Tisagenlecleucel
- Added the following to Minimal emetic risk:
  - Atezolizumab
  - Blinatumomab
- Footnotes e, f, and g are new:
  - 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.
  - 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.
  - Corticosteroid antiemetic premedication should be avoided with immune checkpoint inhibitors when administered without cytotoxic chemotherapy. When immune checkpoint inhibitors are administered concurrently with emetogenic chemotherapy, inconclusive data suggest concurrent corticosteroid administration may negatively impact cancer outcomes. Until more evidence is available, the panel recommends employment of a corticosteroid-sparing approach to antiemetic prophylaxis on a case-by-case and regimen basis.

AE-4 and AE-5
- The dose of Olanzapine was changed to *5–10 mg PO once.*
  - Yanai T, Iwasa S, Hashimoto H, et al. A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. Int J Clin Oncol 2018;23:382-388. Nakashima K, Murakami H, Yokoyama K, et al. A phase II study of palonosetron, aprepitant, dexamethasone and olanzapine for the prevention of cisplatin-based chemotherapy-induced nausea and vomiting in patients with thoracic malignancy. Jpn J Clin Oncol 2017;47:840-843.

AE-6
- The following references were removed from the footnotes and are now listed in the Discussion. ~~Yanai T, Iwasa S, Hashimoto H, et al. A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. Int J Clin Oncol 2018;23:382-388. Nakashima K, Murakami H, Yokoyama K, et al. A phase II study of palonosetron, aprepitant, dexamethasone and olanzapine for the prevention of cisplatin-based chemotherapy-induced nausea and vomiting in patients with thoracic malignancy. Jpn J Clin Oncol 2017;47:840-843~~
- Added the following statement to the end of footnote s: *If dexamethsone eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (eg, olanzapine).*
- Footnote t is new: Use of corticosteroid premedications should be avoided with cellular therapies and immune checkpoint inhibitors if at all possible. See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
- Modified footnote u: *Emerging data from smaller studies and clinical practice suggests a 5 mg dose may be considered, especially for elderly or oversedated patients.*
- Modified footnote x: No further *5-HT3* therapy required if palonosetron, granisetron extended-release injection, or granisetron transdermal patch given on day 1.

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Updates in Version 1.2019 of the NCCN Guidelines for Antiemesis from Version 2.2018 include:

AE-8

- Footnote z is new: 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.
- Added the following to Minimal to low emetic risk:
  - Acalabrutinib
  - Binimetinib
  - Dacomitinib
  - Duvelisib
  - Encorafenib
  - Glasdegib
  - Gilteritinib
  - Ivosidenib
  - Larotrectinib
  - Lorlatinib
  - Panobinostat
  - Talazoparib tosylate

AE-10

- Modified: Promethazine 25 mg supp PR every 6 h or 12.5–25 mg PO/~~IV(central line only)~~ every 4–6 h.

AE-B (1 of 3)

- Added the following bullets under corticosteroids:
  - 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 use a corticosteroid-sparing approach to antiemetic prophylaxis.
  - Corticosteroid antiemetic premedication should be avoided with immune checkpoint inhibitors when administered without cytotoxic chemotherapy. When immune checkpoint inhibitors are administered concurrently with emetogenic chemotherapy, inconclusive data suggest concurrent corticosteroid administration may negatively impact cancer outcomes. Until more evidence is available, the panel recommends use of a corticosteroid-sparing approach to antiemetic prophylaxis on a case-by-case and regimen basis.

AE-B (2 of 3)

- Modified the following bullet: Intramuscular olanzapine use with concomitant parenteral benzodiazepine use is contraindicated. Toxicity may occur with this combination regardless of the route of administration. ***For olanzapine-containing regimens, use only PO lorazepam if needed.***

AE-C

- Added new bullet: ***Possibly switch to a different NK1 RA with different pharmacokinetic/pharmacodynamic profile. Although no available head-to-head clinical trial data supports this, anecdotal evidence suggests it may be helpful.***

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 chemotherapy of high and moderate emetic risk lasts for at least 3 days for high and 2 days for moderate after the last dose of chemotherapy. Patients need to be protected throughout the full period of risk.
- Oral and parenteral serotonin receptor antagonists (5-HT3 RA) 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.
- 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
- For use of antiemetics for nausea/vomiting that are not related to radiation and/or chemotherapy, see NCCN Guidelines for Palliative Care.
- For multi-drug regimens, select antiemetic therapy based on the drug with the highest emetic risk. See Emetogenic Potential of Parenteral Anticancer Agents (AE-2, and AE-3), and see Emetogenic Potential of Oral Anticancer Agents (AE-8).
- Consider using an H2 blocker or proton pump inhibitor to prevent dyspepsia, which can mimic nausea.
- Lifestyle measures may help to alleviate nausea/vomiting, such as eating small frequent meals, choosing healthful foods, controlling the amount of food consumed, and eating food at room temperature. A dietary consult may also be useful. See NCI's "Eating Hints: Before, During, and After Cancer Treatment." (http://www.cancer.gov/cancertopics/coping/eatinghints/page2#4)
- While chemotherapy 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 chemotherapy 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]	• 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 • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis)[b,c]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC <4[d] • Carmustine[d] ≤250 mg/m² • Clofarabine • Cyclophosphamide ≤1500 mg/m²[d] • Cytarabine >200 mg/m²	• Dactinomycin[d] • Daunorubicin[d] • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Dinutuximab • Doxorubicin[d] <60 mg/m² • Epirubicin[d] ≤90 mg/m² • Idarubicin • Ifosfamide[d] <2 g/m² per dose • Interferon alfa ≥10 million IU/m² • Irinotecan[d]	• Irinotecan (liposomal) • Melphalan • Methotrexate[d] ≥250 mg/m² • Oxaliplatin[d] • Temozolomide • Trabectedin[d]

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:S43-47.

[a] Potential drug interactions between antineoplastic agents/antiemetic therapies 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] These agents may be highly emetogenic in certain patients.

Low Emetic Risk (See AE-3)
Minimal Emetic Risk (See AE-3)
Oral Chemotherapy (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,e]	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/m² • Amifostine ≤300 mg/m² • Axicabtagene ciloleucel[f] • Belinostat • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Copanlisib • Cytarabine (low dose) 100–200 mg/m²	• Docetaxel • Doxorubicin (liposomal) • Eribulin • Etoposide • 5-Fluorouracil (5-FU) • Floxuridine • Gemcitabine • Gemtuzumab ozogamicin • Inotuzumab ozogamicin • Interferon alfa >5 - <10 million international units/m²	• Ixabepilone • Methotrexate >50 mg/m² - <250 mg/m² • Mitomycin • Mitoxantrone • Necitumumab • Olaratumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed	• Pentostatin • Pralatrexate • Romidepsin • Talimogene laherparepvec • Thiotepa • Tisagenlecleucel[f] • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of emesis)[b,e]	• Alemtuzumab • Atezolizumab[g] • Avelumab[g] • Asparaginase • Bevacizumab • Bleomycin • Blinatumomab • Bortezomib • Cetuximab • Cladribine • Cytarabine <100 mg/m²	• Daratumumab • Decitabine • Denileukin diftitox • Dexrazoxane • Durvalumab[g] • Elotuzumab • Fludarabine • Interferon alpha ≤5 million IU/m² • Ipilimumab[g] • Methotrexate ≤50 mg/m²	• Nelarabine • Nivolumab[g] • Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Pembrolizumab[g] • Pertuzumab • Ramucirumab • Rituximab	• Rituximab and hyaluronidase human injection for SQ use • Siltuximab • Temsirolimus • Trastuzumab • 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:S43-47.

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

[b] Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.

[e] 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.

[f] 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.

[g] Corticosteroid antiemetic premedication should be avoided with immune checkpoint inhibitors when administered without cytotoxic chemotherapy. When immune checkpoint inhibitors are administered concurrently with emetogenic chemotherapy, inconclusive data suggest concurrent corticosteroid administration may negatively impact cancer outcomes. Until more evidence is available, the panel recommends employment of a corticosteroid-sparing approach to antiemetic prophylaxis on a case-by-case and regimen basis.

