National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Antiemesis

Version 2.2016

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Clinical Trials: NCCN believes that the best management for any cancer patient 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/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2016 Updates Antiemesis

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Updates in Version 2.2016 of the NCCN Guidelines for Antiemesis from Version 1.2016 include:

AE-5
- High emetic risk intravenous chemotherapy - acute and delayed emesis prevention, clarified by adding "(any combination of an NK-1 antagonist + 5-HT3 antagonist + steroid [category 1])."

AE-6
- Moderate emetic risk intravenous chemotherapy - acute and delayed emesis prevention, removed "category 1" from rolapitant.
- Added dose to "± dexamethasone 8 mg PO/IV daily on days 2-3."

AE-8
- Oral chemotherapy - emesis prevention, included "Granisetron 3.1 mg/24 h transdermal patch every 7 days."

Discussion
- The discussion section was updated to reflect the changes to the algorithm.

Updates in Version 1.2016 of the NCCN Guidelines for Antiemesis from Version 2.2015 include:

AE-1
- There are other potential causes of emesis in cancer patients:
  - Changed "opiates" to "opioids": "Concomitant drug treatments, including ~~opiates~~ opioids."
  - Added a new bullet ,"Malignant ascites," to the list.

AE-2
- Emetogenic Potential of Intravenous Antineoplastic Agents: this page was moved to the beginning of the guideline (previously page AE-7).
- Moderate emetic risk, added dinutuximab and trabectedin.

AE-3
- Emetogenic Potential of Intravenous Antineoplastic Agents: this page was moved to the beginning of the guideline (previously page AE-8).
- Low emetic risk, added irinotecan (liposomal), necitumumab, and talimogene laherparepvec.
- Minimal emetic risk, added daratumumab and elotuzumab.

AE-4
- Emetogenic Potential of Oral Antineoplastic Agents: this page was moved to the beginning of the guideline (previously page AE-9).
- Moderate to high emetic risk, added trifluridine/tipiracil.
- Moved vismodegib from moderate to high down to minimal to low.
- Minimal to low, added alectinib, cobimetinib, ixazomib, osimertinib, and sonidegib.

AE-5
- Added footnote j : "See Pharmacologic Considerations for Antiemetic Prescribing" (AE-B). (applies to AE-5–10)
- Incorporated previous footnote f into Pharmacological Considerations (AE-B): "Serotonin (5-HT3) antagonists, haloperidol, and metoclopramide may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion."
- Removed: "Data with palonosetron are based on randomized studies in combination with steroids only."
- Incorporated footnote m into Pharmacological Considerations (AE-B): "Use of steroids is not recommended with drugs such as interleukin-2 (ie, IL-2, aldesleukin), interferon, ipilimumab, nivolumab, and pembrolizumab."
- Modified footnote l: "If ~~neither aprepitant nor fosaprepitant~~ NK1 antagonists are not given on day 1, then recommend dexamethasone 20 mg PO/IV once on day 1, followed by 8 mg BID PO/IV on days 2, 3, and 4 (category 2B)."
- Removed "If rolapitant given: Dexamethasone 20 mg PO/IV once"
- Changed the dexamethasone recommendation for consistency to "Dexamethasone 12 mg[m] PO/IV once"
- Added footnote m: "Dexamethasone dose may be individualized based on patient characteristics. See Discussion."
- Added footnote n: "Available as a combination product only." (also applies to AE-6)

AE-6
- Removed the reference, "Aapro M, Rugo H, Rossi G, et al. Ann Oncol 2014;25:1328-1333."

Note: All recommendations are category 2A unless otherwise indicated.
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Updates in Version 1.2016 of the NCCN Guidelines for Antiemesis from Version 2.2015 include:

AE-7

- Low emetic risk IV chemotherapy, change the dose for:
  - Dexamethasone 8–12 mg PO/IV daily.
  - Metoclopramide 10–20 ~~40~~ mg PO/IV (applies to AE-8, -9) and then every 6 h.
- Incorporated previous footnote s into Pharmacological Considerations (AE-B): "Monitor for dystonic reactions."