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

DAY 1: Select option A, B, or C (order does not imply preference) All are category 1, start before chemotherapy:[j]	DAYS 2, 3, 4:
A • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[m] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[n] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[n] ▸ Rolapitant 180 mg PO once[o] • 5-HT3 RA (choose one):[p,q] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[r] 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 chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[s,t]	**A** • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[s,t] PO/IV daily on days 2, 3, 4
B • Olanzapine 5–10 mg PO once[u] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[s,t]	**B** • Olanzapine 5–10 mg PO daily on days 2, 3, 4[u]
C • Olanzapine 5–10 mg PO once[u,v,w] • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[m] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[n] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[n] ▸ Rolapitant 180 mg PO once[o] • 5-HT3 RA (choose one):[p,q] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[r] 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 chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[s,t]	**C** • Olanzapine 5–10 mg PO daily on days 2, 3, 4[u] • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[s,t] PO/IV daily on days 2, 3, 4

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Footnotes

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

DAY 1: Select option D, E, or F (order does not imply preference). All are category 1, start before chemotherapy:[j]	DAYS 2, 3:
D • 5-HT3 RA (choose one): ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once[r] (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 chemotherapy. ▸ 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[s,t]	**D** • Dexamethasone 8 mg[s,t] PO/IV daily on days 2, 3 OR • 5-HT3 RA monotherapy[x]: ▸ 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
E • Olanzapine 5–10 mg PO once[u] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[s,t]	**E** • Olanzapine 5–10 mg PO daily on days 2, 3[u]
F Note: An NK1 RA should be added (to dexamethasone and a 5-HT3 RA regimen) for select patients with additional risk factors or previous treatment failure with a corticosteroid + 5-HT3 RA alone. • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[m] ▸ Fosaprepitant 150 mg IV once[n] ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[n] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[n] ▸ Rolapitant 180 mg PO once[o] • 5-HT3 RA (choose one):[p,q] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[r] 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 chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[s,t]	**F** • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • ± Dexamethasone 8 mg[s,t] PO/IV daily on days 2, 3

Footnotes

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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 Regimens (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. For olanzapine-containing regimens, only use PO lorazepam if needed. See Principles of Emesis Control for the Cancer Patient (AE-1).
[l] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[m] Aprepitant injectable emulsion is a unique formulation of aprepitant and is NOT interchangeable with the intravenous formulation of fosaprepitant.
[n] Available as a fixed combination product only.
[o] Rolapitant has an extended half-life and should not be administered at less than 2-week intervals.
[p] If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product used, no further 5-HT3 RA is required.
[q] When used in combination with an NK1 RA, there is no preferred 5-HT3 RA. See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[r] 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.
[s] 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.
[t] Use of corticosteroid premedications should be avoided with cellular therapies and immune checkpoint inhibitors if at all possible. See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[u] Emerging data from smaller studies and clinical practice suggest a 5 mg dose may be considered, especially for elderly or oversedated patients. See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[v] Consider escalating to this option (C) when emesis occurred during a previous cycle of chemotherapy using an olanzapine regimen (B, E) or an NK1 RA-containing regimen (A, D, or F). See Principles for Managing Breakthrough Emesis (AE-C).
[w] Combination of olanzapine, aprepitant or fosaprepitant, any 5-HT3 RA, and dexamethasone, was studied in patients receiving cisplatin or AC. See Discussion.
[x] No further 5-HT3 therapy required if palonosetron, granisetron extended-release injection, or granisetron transdermal patch given on day 1.

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

Low →

Start before chemotherapy (order does not imply preference)[i,j,y]
Repeat daily for multiday doses of chemotherapy

- **Dexamethasone 8–12 mg PO/IV once[l,y]**
  or
- **Metoclopramide 10–20 mg PO/IV once[l,y]**
  or
- **Prochlorperazine 10 mg PO/IV once[l,y]**
  or
- **5-HT3 RA[l,y] (select one):**
  - ◊ **Dolasetron 100 mg PO once**
  - ◊ **Granisetron 1–2 mg (total dose) PO once**
  - ◊ **Ondansetron 8–16 mg PO once**

Minimal → **No routine prophylaxis →**

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

[h] See Emetogenic Potential of Parenteral Anticancer Agents (AE-3).
[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 Regimens (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).

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EMETOGENIC POTENTIAL OF ORAL ANTICANCER AGENTS[a]

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

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:S43-47.

[a] Potential drug interactions between antineoplastic agents/antiemetic therapies 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] Temozolomide ≤75 mg/m²/d should be considered moderately emetogenic with concurrent radiotherapy.

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.

ORAL CHEMOTHERAPY - EMESIS PREVENTION[i,j,bb,cc]

High to moderate emetic risk →

Start before chemotherapy 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 Chemotherapy-Induced Nausea/Vomiting (AE-10)**

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

Start before chemotherapy 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/d)[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 Chemotherapy-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 Regimens (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).
[bb] See Emetogenic Potential of Oral Anticancer Agents (AE-8).
[cc] 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 CHEMOTHERAPY-INDUCED NAUSEA/VOMITING[j,dd]

Any nausea/ vomiting

The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen.
(order does not imply preference)

- **Atypical antipsychotic:[l]**
  - **Olanzapine 5–10 mg PO daily (category 1)[ee,ff]**
- **Benzodiazepine:[l]**
  - **Lorazepam 0.5–2 mg PO/SL/IV every 6 h[ff]**
- **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 16–24 mg PO daily 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 Regimens (AE-A).
[l] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[dd] See Principles for Managing Breakthrough Emesis (AE-C).

[ee] When not used as part of the acute and delayed emesis prevention regimen.
[ff] For olanzapine-containing regimens, only use PO lorazepam. See Principles of Emesis Control for the Cancer Patient (AE-1).
[gg] Dronabinol oral solution has greater oral bioavailability than dronabinol capsules; 2.1 mg oral solution = 2.5 mg capsules.

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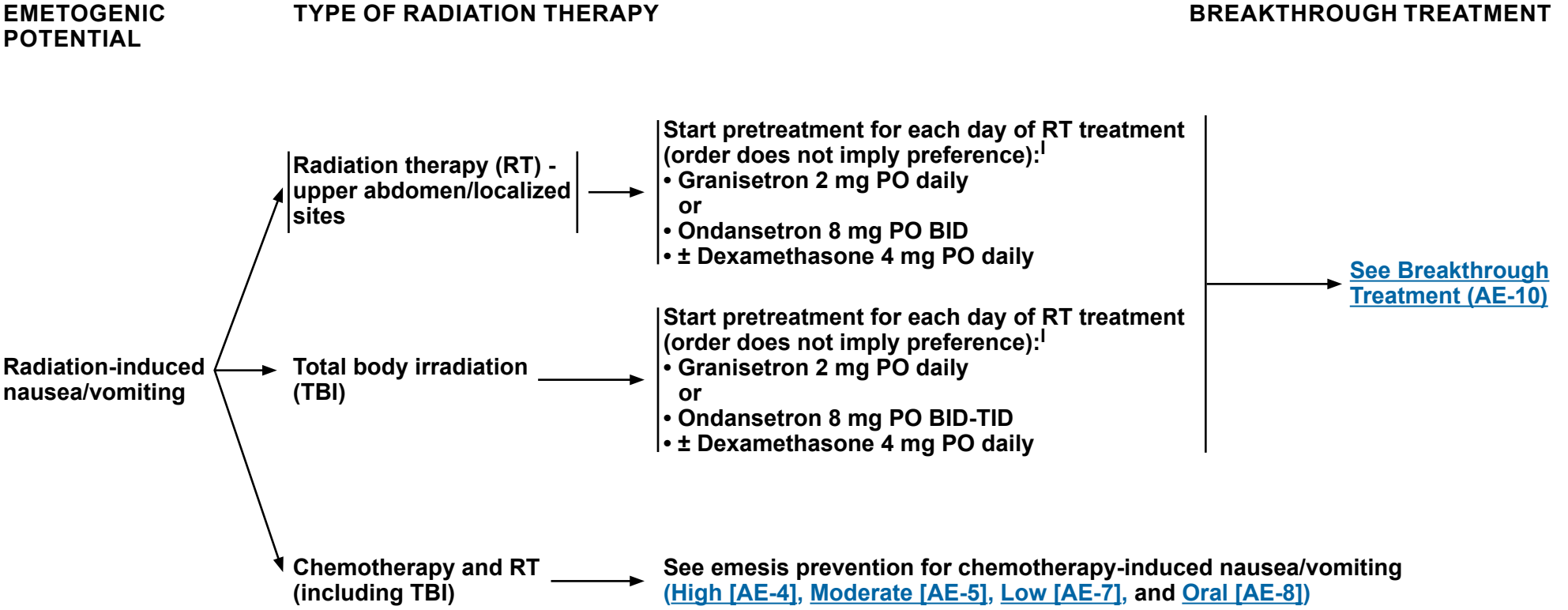
RADIATION-INDUCED EMESIS PREVENTION/TREATMENT



[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 chemotherapy begins**

→ **See Emesis Prevention and Breakthrough Treatment for Chemotherapy-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 versus 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 (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 chemotherapy-induced nausea and vomiting (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.[1,2,3,4] 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:
- **Depending on the route of administration and dose, 5-HT3 RA may increase the risk of developing prolongation of the QT interval of the electrocardiogram (ECG).[a] The palonosetron, granisetron extended-release injection, and granisetron transdermal patch drug package inserts do not contain this warning.**
- **The FDA recommends a maximum of 16 mg for a single dose of intravenous ondansetron.**
- **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.**
- **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: 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:
- **The use of corticosteroids as an antiemetic is not recommended with immunotherapies and cellular therapies.**
- **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. Antiemetic regimens used during lymphodepleting chemotherapy regimens should also use a corticosteroid-sparing approach to antiemetic prophylaxis.**
- **Corticosteroid antiemetic premedication should be avoided with immune checkpoint inhibitors when administered without cytotoxic chemotherapy. When immune checkpoint inhibitors are administered concurrently with emetogenic chemotherapy, inconclusive data suggest concurrent corticosteroid administration may negatively impact cancer outcomes. Until more evidence is available, the panel recommends use of a corticosteroid-sparing approach to antiemetic prophylaxis on a case-by-case and regimen basis.**

[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

Atypical antipsychotic

- **Olanzapine:**
  - **Use caution when prescribing olanzapine with metoclopramide or haloperidol, as excessive dopamine blockade can increase the risk of extrapyramidal symptoms (EPS). Use of intermittent phenothiazine antiemetics (prochlorperazine or promethazine) for breakthrough CINV was safe in randomized clinical trials investigating the use of olanzapine but should be used with caution.**
  - **Olanzapine may increase the risk of developing prolongation of the QT interval of the ECG, when used in combination with other QT-prolonging agents.[a]**
  - **Intramuscular olanzapine use with concomitant parenteral benzodiazepine use is contraindicated. Toxicity may occur with this combination regardless of the route of administration. For olanzapine-containing regimens, use only PO lorazepam if needed.**
  - **Monitor for dystonic reactions[b]**
  - **CNS depression; use olanzapine with caution 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. Data suggest that sedation is most notable on day 2 and improves over time.**

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.**
- **Intramuscular olanzapine use with concomitant parenteral benzodiazepine use is contraindicated. Toxicity may occur with this combination regardless of the route of administration. For olanzapine-containing regimens, use only PO lorazepam if needed.**
- **Use caution in patients with scheduled opioids.**

Phenothiazines:

- **CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail).**
- **When administered parenterally, promethazine may cause severe tissue injury.**
- **The concomitant prescribing of any combination of prochlorperazine, promethazine, metoclopramide, or haloperidol should be used with caution, as excessive dopamine blockade can increase the risk of EPS.**
- **Monitor for dystonic reactions.[b]**
- **Clinical pearl: Promethazine has more histamine blockade than prochlorperazine and is therefore more sedating.**

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

Continued

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PHARMACOLOGIC CONSIDERATIONS FOR ANTIEMETIC PRESCRIBING

Other

- **Metoclopramide:**
  - May cause tardive dyskinesia; the risk increases with increasing cumulative dose and duration of treatment.
  - Avoid concomitant prescribing with olanzapine, the phenothiazines, or haloperidol, as excessive dopamine blockade can increase the risk of EPS.
  - Use caution in patients at risk for falls (eg, elderly, debilitated, frail) given the increased risk for EPS.
  - Monitor for QT prolongation[a]
  - Monitor for dystonic reactions[b]
  - Clinical pearl: Metoclopramide increases gut motility and may cause diarrhea and can be utilized to help manage gastroparesis.

- **Haloperidol:**
  - CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail).
  - Avoid concomitant prescribing with olanzapine, the phenothiazines, or metoclopramide, as excessive dopamine blockade can increase the risk of EPS.
  - Monitor for QT prolongation.[a] Higher-than-recommended doses (regardless of route) and intravenous administration of haloperidol appear to be associated with a higher risk of QT prolongation.
  - 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), at risk for dependence or orthostatic hypotension, or with underlying psychiatric disorders.
  - Clinical pearl: May stimulate appetite. To minimize paranoia/hallucinations, consider starting with lower doses (especially in elderly or marijuana-naïve patients) and titrate upwards to effect as clinically appropriate.

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

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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 therapy 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 chemotherapy the patient should be reassessed, with attention given to various possible non-chemotherapy–related reasons for breakthrough emesis with the current cycle:
  - Brain metastases
  - Electrolyte abnormalities
  - Tumor infiltration of the bowel or other gastrointestinal abnormality
  - Other comorbidities
- Prior to the next cycle of chemotherapy, reassess both the day 1 and post-chemotherapy antiemetic regimen, which did not protect the patient during the present cycle, and consider alternatives: (Suggestions are not in order of preference)
  - Add 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 Chemotherapy - 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 chemotherapy 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 chemotherapy is non-curative, consider other appropriate regimens, if any, that might be less emetogenic.
  - It may be beneficial to add an anxiolytic agent in combination with the antiemetic agents.
- Consider antacid therapy if patient has dyspepsia (H2 blocker or proton pump inhibitor).

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.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/27/18

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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Overview

Anticancer therapy-induced, or radiation therapy (RT)-induced, vomiting (emesis) and nausea can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy or RT.[1] In addition, nausea and 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.[2-5] Anticancer therapy includes chemotherapy, targeted therapy, and immunotherapy, which will all be referred to as *chemotherapy* throughout this Discussion text.

The incidence and severity of nausea and/or vomiting in patients receiving chemotherapy, RT, or chemoradiation 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, age, sex, prior chemotherapy, history of alcohol use).[6,7] 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.[6,8,9] Although vomiting can often be prevented or substantially decreased by using prophylactic antiemetic regimens, nausea is harder to control.[10-12]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis are intended to provide an overview of the treatment principles for preventing anticancer therapy-induced or RT-induced vomiting and nausea, and recommendations for antiemetic prophylaxis according to the emetogenic potential of anticancer agents. This Discussion text for antiemesis describes the algorithms in greater detail, for example, by including the clinical trial data and references that support the NCCN Panel's recommendations. The NCCN Guidelines® for Antiemesis are updated at least once a year by a multidisciplinary panel of experts. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2018, which are described in greater detail in this Discussion; recent references have been added (see the NCCN Guidelines for Antiemesis). Major updates for 2018 are summarized in this Discussion (see *Summary* in this Discussion). Additional supplementary material in the NCCN Guidelines for Antiemesis includes *Principles of Managing Multiday Emetogenic Chemotherapy Regimens, Pharmacologic Considerations for Antiemetic Prescribing,* and *Principles for Managing Breakthrough Emesis*. The NCCN Guidelines have also been modified for resource-restricted settings.[13] By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

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. The PubMed database was chosen, because it is the most widely used resource for medical literature and indexes only 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.[6,14,15] 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 chemotherapy-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.[14,17,18] 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.[14]

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

Nausea

With use of effective antiemetic regimens, patients receiving emetogenic chemotherapy often experience more nausea than vomiting.[10,21-25] Vomiting and nausea are related; however, they may occur via different mechanisms.[26,27] In general, younger patients are more likely to have nausea than older patients. Younger women receiving chemotherapy for breast cancer are more prone to nausea than other populations.[12] 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).[25]

Types of Nausea and/or Vomiting

Chemotherapy-Induced Nausea and/or Vomiting

Nausea and/or vomiting induced by anticancer agents is often 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 drug administration and commonly resolves within the first 24 hours. The intensity of acute-onset emesis generally peaks after 5 to 6 hours. The occurrence of acute emesis is increased in younger (<50 years) women with low ethanol use, history of motion sickness, and history of morning sickness. Other factors that influence acute emesis include history of nausea and vomiting, environment in which chemotherapy is administered, dosage of the emetogenic agent, and efficacy of the antiemetic regimen.[28]

Delayed-onset CINV develops in patients more than 24 hours after chemotherapy administration.[29,30] It occurs commonly with the administration of cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin. For cisplatin, emesis reaches its maximal intensity 48 to 72 hours after administration and can last 6 to 7 days.

Anticipatory CINV occurs before patients receive their next chemotherapy treatment. Because it is primarily considered a conditioned response, anticipatory emesis typically occurs after a negative past experience with chemotherapy. The incidence of anticipatory CINV ranges from 18% to 57%, and nausea is more common than vomiting.[31,32] Younger patients may be more susceptible to anticipatory nausea and vomiting, because they generally receive more aggressive chemotherapy and, overall, have poorer emesis control than older patients.[33]

Breakthrough CINV refers to nausea and/or vomiting that occurs despite prophylactic treatment and/or requires rescue with antiemetic agents.[34] *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.[35]

Radiation-Induced Nausea and/or Vomiting

Patients receiving total body RT (>90% emesis) have the greatest likelihood of developing nausea and/or vomiting; those receiving upper abdominal RT are at moderate risk of emesis (30%–90%).[34,36-38] 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.[34,39]

Emetogenicity of Chemotherapy

The frequency of chemotherapy-induced emesis depends primarily on the emetogenic potential of the specific chemotherapeutic agents used. Several classifications have been developed to define the emetogenicity of chemotherapy; however, none has been universally accepted.[16,40-43]

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.[8] The classification was updated by Grunberg et al and more recently by Jordan et al; it divides chemotherapeutic agents into 4 levels according to the percentage of patients who experience acute emesis when they do not receive antiemetic prophylaxis.[11,44,45] This classification is used in these NCCN Guidelines and is updated each year by the NCCN Panel with recently introduced drugs. For example, the NCCN Panel classified the emetogenic potential of 11 new drugs for the 2018 update—such as enasidenib, midostaurin, niraparib, and dual-drug liposomal encapsulation of cytarabine/daunorubicin—which are classified as moderate emetic risk. See *Emetogenic Potential of Intravenous [and Oral] Anticancer Agents* in the algorithm. The percentage of nausea and vomiting for each anticancer therapy agent is based on clinical trial data (see the package inserts).[46-50]

The NCCN Guidelines currently outline treatment using 4 categories of emetogenic potential for intravenous agents, which correspond to the 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 chemotherapy drugs 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 a single algorithm. The NCCN Panel has also categorized the emetogenic potential of oral anticancer agents.[11]

For the 2018 update, panel members added a caveat that clinicians should avoid overuse of antiemetic agents, especially in settings where the anticancer therapy is of minimal or low emetic risk, to avoid exposing patients to adverse effects from antiemetic agents and to prevent unnecessary expense (see *Principles of Emesis Control for the Cancer Patient* in the algorithm).[36,51,52] If clinicians use the emetogenic classification of anticancer agents in the algorithm, this will decrease unnecessary prescribing of antiemetic agents.