AE-9

- For "Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting, granisetron 1–2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV daily," added "or 3.1 mg/24-h transdermal patch every 7 days."

Modified the recommendation "Re-evaluate and consider dose adjustments and/or sequentially add one agent from a different drug class."~~switching to a different therapy~~

AE-A (1 of 2)

- Changed the 3rd bullet: "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 (IV, oral, or transdermal), duration of action of the serotonin antagonist and appropriate associated dosing intervals, tolerability of daily antiemetics (eg, corticosteroids), ~~and~~ adherence/compliance issues*, and individual risk factors."*
- General principles, corticosteroids, moved the last bullet to page AE-B: "Side effects associated with prolonged dexamethasone administration should be carefully considered."
- Under Palonosetron:
  - Added the following bullet: "When palonosetron is used as part of an antiemetic regimen that does NOT contain an NK-1 antagonist, palonosetron is the preferred serotonin antagonist. (Saito M et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol 2009 Feb;10(2):115-24.)"
  - Modified the following bullet "In terms of efficacy, limited data are available for multiday dosing.[2] ~~the need for repeat dosing with palonosetron, either daily or less frequently, in the setting of multiday chemotherapy is not yet known."~~
  - Added reference Giralt SA, Mangan KF, Maziarz RT, et al. Three palonosetron regimens to prevent CINV in myeloma patients receiving multiple-day high-dose melphalan and hematopoietic stem cell transplantation. Ann Oncol 2011; 22:939-946.

AE-A (2 of 2)

- First bullet, replaced "aprepitant or fosaprepirant with "NK1."
- Modified the first bullet, *"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."
- Second bullet, removed the statement "Alternatively, for highly emetogenic regimens, fosaprepitant 150 mg IV with recommended dexamethasone dosing may be given on day 1 with no need for oral aprepitant on days 2 and 3."
- Third bullet, modified the statement "If the oral aprepitant regimen is chosen, *limited* data exist to support administration of aprepitant on days 4 and 5 after multiday chemotherapy." Removed the last sentence "It is not yet known if dosing aprepitant after day 3 improves control of nausea or emesis in this clinical setting."
- Modified fifth bullet: *"Studies investigating repeat dosing of fosaprepitant, netupitant, and rolapitant are not available."*
- New bullet: "Fosaprepitant, aprepitant, and netupitant inhibit the metabolism of dexamethasone and may cause higher dexamethasone concentrations. Rolapitant does not inhibit dexamethasone metabolism."

AE-B

- "Pharmacologic Considerations For Antiemetic Prescribing" is a new section in the Guidelines.

AE-C

- Modified the second bullet: "The general principle of breakthrough treatment is to give an additional agent from a different drug class. ~~No one drug class has been shown to be superior for the management of breakthrough emesis, and~~ The choice of agent should be based on assessment of the current prevention strategies used. Some patients may require several agents utilizing differing mechanisms of action."
- New bullet: "Consider changing from NK1-containing regimens to olanzapine-containing regimen, or vice versa."

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PRINCIPLES OF EMESIS CONTROL FOR THE CANCER PATIENT

- **Prevention of nausea/vomiting is the goal.**
  - **The risk of nausea/vomiting 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 intravenous 5-HT3 antagonists have equivalent efficacy when used at the appropriate doses.**
- **Consider the toxicity of the specific antiemetic(s).**
- **Choice of antiemetic(s) used should be based on the emetic risk of the therapy, prior experience with antiemetics, and patient factors.**
- **There are other potential causes of emesis in cancer patients.**
  These may include:
  - **Partial or complete bowel obstruction**
  - **Vestibular dysfunction**
  - **Brain metastases**
  - **Electrolyte imbalance: hypercalcemia, hyperglycemia, or hyponatremia**
  - **Uremia**
  - **Concomitant drug treatments, including opioids**
  - **Gastroparesis: tumor or chemotherapy (eg, vincristine) induced or other causes (eg, diabetes)**
  - **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 Intravenous Antineoplastic Agents (AE-2).**
- **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)**

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EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[a]

High emetic risk (>90% frequency of emesis)[b,c]	• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide • 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[d] • Carmustine[d] ≤250 mg/m²	• Clofarabine • Cyclophosphamide ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin[d] • Daunorubicin[d] • 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] • Melphalan • Methotrexate[d] ≥250 mg/m² • Oxaliplatin • Temozolomide • Trabectedin

Adapted with permission from:
Hesketh PJ, 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. 2010;19:S43-47.

Low Emetic Risk (See AE-3)

Minimal Emetic Risk (See AE-3)

Oral Chemotherapy (See AE-4)

[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.

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EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[a]

LEVEL	AGENT		
Low emetic risk (10%–30% frequency of emesis)[b]	• Ado-trastuzumab emtansine • Amifostine ≤300 mg/m^2 • Aldesleukin ≤12 million IU/m^2 • Belinostat • Blinatumomab • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Cytarabine (low dose) 100–200 mg/m^2 • Docetaxel • Doxorubicin (liposomal) • Eribulin	• Etoposide • 5-FU • Floxuridine • Gemcitabine • Interferon alfa >5 - <10 million international units/m^2 • Irinotecan (liposomal) • Ixabepilone • Methotrexate >50 mg/m^2 - <250 mg/m^2 • Mitomycin • Mitoxantrone	• Necitumumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Talimogene laherparepvec • Thiotepa • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of emesis)[b]	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine (2-chlorodeoxyadenosine) • Cytarabine <100 mg/m^2 • Daratumumab • Decitabine • Denileukin diftitox • Dexrazoxane	• Elotuzumab • Fludarabine • Interferon alpha ≤5 million IU/m^2 • Ipilimumab • Methotrexate ≤50 mg/m^2 • Nelarabine • Nivolumab • Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase	• Peginterferon • Pembrolizumab • Pertuzumab • Ramucirumab • Rituximab • Siltuximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

Adapted with permission from:
Hesketh PJ, 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. 2010;19:S43-47.

High Emetic Risk (See AE-2)

Moderate Emetic Risk (See AE-2)

Oral Chemotherapy (See AE-4)

[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.

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EMETOGENIC POTENTIAL OF ORAL ANTINEOPLASTIC AGENTS[a]

LEVEL	AGENT		
Moderate to high emetic risk	• Altretamine • Busulfan (≥4 mg/d) • Ceritinib • Crizotinib • Cyclophosphamide (≥100 mg/m²/d)	• Estramustine • Etoposide • Lenvatinib • Lomustine (single day) • Mitotane	• Olaparib • Panobinostat • Procarbazine • Temozolomide (>75 mg/m²/d) • Trifluridine/tipiracil
Minimal to low emetic risk	• Afatinib • Alectinib • Axitinib • Bexarotene • Bosutinib • Busulfan (<4 mg/d) • Cabozantinib • Capecitabine • Chlorambucil • Cobimetinib • Cyclophosphamide (<100 mg/m²/d) • Dasatinib • Dabrafenib • Erlotinib • Everolimus • Fludarabine	• Gefitinib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib • Ixazomib • Lapatinib • Lenalidomide • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Osimertinib • Palbociclib • Pazopanib • Pomalidomide • Ponatinib	• Regorafenib • Ruxolitinib • Sonidegib • Sorafenib • Sunitinib • Temozolomide (≤75 mg/m²/d)[e] • Thalidomide • Thioguanine • Topotecan • Trametinib • Tretinoin • Vandetanib • Vemurafenib • Vismodegib • Vorinostat

Adapted with permission from:
Hesketh PJ, 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. 2010;19:S43-47.