Types of Antiemetic Therapies

In general, to provide maximal protection against chemotherapy-induced emesis, antiemetic therapy should be initiated before chemotherapy. The antiemetic therapy should also be continued for the same length of time as the duration of the emetic activity of the chemotherapeutic agent being used. However, daily use of certain antiemetics, such as dexamethasone, may not be recommended for some therapeutic agents that are taken long term on a regular basis (eg, the oral anticancer agents of moderate/high emetic risk that are listed in the algorithm). Antiemetic agents can be administered by the oral, sublingual, rectal, intravenous, intramuscular, subcutaneous, or transdermal route. Oral and intravenous 5-HT3 antagonists have equivalent efficacy when used at the appropriate doses.[9,39] However, subcutaneous granisetron extended-release injection and intravenous granisetron are not interchangeable; the subcutaneous formulation should not be given intravenously and vice versa. Aprepitant injectable emulsion and intravenous 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 routes are recommended. Although studies may show drugs to be equally effective on a population basis, individual patients may respond differently. Therefore, some drug options may be based on a patient's individual experience.

Serotonin (5-HT3) 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 cancer chemotherapy.[53-69] 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.[70-87] A meta-analysis found no difference in efficacy between the first-generation 5-HT3 antagonists.[88] 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.[89]

A meta-analysis of randomized controlled trials 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 moderately emetogenic chemotherapy (MEC);

most patients receiving MEC actually received anthracycline and cyclophosphamide (AC regimens).[90] However, AC regimens are now classified as HEC, although they were previously classified as MEC.[36,91] Based on this meta-analysis and clinical practice, some NCCN Panel Members feel that palonosetron should be a preferred 5-HT3 antagonist for both HEC and MEC. However, the majority of the NCCN Panel previously decided that palonosetron is only preferred for MEC if the regimen does not contain an NK1 receptor antagonist (RA) (see *Palonosetron* in this Discussion).[71] 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 algorithm).[92]

Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis but appear to be less effective for delayed emesis. A meta-analysis of randomized controlled trials found that adding a 5-HT3 antagonist to dexamethasone did not improve the antiemetic effect of dexamethasone for preventing delayed emesis.[93] Another study found that 5-HT3 antagonists (except palonosetron, which was not studied) were not more effective than prochlorperazine in preventing delayed emesis.[25] A single dose of intravenous palonosetron appears to be effective for preventing both delayed and acute emesis.

The NCCN Guidelines recommend intravenous 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 algorithm).[71] Several studies[94-97] have evaluated the efficacy of a 3-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 intravenous palonosetron in a 2-drug regimen with dexamethasone for patients receiving HEC or MEC.[92] Two doses of subcutaneous granisetron extended-release injection were assessed: 5 and 10 mg. The data show that subcutaneous granisetron extended-release injection is not inferior to intravenous 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 dose were 77.7% (−12.1, 6.1) and 81.3% (−8.2, 9.3), respectively, compared with 80.7% for those receiving palonosetron 0.25 mg intravenous dose. 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 chemotherapy regimens. Based on this trial and the FDA approval, the NCCN Panel now recommends intravenous palonosetron or subcutaneous granisetron extended-release injection as preferred 5-HT3 antagonists for MEC when used with dexamethasone in antiemetic regimens that do not contain an NK1 RA. The panel does not recommend a 2-drug antiemetic regimen containing dexamethasone with either palonosetron or subcutaneous granisetron extended-release injection for HEC; the panel recommends a 3-drug regimen, which should include an NK1 RA or olanzapine, or a 4-drug regimen (which includes olanzapine and an NK1 RA).

A phase 3 trial (MAGIC) assessed a single dose of subcutaneous granisetron extended-release injection compared with a single dose of

intravenous ondansetron in a 3-drug regimen with dexamethasone and fosaprepitant for patients receiving HEC.[98] 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) when compared with the ondansetron regimen (P = .014). This is the first published trial that compared a single dose of 2 different 5-HT3 antagonists when used in combination with dexamethasone and an NK1 RA. As a result, granisetron extended-release injection is the first FDA-approved 5-HT3 antagonist indicated for the prevention of delayed CINV associated with AC chemotherapy. 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.[92,98] 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 intravenous 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 intravenous 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] Oral dolasetron is still recommended. A single intravenous dose of 32 mg of ondansetron is no longer recommended based on FDA review of clinical data suggesting prolongation of the QT interval at this dose.[99,101,102] At this time, the FDA recommends a maximum single intravenous 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.[102] Oral administration of ondansetron poses less of a risk of cardiac arrhythmias than intravenous administration.[99]

In addition, the FDA has approved the use of a granisetron transdermal system for CINV. The patch containing 3.1 mg of granisetron/24 hours is applied approximately 24 to 48 hours before the first dose of chemotherapy; the maximum duration of the patch is 7 days. A phase 3 randomized trial compared the patch to oral granisetron in patients receiving either HEC or MEC. The patch proved non-inferior to repeat dosing of the oral antiemetic granisetron over 3 to 5 days.[103,104] A phase 4 trial assessed a transdermal granisetron regimen versus a palonosetron regimen for patients receiving MEC; transdermal granisetron was not inferior to palonosetron in preventing nausea and vomiting in the acute stage.[105]

The addition of dexamethasone improves the efficacy of the antiemetic regimen 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.[106]

Cardiac Side Effects

Ondansetron, granisetron, and dolasetron have been associated with an increased risk for developing abnormal electrical activity of the heart (detectable on ECG, including prolongation of electrocardiographic intervals such as PR or QT intervals).[99,100,107-114] However, this warning is not in the package inserts for palonosetron, granisetron extended-release

injection, and the granisetron transdermal patch. 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.[100,111,115] Routine ECG monitoring during treatment with regimens that include 5-HT3 antagonists may be useful for these patients who may have concomitant risk factors for QT prolongation. As previously mentioned, intravenous 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.[55] Data suggest that palonosetron is associated with prolonged inhibition of the 5-HT3 receptor and thus differs from ondansetron, granisetron, and dolasetron.[116,117] 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 moderate and high emetic risk chemotherapy regimens, particularly for delayed emesis.[70-73] 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 intravenous) was found to be superior to a single dose of ondansetron (32 mg intravenous) 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.[73] The safety and side-effect profiles of palonosetron were indistinguishable from the control 5-HT3 antagonists (ondansetron and dolasetron). Note that the FDA now recommends a maximum of 16 mg for a single dose of intravenous ondansetron.[99]

In a phase 3 randomized trial that compared palonosetron with ondansetron in patients receiving HEC (N = 667), the majority (67%) had received dexamethasone on day 1 of antiemetic therapy; NK1 RAs were not used in this trial.[70] Among this subgroup of patients who received concomitant dexamethasone (n = 447), palonosetron (0.25 mg intravenous) was similar to ondansetron (32 mg intravenous) 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 intravenous) with a single dose of granisetron (40 mcg/kg intravenous), 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%), with superior activity in preventing delayed emesis (CR rate, 57% vs. 44.5%; $P < .0001$).[71] However, 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 this study 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. As previously mentioned, the NCCN Panel now recommends either palonosetron or subcutaneous granisetron extended-release

injection as preferred 5-HT3 antagonists for MEC when used with dexamethasone in 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 algorithm).[92] Palonosetron (0.25 mg intravenous) 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.

Intravenous palonosetron is superior to other first-generation 5-HT3 antagonists in preventing delayed nausea.[23,70-73] Repeat dosing of palonosetron on days 2 or 3 after chemotherapy is likely to be safe. However, in the setting of multiday chemotherapy, limited data are available to recommend multiday dosing with palonosetron (see *Principles of Managing Multiday Emetogenic Chemotherapy Regimens* in the algorithm).[118]

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 aprepitant, fosaprepitant, rolapitant, or netupitant. It is important to note that netupitant is only available combined with palonosetron (NEPA); netupitant is not available as a single agent. A 2-drug regimen of one of the 5-HT3 options plus dexamethasone, but without an NK1 RA or olanzapine, is recommended for MEC but not HEC. For the 2018 update, the panel clarified the use of NK1 RAs in patients receiving MEC as follows. An NK1 RA should be added to a 5-HT3/dexamethasone regimen (2-drug antiemetic regimen) for patients receiving MEC anticancer therapy who have additional risk factors or previous treatment failure with the 2-drug regimen. Patients receiving anticancer therapy that is associated with a higher risk for emesis (eg, irinotecan, oxaliplatin) are at greater risk for emesis and may need the addition of an NK1 RA.