High Emetic Risk (See AE-2)

Moderate Emetic Risk (See AE-2)

Low Emetic Risk (See AE-3)

Minimal Emetic Risk (See AE-3)

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

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HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[f,g]

DAY 1: Select option A, B, or C (order does not imply preference) Start before chemotherapy:[h]	DAYS 2, 3, 4:	
A: Neurokinin-1 (NK1) antagonist-containing regimen (netupitant, see option B):[i,j] select one agent from each of the following groups (any combination of an NK-1 antagonist + 5-HT3 antagonist + steroid [category 1]): • NK1 antagonist: ▸ Aprepitant 125 mg PO once ▸ Fosaprepitant 150 mg IV once ▸ Rolapitant 180 mg PO once[k] AND • Serotonin (5-HT3) antagonist:[j] ▸ Dolasetron 100 mg PO once ▸ Granisetron 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 AND • Steroid:[j,l] ▸ Dexamethasone 12 mg[m] PO/IV once	**A:**[q] • If aprepitant PO given day 1, then ▸ Aprepitant 80 mg PO daily on days 2, 3 AND ▸ Dexamethasone 8 mg[m] PO/IV daily on days 2, 3, 4 • If fosaprepitant given day 1, then ▸ No further NK1 antagonist is needed on days 2, 3 AND ▸ Dexamethasone 8 mg[m] PO/IV once on day 2, 8 mg PO/IV twice daily on days 3, 4 • If rolapitant given day 1, then ▸ No further NK1 antagonist is needed on days 2, 3 AND ▸ Dexamethasone 8 mg[m] PO/IV twice daily on days 2, 3, 4	See Breakthrough Treatment (AE-9)
B: Netupitant-containing regimen:[i,j,n,o] ▸ Netupitant 300 mg/palonosetron 0.5 mg PO once ▸ Dexamethasone 12 mg[m] PO/IV once	**B:** ▸ Dexamethasone 8 mg[m] PO/IV daily on days 2, 3, 4	
C: Olanzapine-containing regimen:[i,j,p] ▸ Olanzapine 10 mg PO ▸ Palonosetron 0.25 mg IV once ▸ Dexamethasone 20 mg[m] IV once	**C:** ▸ Olanzapine 10 mg PO daily on days 2, 3, 4	

[f] See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-2).
[g] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[h] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[i] 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).
[j] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[k] Rapoport BL, et al. Lancet Oncol 2015;16:1079-1089.
[l] If NK1 antagonists are not given on day 1, then recommend dexamethasone 20 mg PO/IV once on day 1, followed by 8 mg BID PO/IV on days 2, 3, and 4 (category 2B).
[m] Dexamethasone dose may be individualized based on patient characteristics. See Discussion.
[n] Available as a combination product only.
[o] Hesketh PJ, Rossi G, Rizzi G, et al. Ann Oncol 2014;25:1340-1346.
[p] Navari RM, Gray SE, Kerr AC. J Support Oncol 2011;9:188-195.
[q] Some NCCN Member Institutions use a 5-HT3 antagonist (unless palonosetron or granisetron patch given on day 1) on days 2, 3, and 4 in addition to steroid and NK1 antagonist therapy.

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MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[f,g]

DAY 1: Select option A, B, or C (order does not imply preference)
Start before chemotherapy:[h]

DAY 1	DAYS 2 and 3
A: Serotonin (5-HT3) antagonist + steroid (category 1) ± NK1 antagonist[i,j] (netupitant, see option B) • Serotonin (5-HT3) antagonist (Select one):[j] ▸ Dolasetron 100 mg PO once ▸ Granisetron 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) AND • Steroid[j] ▸ Dexamethasone 12 mg[m] PO/IV once WITH/WITHOUT • NK1 antagonist: [j,r] ▸ Aprepitant 125 mg PO once ▸ Fosaprepitant 150 mg IV once ▸ Rolapitant 180 mg PO once[s]	**A:** If no NK1 antagonist given on day 1: • Serotonin (5-HT3) antagonist monotherapy [j,t] (Select one): ▸ Dolasetron 100 mg PO daily on days 2, 3 ▸ Granisetron 1–2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV daily on days 2, 3 ▸ Ondansetron 8 mg PO BID or 16 mg PO daily or 8–16 mg IV daily on days 2, 3 OR • Steroid monotherapy[j]: ▸ Dexamethasone 8 mg[m] PO/IV daily on days 2, 3 If NK1 antagonist given on day 1: • If aprepitant given day 1, then ▸ Aprepitant 80 mg PO daily on days 2, 3 ± dexamethasone 8 mg PO/IV daily on days 2, 3 • If fosaprepitant given day 1, then ▸ No further NK1 antagonist is needed on days 2, 3 ± dexamethasone on days 2, 3 • If rolapitant given day 1, then ▸ No further NK1 antagonist is needed on days 2, 3 ± dexamethasone on days 2, 3
B: Netupitant-containing regimen:[i, j,n] ▸ Netupitant 300 mg/palonosetron 0.5 mg PO once[r] ▸ Dexamethasone 12 mg[m] PO/IV once	**B:** ▸ ± Dexamethasone 8 mg[m] PO/IV daily on days 2, 3
C: Olanzapine-containing regimen:[i,j,p] ▸ Olanzapine 10 mg PO ▸ Palonosetron 0.25 mg IV once ▸ Dexamethasone 20 mg[m] IV once	**C:** ▸ Olanzapine 10 mg PO daily days 2, 3