Aprepitant

Aprepitant selectively blocks the binding of substance P at the NK1 receptor in the central nervous system. Thus, aprepitant provides a different and complementary mechanism of action to other commercially available antiemetics. Aprepitant has been shown to augment the antiemetic activity of the 5-HT3 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 new formulation of aprepitant that was recently approved by the FDA for HEC and MEC when used in combination with other antiemetic regimens.[122]

Aprepitant Injectable Emulsion

Intravenous fosaprepitant contains polysorbate 80 and other surfactants that may cause infusion-site reactions including pain, erythema, and swelling.[122,123] Aprepitant injectable emulsion is a new formulation of aprepitant that does not contain polysorbate 80 and other surfactants. A recent phase 1 bioequivalence sturdy (n = 100) compared intravenous fosaprepitant with aprepitant injectable emulsion.[122] The data showed that patients receiving aprepitant injectable emulsion had fewer treatment-emergent adverse effects when compared with those receiving intravenous fosaprepitant (1% vs. 20%), which all resolved. Three patients receiving intravenous fosaprepitant had dyspnea. None of the patients had severe treatment-emergent adverse effects, serious adverse events, or died. Aprepitant injectable emulsion was bioequivalent to intravenous fosaprepitant (bioequivalence bounds, 80%–125%). For the 2018 update, the NCCN Panel now recommends that aprepitant injectable emulsion be

considered as an NK1 RA option based on the phase 1 bioequivalence sturdy and the recent FDA approval.[122] As previously mentioned, aprepitant injectable emulsion is not interchangeable with intravenous fosaprepitant.

Oral Aprepitant

A randomized phase 3 trial compared ondansetron 32 mg intravenous and oral dexamethasone with or without the addition of oral aprepitant in patients receiving emetogenic chemotherapy 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 meta-analysis (of 7 randomized controlled trials) 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] A larger meta-analysis (of 17 randomized controlled trials) 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 time frame from 0 to 120 hours after starting chemotherapy.[125] The significant increase in CR rate associated with oral aprepitant was observed for both the acute and delayed periods. Based on data from 3 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.[125] 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 chemotherapy (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.[126] 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 3-drug combination of palonosetron (0.25 mg intravenous day 1), oral aprepitant (125 mg day 1; 80 mg days 2, 3), and dexamethasone (20 mg intravenous 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).[96] 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%).[96] A phase 2 study evaluated a higher dose of palonosetron (0.75 mg intravenous 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 during the overall study period (0–120 hours) was 81%.[97] 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.[97]

A phase 3 trial added oral aprepitant to a control antiemetic regimen of oral granisetron and oral dexamethasone in patients receiving MEC. The data showed that the addition of oral aprepitant improved control of nausea, vomiting, and quality of life when compared with granisetron and dexamethasone.[127] A phase 2 study (N = 58) found that combining palonosetron (0.25 mg intravenous 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 time frame, from 0 to 120 hours after initiation of emetogenic therapy.[94] 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 intravenous), 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.[95]

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).[128] Dexamethasone was only given on day 1 for both treatment groups. A significantly higher proportion of patients in the 3-drug regimen with oral aprepitant had no vomiting compared with the control antiemetic regimen (76% vs. 62%; $P < .001$) during the overall time frame from 0 to 120 hours after starting chemotherapy. In addition, the CR (no emetic episodes, no rescue medications) rate was significantly increased in the 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 3-drug regimen was well tolerated, and the incidence of adverse events was similar between treatment groups.[128]

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 chemotherapy) and then 80 mg on days 2 and 3 (after chemotherapy).[129] An intravenous version of aprepitant (fosaprepitant dimeglumine), which can be given on day 1 only, is also FDA approved. As previously mentioned, intravenous fosaprepitant is NOT interchangeable with aprepitant injectable emulsion. Intravenous fosaprepitant is given 30 minutes before chemotherapy on day 1 only, per the package insert. If a higher dose of fosaprepitant is used (150 mg intravenous) on day 1, then it is not necessary to give oral aprepitant on days 2 to 3.[130,131] 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 intravenous) per the package insert. A single dose of 150 mg intravenous fosaprepitant was shown to be non-inferior to the control antiemetic regimen with 3-day oral aprepitant in a randomized study.[132] 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.

Drug Interactions

Aprepitant is simultaneously a substrate, moderate inducer, and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4); aprepitant also induces CYP2C9.[133] 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 intravenous 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 chemotherapy doses were not adjusted for potential drug interactions in phase 3 trials, caution is urged when using any chemotherapeutic agent that is metabolized by CYP3A4.

Aprepitant has been shown to interact with several non-chemotherapeutic drugs (including warfarin, dexamethasone, methylprednisolone, and oral contraceptives). Again, these interactions are more significant with orally administered forms of these drugs than with intravenous forms because of first-pass metabolism. Induction of warfarin metabolism by aprepitant may lead to clinically significant reductions in 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 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; NEPA is approved by the FDA for the prevention of nausea and vomiting in patients receiving HEC and MEC based on several randomized trials.[134-137] Similar to the other NK1 RAs (ie, aprepitant, fosaprepitant, and rolapitant), netupitant improves control for delayed emesis when compared with traditional antiemetic regimens. Netupitant is only available combined with palonosetron (NEPA); netupitant is not available as a single agent. For patients receiving HEC and MEC, the NCCN Panel recommends several options for prophylactic antiemetic regimens; NEPA combined with dexamethasone is recommended (category 1) for acute and delayed emesis prevention based on the FDA approval and randomized trials. Netupitant inhibits 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.

A randomized trial in patients receiving HEC assessed dexamethasone plus 3 varying dose levels of prophylactic oral NEPA compared with oral palonosetron plus dexamethasone.[134] The data show that the oral NEPA fixed-dose combination of 300 mg of netupitant decreased nausea and vomiting in the acute, delayed, and overall phases when compared with palonosetron alone. The CR for the NEPA300 arm was 89.6% versus 76.5% for the palonosetron arm ($P < .050$). A phase 3 trial in patients receiving AC regimens assessed NEPA plus dexamethasone compared with palonosetron plus dexamethasone.[136] More patients in the NEPA arm had CR during the delayed phase when compared with the control arm (76.9% vs. 69.5%; $P = .001$). In addition, patients in the 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 recent phase 3 randomized trial assessed a single dose of NEPA compared with a 3-day aprepitant/granisetron regimen in patients (n = 828) receiving HEC; all patients received oral dexamethasone on days 1 through 4.[138] The NEPA regimen was non-inferior to the aprepitant regimen (overall CR: NEPA, 73.8% vs. aprepitant/granisetron, 72.4% [95% CI, -4.5%–7.5%]). Similar rates were observed for both groups for no emesis (NEPA, 75.0% vs. aprepitant/granisetron, 74.0% [95% CI, -4.8%–6.9%]) and no significant nausea (NEPA, 75.7% vs. aprepitant/granisetron, 70.4% [95% CI, -0.6%–11.4%]).

Rolapitant

Rolapitant is another NK1 RA that is approved by the FDA for the prevention of nausea and vomiting in patients receiving HEC and MEC based on several phase 3 randomized trials.[139,140] In the phase 3 trials 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.[140] More patients receiving the oral rolapitant-containing regimen had CRs for prevention of delayed emesis when 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 rolapitant regimen is recommended for acute and delayed emesis prevention based on the FDA approvals and the phase 3 randomized trial.[140]

A 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 of 4 or more). 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).[91,139] 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.[139] 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 approvals and phase 3 randomized trial.[139]

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, rolapitant improves control for delayed emesis when 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). In addition, there are fewer drug interactions with rolapitant when compared with the other NK1 RAs (ie, aprepitant, fosaprepitant, netupitant).

Other Antiemetics

Before the advent of the 5-HT3 antagonists and NK1 RAs, the available antiemetic agents included phenothiazines,[141] substituted benzamides,[142,143] antihistamines,[144] butyrophenones,[145] corticosteroids,[146-148] benzodiazepines,[149,150] and cannabinoids.[151,152] Based on clinical trial data, the NCCN Panel added 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

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 day 1 dose range of dexamethasone was 8 to 100 mg, and the mean total dose (acute and delayed) was 56 mg.[153] The authors concluded dexamethasone offered a clear advantage over placebo for protection against chemotherapy-induced emesis in both 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 2 randomized, double-blinded, multicenter trials to determine the dose of dexamethasone to be given on day 1 of an antiemetic regimen.[154,155] The first trial was conducted in chemo-naive patients receiving 50 mg/m^2 or more of cisplatin, which is considered HEC.[154] Intravenous dexamethasone day 1 doses were 4, 8, 12, and 20 mg (approximately 130 patients/arm). All patients received the following: 1) ondansetron 8 mg intravenous 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 when 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 4 groups.