See Breakthrough Treatment (AE-9)

[f] See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-2).
[g] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[h] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[i] 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).
[j] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[m] Dexamethasone dose may be individualized based on patient characteristics. See Discussion.
[n] Available as a combination product only.
[p] Navari RM, Gray SE, Kerr AC. J Support Oncol 2011;9:188-195.
[r] As per high emetic risk prevention, an NK1 antagonist should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients with additional risk factors or treatment failing therapy with a steroid + 5HT3 antagonist alone (See AE-5).
[s] Schwartzberg LS, et al. Lancet Oncol 2015;16:1071-1078.
[t] No further therapy required if palonsetron or granisetron patch given on day 1.

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LOW AND MINIMAL EMETIC RISK INTRAVENOUS CHEMOTHERAPY - EMESIS PREVENTION[g,h,u]

Low →

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

- **Dexamethasone 8–12 mg PO/IV daily[i,j]**
  or
- **Metoclopramide 10–20 mg PO/IV and then every 6 h PRN[j]**
  or
- **Prochlorperazine 10 mg PO/IV and then every 6 h PRN (maximum 40 mg/d)[j]**
  or
- **Serotonin (5-HT3) antagonist[j] (select one):**
  - ◊ **Dolasetron 100 mg PO daily**
  - ◊ **Granisetron 1–2 mg (total dose) PO daily**
  - ◊ **Ondansetron 8–16 mg PO daily**

→ **Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-9)**

Minimal → **No routine prophylaxis** →

[g]Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[h]See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[i]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).
[j]See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[u]See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-3).

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

ORAL CHEMOTHERAPY - EMESIS PREVENTION[g,h,v,x]

High to moderate emetic risk →

Start before chemotherapy and continue daily (order does not imply preference)[i]
- **Serotonin (5-HT3) antagonist (Choose one):[j]**
  - **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 16–24 mg (total dose) PO daily**

→ **Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-9)**

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

Start before chemotherapy and continue daily (order does not imply preference)[i]
- **Metoclopramide 10–20 mg PO or every 6 h PRN[j]**
  or
- **Prochlorperazine 10 mg PO and then every 6 h PRN (maximum 40 mg/d)[j]**
  or
- **Haloperidol 1–2 mg PO every 4 or every 6 h PRN[j]**
  or
- **Serotonin (5-HT3) antagonist (Choose one):[j]**
  - ◊ **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-9)**

[g] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.

[h] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).

[i] 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).

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

[v] See Emetogenic Potential of Oral Antineoplastic Agents (AE-4).

[x] 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[h,y]

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:[j]**
  - **Olanzapine 10 mg PO daily[z]**
- **Benzodiazepine:[j]**
  - **Lorazepam 0.5–2 mg PO/SL/IV every 6 h**
- **Cannabinoid:[j]**
  - **Dronabinol 5–10 mg PO every 3–6 h**
  - **Nabilone 1–2 mg PO BID**
- **Other:**
  - **Haloperidol 0.5–2 mg PO/IV every 4–6 h[j]**
  - **Metoclopramide 10–20 mg PO/IV every 4–6 h[j]**
  - **Scopolamine transdermal patch 1 patch every 72 h**
- **Phenothiazine:[j]**
  - **Prochlorperazine 25 mg supp pr every 12 h or 10 mg PO/IV every 6 h[j]**
  - **Promethazine 25 mg supp pr every 6 h or 12.5–25 mg PO/IV (central line only) every 4–6 h[j]**
- **Serotonin 5-HT3 antagonists:[j]**
  - **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 mg PO/IV daily**
- **Steroid:[j]**
  - **Dexamethasone 12 mg PO/IV daily**