The second study compared 3 dosing regimens of dexamethasone on day 1 in patients receiving anthracyclines, cyclophosphamide, or carboplatin, either alone or in combination with other chemotherapy agents, which previously were considered to be MEC.[155] 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 intravenous ondansetron: 1) for arm A, 8 mg of intravenous dexamethasone before chemotherapy plus 4 mg oral dexamethasone every 6 hours for 4 doses, starting at the same time of the chemotherapy; 2) for arm B, 24 mg of intravenous single-dose dexamethasone before chemotherapy; or 3) for arm C, 8 mg of intravenous single-dose dexamethasone before chemotherapy. 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 3 groups. The authors concluded that 8 mg of intravenous dexamethasone is the best dose when using dexamethasone in antiemetic regimens for patients receiving chemotherapy 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). 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 NK1 RAs. 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.[154,155]

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 (category 2B) (see the algorithm). 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 steroids (see the NCCN Guidelines for Antiemesis).[106,156-158] Dexamethasone is associated with side effects, such as insomnia. For the 2018 update, the NCCN Panel simplified the dosing for dexamethasone for the intravenous HEC and MEC regimens. For the olanzapine/palonosetron/dexamethasone regimen for HEC and MEC, the dose of dexamethasone was decreased to 12 mg PO/IV 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 PO/IV on day 1 in the 3-drug olanzapine regimen. For all the HEC regimens, the panel also simplified the dosing for delayed dexamethasone to 8 mg PO/IV daily on days 2 to 4 (previously, some of the HEC regimens had used twice-daily dosing of dexamethasone). For the 2018 update, the NCCN Panel feels 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.[106] 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.[157] 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 2 regimens during the acute (0–24 hours postchemotherapy; 88.6% vs. 84.3%; $P = .262$) and delayed phases (days 2–5; 68.7% vs. 77.7%; $P = .116$).[157]

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] An olanzapine-containing antiemetic 3-drug regimen with dexamethasone and palonosetron is effective for preventing acute and delayed emesis as described in the following sections.[20,159-167] An olanzapine-containing 4-drug antiemetic regimen is also effective for preventing acute and delayed emesis.[168] The NCCN Panel recommends (category 1) olanzapine-containing 3-drug or 4-drug regimens for both HEC and MEC based on the clinical trial data as described in the following sections.[36] For the 2018 update, the NCCN Panel added a caveat that olanzapine can be substituted for dexamethasone if patients cannot tolerate dexamethasone (eg, diabetics).

Common side effects with olanzapine include fatigue, drowsiness, and sleep disturbances. 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).[169] Data suggest that a 5-mg dose of olanzapine may be considered in elderly or over-sedated patients.[170-172] Parenteral olanzapine use combined with parenteral benzodiazepine use is contraindicated to avoid excessive sedation, hypotension, and decreased respiration; toxicity may occur with this combination regardless of the routes of administration.[173] To avoid excessive dopamine blockade, caution is recommended when giving olanzapine concurrently with metoclopramide or haloperidol.

Three-Drug Regimen

An olanzapine-containing antiemetic 3-drug regimen with dexamethasone and palonosetron is effective for preventing acute and delayed emesis based on phase 3 trials, phase 2 trials, and a meta-analysis.[20,159-167] 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 intravenous) and dexamethasone administered on day 1.[166] 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.[166] A systematic review summarized the phase 1 and 2 studies of olanzapine for preventing acute and delayed emesis.[20] Across 4 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 showed the value of olanzapine for delayed, refractory, and breakthrough emesis and nausea.[161-164,171]

The NCCN Panel recommends (category 1) an olanzapine-containing 3-drug regimen for both HEC and MEC based on the phase 3 and phase 2 trials. As previously mentioned, the NCCN Panel decided to decrease the dose of dexamethasone to 12 mg PO/IV on day 1 for the 3-drug regimen with olanzapine/palonosetron/dexamethasone, because all the other antiemetic regimens use a dexamethasone dose of 12 mg PO/IV on day 1. Previously, the panel had recommended a dexamethasone dose of 20 mg PO/IV on day 1 in the 3-drug olanzapine regimen based on the clinical trial data.[166] The panel also agreed that palonosetron should be used in the 3-drug olanzapine regimen; no data are available to support substituting any of the other 5-HT3 antagonists.

Four-Drug Regimen

A recent 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.[168] The data showed that the 4-drug regimen with olanzapine increased the CR rate (no emesis, no rescue) when compared with placebo during 3 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 4-drug olanzapine regimen had no chemotherapy-induced nausea when compared with placebo during the 3 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). Based on this trial, the NCCN Panel recommends (category 1) the 4-drug olanzapine regimen as a first-line regimen. In addition, clinicians can consider switching patients to the 4-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 3-drug olanzapine regimen (olanzapine/dexamethasone/palonosetron).[36] For the 2018 update, the panel agreed that any NK1 RA (ie, not just fosaprepitant or oral aprepitant) could be used in the 4-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 4-drug olanzapine regimen on day 1; however, none of these agents is continued on days 2 to 4.

Treatment Issues

As new data on the use of antiemetics in patients receiving anticancer therapy become available, clinicians should consider these data when caring for such patients. In contrast to other NCCN Guidelines in which most of the recommendations are category 2A, many of the recommendations for antiemetic management are classified as category 1, reflecting the large number of randomized controlled trials that have focused on antiemetic management. These NCCN Guidelines include a section on pharmacologic considerations for the different antiemetics describing: 1) the major classes of antiemetic agents; 2) clinical pearls associated with the different types of agents; and 3) possible drug-drug or drug-disease interactions among the different antiemetic agents (see *Pharmacologic Considerations for Antiemetic Prescribing* in the NCCN Guidelines for Antiemesis*).*

Principles of Emesis Control

These principles are described in the algorithm and are summarized here (see *Principles of Emesis Control for the Cancer Patient* in the NCCN Guidelines for Antiemesis). The goal of emesis control is to prevent nausea and/or vomiting. Antiemetic regimens should be chosen based on the drug with the highest emetic risk in the chemotherapy regimen, previous experience with antiemetics, and patient-specific risk factors.[11] Patients need to be protected throughout the entire period of risk, which lasts for at least 3 days for high emetic risk agents and 2 days for moderate emetic risk agents after the last dose of anticancer therapy. In addition to using antiemetic regimens, patients can adjust their eating habits and adopt other lifestyle measures that may alleviate nausea and vomiting (see *Eating Hints: Before, During, and After Cancer Treatment* from the National Cancer Institute).[174] 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 chemotherapy and then should cover the first 24 hours. In the NCCN Guidelines for Antiemesis, the specific antiemetic regimens are described for patients receiving highly emetogenic intravenous drugs, moderately emetogenic intravenous drugs, low emetogenic intravenous drugs, and minimally emetogenic intravenous drugs. Emesis prevention for oral chemotherapeutic agents is also described in the NCCN Guidelines. This section discusses prechemotherapy and postchemotherapy emesis prevention rather than primary treatment.

Prechemotherapy Emesis Prevention

The NCCN Guidelines specify different prophylactic antiemetic regimens for cancer patients receiving anticancer therapy of different emetogenic potential (ie, high, moderate, low, minimal). Prophylactic antiemetics should be administered before anticancer therapy. The recommendations for prophylactic antiemetic treatment include drug dosages. The guidelines reflect accumulating experience with the 5-HT3 antagonists, demonstrating their effectiveness in a range of doses. Unless indicated,

the order of listed antiemetics in the NCCN Guidelines does not reflect preference.

Highly emetogenic intravenous 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), or AC combination regimens at any dose (eg, doxorubicin or epirubicin with cyclophosphamide). Most of these drugs are also considered highly emetogenic by the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) guidelines.[9,175] The NCCN Guidelines for highly, moderately, low, and minimally emetogenic agents differ slightly from the MASCC/ESMO guidelines based on the experience and expertise of the panel members.[176-179]

The NCCN Panel recently changed the emetogenic classification for carboplatin. When dosed at an AUC of 4 or more, carboplatin is now considered highly emetogenic; carboplatin at an AUC of less than 4 is now considered moderately emetogenic. The NCCN Panel revised the classification of carboplatin based on published data suggesting that carboplatin, while less emetogenic than cisplatin, is perhaps on the higher end of emetogenic potential within the MEC classification.[180] Several trials and a subset analysis have shown benefit, in terms of CR in the overall and delayed phases, of adding an NK1 RA to the 2-drug regimen of 5-HT3 antagonist and dexamethasone for the prevention of CINV associated with carboplatin-based regimens.[139,180-182] All of the commercially available NK1 RAs have an FDA-approved indication for MEC, but previous NCCN Guidelines have 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 steroid and 5-HT3 antagonist alone.

The panel did not want to create a “carboplatin subset” within the MEC classification; therefore, carboplatin at an AUC of 4 or more was escalated to the HEC classification, where a triple-drug regimen (NK1 RA plus 5-HT3 antagonist plus steroid) would be preferred for all patients.

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], dactinomycin, daunorubicin, doxorubicin [<60 mg/m^2], epirubicin [≤90 mg/m^2], 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.[91]

The NCCN Guidelines recommend several different antiemetic regimen options for patients receiving highly emetogenic agents. Recommended antiemetic regimens contain 5-HT3 antagonists, dexamethasone, NK1 RAs (such as aprepitant [or fosaprepitant] and rolapitant), and olanzapine. 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.[34,39,120] Regimens for day 1 therapy (all are category 1) include those containing dexamethasone, a 5-HT3 antagonist, and one of the following: aprepitant, fosaprepitant, or rolapitant. Other antiemetic regimens (category 1) for highly emetogenic agents on day 1 include: 1) NEPA and dexamethasone; 2) olanzapine, palonosetron, and dexamethasone; or 3) olanzapine, aprepitant or fosaprepitant, palonosetron, and dexamethasone (see *Olanzapine* in this Discussion). Note that the regimens and doses are often modified on days 2 to 4 after anticancer therapy.