RESPONSE TO BREAKTHROUGH ANTIEMETIC TREATMENT

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

[h] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[j] See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
[y] See Principles of Managing Breakthrough (AE-C).
[z] Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 2013;21:1655-1663.

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RADIATION-INDUCED EMESIS PREVENTION/TREATMENT

EMETOGENIC POTENTIAL	TYPE OF RADIATION THERAPY	BREAKTHROUGH TREATMENT

Radiation-induced nausea/vomiting

- **Radiation therapy (RT) - upper abdomen/localized sites** →
  Start pretreatment for each day of RT treatment (order does not imply preference):[j]
  - Granisetron 2 mg PO daily
    or
  - Ondansetron 8 mg PO BID
  - ± Dexamethasone 4 mg PO daily
- **Total body irradiation (TBI)** →
  Start pretreatment for each day of RT treatment (order does not imply preference):[j]
  - Granisetron 2 mg PO daily
    or
  - Ondansetron 8 mg PO BID-TID
  - ± Dexamethasone 4 mg PO daily

→ See Breakthrough Treatment (AE-9)

- **Chemotherapy and RT (including TBI)** → See emesis prevention for chemotherapy-induced nausea/vomiting (High [AE-5], Moderate [AE-6], Low [AE-7], and Oral [AE-8])

[j] 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**
- **Behavioral therapy:**
  - **Relaxation/systematic desensitization**
  - **Hypnosis/guided imagery**
  - **Music therapy**
- **Acupuncture/acupressure**
- **Consider anxiolytic therapy:**
  - **For example, alprazolam 0.5–1 mg or 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 Primary and Breakthrough Treatments for Chemotherapy-Induced Nausea/Vomiting (Antiemesis TOC)

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

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PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS[1]

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 (IV, oral, or transdermal), duration of action of the serotonin antagonist 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 or highly emetogenic chemotherapy, 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.**

Serotonin Antagonists:

- **A serotonin antagonist 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 serotonin antagonist depends on the agent chosen and its mode of administration (IV, oral, or 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 serotonin antagonist.**
  - **When palonosetron is used as part of an antiemetic regimen that does NOT contain an NK-1 antagonist, palonosetron is the preferred serotonin antagonist.[2]**
  - **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.[3]**

[1]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.

[2]Saito M et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol 2009 Feb;10(2):115-24.

[3]Giralt SA, Mangan KF, Maziarz RT, et al. Three palonosetron regimens to prevent CINV in myeloma patients receiving multiple-day high-dose melphalan and hematopoietic stem cell transplantation. Annals of Oncology 22:939-946, 2011.

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PRINCIPLES OF MANAGING MULTIDAY EMETOGENIC CHEMOTHERAPY REGIMENS[1]

NK1 Antagonists:

- **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.**
- **Category 1 evidence is available for single-day chemotherapy regimens only with aprepitant administered orally (as a 3-day regimen) in combination with a serotonin antagonist and corticosteroid (as noted on 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 antagonist (days 1–5) and dexamethasone (20 mg days 1, 2) in patients with germline cancers treated with a 5-day cisplatin-based chemotherapy.[2]**
- **Studies investigating repeat dosing of fosaprepitant, netupitant, and rolapitant are not available.**
- **Fosaprepitant, aprepitant, and netupitant inhibit the metabolism of dexamethasone and may cause higher dexamethasone concentrations. Rolapitant does not inhibit dexamethasone metabolism.**

[1]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.

[2]Albany C, Brames MJ, Fausel C, et al. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study. J Clin Oncol 2012;30:3998-4003.