Although it is not recommended as a single agent, lorazepam is a useful adjuvant because it decreases anxiety.[39,150] Lorazepam is also recommended for patients who are at risk for anticipatory nausea and/or vomiting (see *Anticipatory Emesis Prevention/Treatment* in the algorithm). 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, intravenous, or sublingual) may be used with each of these regimens.

For intravenous regimens with high emetogenic potential, aprepitant is used at an oral dosage of 125 mg on day 1 and then 80 mg on days 2 and 3. When given with aprepitant, dexamethasone is used at a dosage of 12 mg on day 1; the dexamethasone dose can be oral or intravenous. Note that aprepitant injectable emulsion or intravenous fosaprepitant may be substituted for 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.[71] 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 intravenous); 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 intravenous HEC includes olanzapine (10 mg oral days 1–4), palonosetron (0.25 mg intravenous day 1 only), and dexamethasone (20 mg intravenous day 1 only).[166]

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.[183] 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.

The NCCN Guidelines recommend several antiemetic regimens for intravenous MEC, including: 1) dexamethasone and a 5-HT3 antagonist with or without NK1 RAs such as aprepitant, fosaprepitant, netupitant, or rolapitant; or 2) olanzapine, palonosetron, and dexamethasone. If needed, lorazepam, an H2 blocker, or a proton pump inhibitor may be added (alone or in any combination) to these regimens.[6] Netupitant is only available combined with palonosetron (NEPA); netupitant is not available as a single agent. As per high emetic risk prevention, an NK1 RA 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 steroid and 5-HT3 antagonist alone. Intravenous 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.[71,92]

The antiemetic regimen for low emetogenic intravenous drugs includes dexamethasone, prochlorperazine, metoclopramide, or orally administered 5-HT3 antagonists (see the algorithm). Lorazepam, an H2 blocker, or a proton pump inhibitor may also be added (alone or in any combination) to all of these agents. When using prochlorperazine or metoclopramide, patients should be monitored for dystonic reactions.[184-186] Diphenhydramine can be used for the treatment of dystonic reactions.[187,188] Benztropine may be used in patients who are allergic to diphenhydramine.[185]

The emetogenic potential of oral anticancer agents is shown in the NCCN Guidelines. Oral antiemetic prophylaxis is recommended for the following oral agents, which are of high or moderate emetic risk: altretamine, busulfan (≥4 mg/d), ceritinib, crizotinib, cyclophosphamide (≥100 mg/m^2/d), enasidenib, estramustine, etoposide, lenvatinib, lomustine (single day), midostaurin, mitotane, niraparib, olaparib, panobinostat,

procarbazine, rucaparib, temozolomide (>75 mg/m^2/d or ≤75 mg/m^2/d with concurrent radiotherapy), and trifluridine/tipiracil. For high or moderate emetic risk oral anticancer agents, recommended prophylaxis includes single-agent antiemetic therapy with an oral 5-HT3 antagonist (such as 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 oral 5-HT3 antagonists, metoclopramide, or prochlorperazine; the NCCN Panel recently 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. Some patients receiving oral anticancer therapy of low/minimal emetogenicity may experience nausea/vomiting; these patients should be escalated to the next higher level of antiemetic therapy in future cycles of anticancer therapy.

Postchemotherapy/Delayed Emesis Prevention

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 chemotherapy.[10,21,22,26] Patients rank nausea as more of a problem than vomiting.[10] Data suggest that rolapitant and netupitant are effective at decreasing delayed nausea.[134,136,139,140] 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.[168] More patients receiving the 4-drug regimen with olanzapine had no chemotherapy-induced nausea when 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 when compared with placebo. The data showed that the 4-drug regimen with olanzapine increased the CR rate (no emesis, no rescue) during the delayed time period when compared with placebo (67% vs. 52% (*P* = .007).

Delayed Emesis

The best management for delayed emesis is prevention.[189] A recent survey among oncology nurses found that there is low adherence (only 25%) to antiemetic guidelines for preventing delayed emesis.[190] For HEC, the prophylactic treatment on days 2 to 4 depends on which antiemetics were used before anticancer therapy. 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. For the 2018 update, the NCCN Panel deleted a footnote that previously stated that some NCCN Member Institutions used a 5-HT3 RA on days 2 to 4 in addition to a steroid and NK1 antagonist therapy. The option of adding an 5-HT3 RA is available for breakthrough treatment (ie, rescue).

If oral aprepitant and/or olanzapine was used on day 1, then oral aprepitant and/or olanzapine is continued on days 2 and 3. Dexamethasone is continued on days 2 to 4 for all regimens. 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). It is important to note that the doses are decreased when used on days 2 to 3 of oral aprepitant (80 mg oral) and on days 2 to 4 of dexamethasone (8 mg oral or intravenous) when compared with the

doses given on day 1. However, the dose of olanzapine is not decreased on days 2 to 4.

The antiemetic regimens in the NCCN Guidelines include different options on days 2 to 3 for MEC.[34,39,189] Postchemotherapy emetic prevention depends on which antiemetics were used before chemotherapy. If oral aprepitant and/or olanzapine was used on day 1, then oral aprepitant and/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.[73] Antiemetic therapy on days 2 and 3 may just be single agents. There are several possible MEC antiemetic regimens on 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.[189] If needed, each of these regimens may also include lorazepam, an H2 blocker, or a proton pump inhibitor (alone or in any combination). Again, the doses are decreased when used on days 2 to 3 of both oral aprepitant (80 mg oral) and dexamethasone (8 mg oral or intravenous) when 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 algorithm). Generally, it is much easier to prevent nausea and/or vomiting than to treat it. Thus, routine around-the-clock administration of antiemetics should be strongly considered to prevent emesis, rather than PRN (as required) dosing. The general principle of breakthrough treatment is to add an additional agent as needed from a different drug class.[34] Some patients may require several agents using different mechanisms of action. The oral route may not be feasible because of ongoing vomiting; therefore, rectal, topical, subcutaneous, or intravenous 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 therapy. Olanzapine is possibly more effective than NK1-antagonist–containing regimens for preventing nausea.[20,166,167]

Haloperidol, metoclopramide, olanzapine, scopolamine transdermal patch, corticosteroids, and agents such as lorazepam may be added for breakthrough treatment to the current antiemetic regimen. In a randomized phase 3 trial, the effectiveness of olanzapine (10 mg/d 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 (comprising palonosetron, dexamethasone, and fosaprepitant; n = 108 evaluable).[191] 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.[191] Thus, olanzapine was more effective in controlling breakthrough emesis and nausea compared with metoclopramide in this patient population. The MASCC/ESMO Guidelines recommend olanzapine for breakthrough emesis.[192] The NCCN Panel recommends olanzapine (category 1) 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.[191]

Dronabinol and nabilone (which are cannabinoids) are approved by the FDA for refractory nausea and vomiting when patients have not responded

to conventional antiemetic agents. 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).[193] Recommended starting doses are dronabinol oral solution (4.2 mg/m^2) or dronabinol capsules (5 mg/m^2) both given 3 to 4 times daily. Lower doses are recommended in elderly patients.

Before administering the next cycle of anticancer therapy, the patient should be reassessed for other possible non-anticancer therapy–related reasons for breakthrough emesis with the current cycle (eg, brain metastases, electrolyte abnormalities, tumor infiltration of the bowel or other GI abnormality, excessive secretions [eg, seen in patients with head and neck cancer], other comorbidities; see *Principles for Managing Breakthrough Emesis* and *Principles of Emesis Control for the Cancer Patient* in the algorithm). Adequate hydration or fluid repletion should be ensured, and any possible electrolyte abnormalities should be assessed and corrected. Before the next cycle of anticancer therapy, if the antiemetic regimen (both the day 1 and post-anticancer therapy) did not protect the patient during the present cycle, the antiemetic regimen should be assessed and alternatives should be considered (see *Principles for Managing Breakthrough Emesis* in the algorithm). Because patients sometimes have difficulty discriminating heartburn from nausea, addition of antacid therapy (eg, proton pump inhibitors, H2 blockers) should be considered.

Radiation-Induced Nausea and/or Vomiting

Prophylaxis for RT-induced nausea and/or vomiting is based on the site of RT and whether it is combined with anticancer therapy.[36,37,194,195] When RT is combined with anticancer therapy, prophylaxis is dictated by the emetogenic potential of the chemotherapy regimen. 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.[36,37,196] A meta-analysis suggests that 5-HT3 antagonists are the preferred agents for preventing RT-induced vomiting.[197]

Patients undergoing RT to the upper abdomen may receive antiemetic prophylaxis with oral ondansetron or oral granisetron, with or without oral dexamethasone.[9,37] 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 ($P < .05$).[198] 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.[199] 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; $P = .03$) when 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 when compared with placebo.[200]

The NCCN Panel recommends that patients undergoing total body irradiation or upper abdomen RT receive antiemetic prophylaxis with either ondansetron or granisetron; either agent can be given with or without oral dexamethasone.[9,37,201] Treatment of breakthrough RT-induced emesis is similar to chemotherapy-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 Chemotherapy-Induced Nausea/Vomiting* in the algorithm).