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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 antagonists:

- **Aprepitant, fosaprepitant, and netupitant inhibit the metabolism of dexamethasone, thus increasing dexamethasone serum levels when administered concomitantly. Rolapitant does not share this interaction with dexamethasone.**
- **Clinical pearl: place in therapy is for prevention of chemotherapy-induced nausea/vomiting (CINV), not treatment of CINV. Largest benefit seen in delayed CINV setting.**

Serotonin (5-HT3) antagonists:

- **Dolasetron, granisetron, and ondansetron may increase the risk of developing prolongation of the QT interval of the ECG.[1] The palonosetron drug package insert does not contain this warning.**
- **The FDA recommends a maximum of 16 mg for a single dose of intravenous ondansetron.**
- **Clinical pearl: non-sedating, most common side effects are headache and constipation. Optimal effects seen with scheduled administration, not PRN use.**

Steroid

- **The use of steroids as an antiemetic is not recommended with drugs such as aldesleukin, interferon, ipilimumab, nivolumab, and pembrolizumab.**
- **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.**
- **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.**

Atypical antipsychotic

- **Olanzapine**
  - **Avoid concomitant olanzapine prescribing with metoclopramide or haloperidol, as excessive dopamine blockade can increase the risk of extrapyramidal symptoms (EPS).**
  - **Parenteral olanzapine use with concomitant parenteral benzodiazepine use is contraindicated.**
  - **Monitor for dystonic reactions[2]**
  - **Olanzapine use has been associated with glucose dysregulation; consider monitoring serum glucose prior to therapy and as clinically indicated.**
  - **CNS depression; use olanzapine with caution in patients at risk for falls (eg, elderly, debilitated, frail) or at risk for orthostatic hypotension.**
  - **Clinical pearl: when used for the prevention of CINV (AE-5 and AE-6), consider a dose of 5 mg if the previously administered 10-mg dose caused excessive sedation.**

[1]Use caution and monitor ECG in patients with other risk factors for QT prolongation.
[2]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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PHARMACOLOGIC CONSIDERATIONS FOR ANTIEMETIC PRESCRIBING

Benzodiazepines
- CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail) or in patients at risk for dependence.
- Clinical pearl: consider for anticipatory CINV or when breakthrough CINV has an anxiety component.

Phenothiazines
- CNS depression; use caution in patients at risk for falls (eg, elderly, debilitated, frail).
- When administered parenterally, promethazine may cause severe tissue injury.
- Avoid the concomitant prescribing of any combination of prochlorperazine, promethazine, metoclopramide, or haloperidol, as excessive dopamine blockade can increase the risk of EPS.
- Monitor for dystonic reactions[2]
- Clinical pearl: promethazine has more histamine blockade than prochlorperazine and is therefore more sedating.

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[1]
  - Monitor for dystonic reactions[2]
  - Clinical pearl: metoclopramide increases gut motility and may cause diarrhea.
- 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.[1] Higher-than-recommended doses (regardless of route) and intravenous administration of haloperidol appear to be associated with a higher risk of QT prolongation.[3]
  - Monitor for dystonic reactions.[2]
  - Clinical pearl: generally, lower doses of haloperidol (see AE-8 and AE-9) 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.

[1]Use caution and monitor ECG in patients with other risk factors for QT prolongation.
[2]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.
[3]Haloperidol prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. January 2016.

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PHARMACOLOGIC CONSIDERATIONS FOR ANTIEMETIC PRESCRIBING

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.**

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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, 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 antagonist if not previously included.**
  - **Consider changing from NK1-containing regimens to olanzapine-containing regimen, or vice versa.**
  - **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 antagonist. 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. Although not necessarily likely to be effective, anecdotal and limited investigational trial data suggest it may sometimes be efficacious.**
  - **If the goal of chemotherapy is non-curative, consider other appropriate regimens, if any, that might be less emetogenic.**
  - **It may be beneficial to add an anxiolytic agent in combination with the antiemetic agents.**
- **Consider antacid therapy if patient has dyspepsia (H2 blocker or proton pump inhibitor).**