Anticipatory Nausea and/or Vomiting

About 20% of patients develop anticipatory nausea and/or vomiting.[202] However, the rate of anticipatory nausea and/or vomiting appears to be decreasing (when compared with older studies) with current use of more effective antiemetic regimens.[9] 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.[34,36,203,204] The NCCN Guidelines recommend that patients avoid strong smells that may precipitate symptoms. Behavioral therapy has been used in patients with anticipatory nausea and/or vomiting.[36,205-210] For the 2018 update, the NCCN Panel added yoga, cognitive distraction, progressive muscle relaxation, and biofeedback to the list of useful behavioral therapy options. Systematic desensitization may also be helpful.[206] Hypnosis with guided imagery is another behavioral technique that has shown some success in treating this condition.[207]

The antianxiety agent, lorazepam has been combined with antiemetics for anticipatory nausea and/or vomiting.[204,211,212] 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 anticancer therapy begins. 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. For the 2018 update, the NCCN Panel deleted alprazolam, because rebound anxiety is more prevalent with alprazolam than with lorazepam. The panel added a caveat that lorazepam should be used with caution in patients receiving scheduled opioids.

Multiday Emetogenic Chemotherapy Regimens

Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea and/or vomiting based on the emetogenic potential of the individual chemotherapy agents and their sequence.[34,213-217] It is difficult to recommend a specific antiemetic regimen for each day, especially because acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy. The period of risk for delayed emesis following completion of chemotherapy also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. For multi-drug regimens, antiemetic therapy should be selected based on the drug with the highest emetic risk.[36] 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 algorithm). For antiemetic prophylaxis of multiday emetogenic chemotherapy regimens (eg, cisplatin-containing regimens), the combination of a 5-HT3 antagonist with dexamethasone was previously recommended in the 2011 MASCC/ESMO guidelines.[9,34] The NCCN Guidelines and 2017 MASCC/ESMO guidelines currently recommend a 3-drug regimen of a 5-HT3 RA, oral aprepitant, and dexamethasone as prophylaxis for multiday anticancer regimens with MEC or HEC regimens.[192] The clinical trial data to support these recommendations are described in the following sections.

Dexamethasone

Dexamethasone should be administered once daily either orally or intravenously for every day of MEC or HEC and continued for 2 to 3 days after chemotherapy for regimens that are likely to cause significant delayed emesis. However, dexamethasone should not be added when the chemotherapy regimen already includes a corticosteroid. The use of steroids as antiemetics is not recommended when using treatment regimens containing drugs that elicit an immune response such as

aldesleukin, interferon, ipilimumab, nivolumab, atezolizumab, pembrolizumab, avelumab, or durvalumab.[218] Dexamethasone-sparing strategies or replacing dexamethasone with olanzapine are options for patients who cannot tolerate steroids.

5-HT3 Antagonists

For multiday chemotherapy regimens, a 5-HT3 antagonist should be administered each day before the first dose of MEC or HEC. Intravenous palonosetron, subcutaneous granisetron or transdermal granisetron may be used before the start of a 3-day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT3 antagonists.[219,220] Data regarding repeat dosing with subcutaneous granisetron for multiday regimens is unknown. Repeat dosing of palonosetron (0.25 mg intravenous) is likely to be safe, based on the dose ranging phase 2 trial and the 3 phase 3 trials using palonosetron as a single fixed dose (0.75 mg intravenous).[70,72,73,221] Compared to the approved dose of palonosetron of 0.25 mg intravenous, these higher doses were not associated with significantly different adverse events.

The need for repeat dosing with palonosetron, either daily or less frequently, in the setting of multiday chemotherapy is not yet known. In one study, patients receiving highly emetogenic multiday cisplatin-based chemotherapy for testicular cancer (N = 41) received multiday dosing of palonosetron (0.25 mg intravenous 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.[222] A study assessed palonosetron given for 1, 2, or 3 days in combination with dexamethasone for patients receiving multiday high-dose chemotherapy prior to stem cell transplantation for multiple myeloma (N = 73); during the 7-day emesis prevention period, about 40% 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).[118] Another study found that a palonosetron/dexamethasone regimen appeared to be more effective for multiday chemotherapy than an ondansetron/dexamethasone regimen; patients received a second dose of palonosetron for breakthrough emesis, which was effective in 67% of patients who experienced nausea or vomiting.[219] A review also cited the value of palonosetron for patients receiving multiday chemotherapy.[223] Further studies are needed to define whether a need exists for repeat dosing of palonosetron in the setting of multiday chemotherapy.

NK1 RAs

The potential role of NK1 RAs in the antiemetic management of multiday chemotherapy regimens has been investigated in several studies.[140,192,224-226] In one study, the addition of oral aprepitant to granisetron and dexamethasone was evaluated in patients receiving multiday HEC and MEC (N = 78). In this study, the 3-drug antiemetic regimen was given during chemotherapy; oral aprepitant and dexamethasone were given for an additional 2 days following chemotherapy.[226] A CR (during the time period from day 1 until 5 days after chemotherapy) was observed in 58% and 73% of patients who received antiemetic regimens for HEC and MEC, respectively.[226] 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 chemotherapy cycles with 5-day cisplatin-based regimens (N = 50).[225] During cycle 1 of chemotherapy, 96% of patients had no emesis on day 1 and 82% had no emesis during days 1 to 7. In addition, 71% had no nausea on day 1 of cycle 1, and 27% had no nausea during days 1 to 7. More than 80% of

patients had no emesis on any given day of any given chemotherapy cycle. No unexpected or serious adverse events were reported.[225]

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 2 cycles of a 5-day cisplatin combination chemotherapy regimen (n = 69 evaluable).[224] 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 chemotherapy. 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.[224] 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%; $P < .001$).[224] 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.[224]

NK1 antagonists may be used for multiday chemotherapy regimens likely to be moderately or highly emetogenic and associated with significant risk for delayed nausea and emesis. As per the labeled indication, oral aprepitant should be administered 125 mg 1 hour prior to chemotherapy 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 chemotherapy along with dexamethasone.[213] Repeated dosing of oral aprepitant over multiple cycles of cisplatin-based chemotherapy appears to be feasible and well tolerated; importantly, protection from emesis and from significant nausea was maintained during the subsequent cycles of emetogenic chemotherapy.[213,224] Based on smaller studies, oral aprepitant 80 mg may be safely administered beyond day 3 of initiating chemotherapy.[129,225] Alternatively, for HEC regimens, aprepitant injectable emulsion 130 mg IV or fosaprepitant 150 mg intravenous 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 rolapitant.

Summary

The NCCN Guidelines for Antiemesis provide an overview of the treatment principles for preventing anticancer therapy-induced or RT-induced vomiting and nausea, and provide recommendations for prophylactic antiemetic regimens based on the emetogenic potential of anticancer agents. Prophylactic antiemetic treatment is recommended, because it is harder to control nausea and 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 algorithm in greater detail, for example, by including the clinical trial data and references that support the NCCN Panel's recommendations in the algorithm. Revisions for the 2018 update are described in this Discussion and outlined in *Summary of the Guidelines Updates* in the algorithm.

Some of the updates for 2018 include: 1) aprepitant injectable emulsion is a new NK-1 RA treatment option that is now recommended; and 2) the emetogenic potential of 11 new agents was determined by the NCCN Panel so that health care providers can select the most appropriate

antiemetic regimens for patients receiving these new agents. The panel simplified the dosing for dexamethasone for the intravenous HEC and MEC antiemetic regimens. On day 1, the recommended dose of dexamethasone is now 12 mg PO/IV once. On days 2 to 4, dexamethasone is now 8 mg PO/IV daily. The panel also recommends that if patients cannot tolerate dexamethasone, it can be replaced with olanzapine.

The NCCN Panel clarified the use of NK1 RAs in HEC and MEC antiemetic regimens. The panel agreed that any NK1 RA (ie, not just fosaprepitant or oral aprepitant) could be used in the 4-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 now be used in the 4-drug olanzapine regimen on day 1; however, none of these agents is continued on days 2 to 4. In the 3-drug olanzapine regimen for HEC and MEC (olanzapine/palonosetron/dexamethasone), the panel also agreed that only palonosetron should be used; no data are available to support substituting any of the other 5-HT3 antagonists. The panel recommends that an NK1 RA should be added to a 5-HT3/dexamethasone regimen (2-drug antiemetic regimen) for patients receiving MEC anticancer therapy who have additional risk factors or previous treatment failure with the 2-drug regimen. Alprazolam was deleted as anxiolytic therapy for anticipatory nausea/vomiting, because rebound anxiety is more prevalent with alprazolam than with lorazepam. The panel added a caveat that lorazepam should be used with caution in patients receiving scheduled opioids.

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