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Systemic 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. In addition, nausea and vomiting can result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of the patient's performance status and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment.[1-4] Systemic 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 are 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).[5,6] More than 90% of patients receiving highly emetogenic chemotherapy (HEC) will have episodes of vomiting. However, only about 30% of these patients will vomit if they receive prophylactic (preventive) antiemetic regimens before treatment with HEC.[5,7,8] Although vomiting can often be prevented or substantially decreased by using prophylactic antiemetic regimens, nausea is much harder to control.[9-11]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis are intended to provide an overview of the treatment principles for preventing chemotherapy- or RT-induced vomiting and nausea, and recommendations for antiemetic prophylaxis according to the emetogenic potential of anti-tumor therapies. The NCCN Guidelines® for Antiemesis are updated at least once a year by a multidisciplinary panel of experts. For the 2016 update, the NCCN Panel added a new section to the algorithm on *Pharmacologic Considerations for Antiemetic Prescribing* in addition to other updates (see *Updates* in the NCCN Guidelines for Antiemesis). Netupitant and rolapitant are new antiemetic agents that were added to the NCCN Guidelines for the 2015 updates; these agents are providing patients with more options for chemotherapy-induced nausea and vomiting (CINV) when used appropriately in NCCN-recommended preventive antiemetic regimens.[12]

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for Antiemesis, an electronic search of the PubMed database was performed to obtain key literature in antiemesis, published between September 1, 2014 and September 15, 2015 using the following search terms: antiemetic chemotherapy, antiemetics. 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 PubMed search resulted in 171 citations and their potential relevance was examined. 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 webpage.

Pathophysiology of Emesis

Vomiting results from stimulation of a multistep reflex pathway controlled by the brain.[5,13] 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.[14]

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.[15,16] 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.[17]

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.[18] 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.[9,19-23] Vomiting and nausea are related; however, they may occur via different mechanisms.[24,25] 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.[11] 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).[23]

Types of Nausea and/or Vomiting

Chemotherapy-Induced Nausea and/or Vomiting

Nausea and/or vomiting induced by antineoplastic agents is often referred to as CINV; it is commonly classified as acute, delayed, anticipatory, breakthrough, or refractory. *Acute-onset* nausea and/or vomiting usually occur within a few minutes to several hours after drug administration and commonly resolve within the first 24 hours. The intensity of acute-onset emesis generally peaks after 5 to 6 hours. The occurrence of acute emesis is high 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.[26]

Delayed-onset CINV develops in patients more than 24 hours after chemotherapy administration.[27,28] 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.[29,30] 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.[31]

Breakthrough CINV refers to nausea and/or vomiting that occurs despite prophylactic treatment and/or requires rescue with antiemetic agents.[32] *Refractory* CINV refers to nausea and/or vomiting that occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles.[33]

Radiation-Induced Nausea and/or Vomiting

Patients receiving whole body or upper abdominal RT have the greatest likelihood of developing nausea and/or vomiting.[32,34,35] 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.[32,36]

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.[14,37-40]

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.[7] The classification was updated by Grunberg and colleagues; it divides chemotherapeutic agents into 4 levels according to the percentage of patients who experience acute emesis when they do not receive antiemetic prophylaxis.[10,41] This classification is used in these NCCN Guidelines and is updated each year by the NCCN Panel with recently introduced drugs. Experts representing the panels of all of the published antiemetic treatment guidelines met to prepare a single consensus document. Although this process is ongoing, the consensus guidelines have been published.[8,42] 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—90% or more of patients experience acute emesis;
- Moderate emetic risk—30% to 90% of patients experience acute emesis;
- Low emetic risk—10% to 30% of patients experience acute emesis;
- Minimal emetic risk—fewer than 10% of patients experience acute emesis.

In addition, the NCCN Guidelines attempt to define antiemetic regimens for particular chemotherapy drugs that cover the entire duration of time

a patient is at risk for nausea and/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 antineoplastic agents.[10]

Types of Antiemetic Therapies

In general, to provide maximal protection against chemotherapy-induced emesis, antiemetic therapy should be initiated before chemotherapy. The antiemetic therapy should also be continued for the same length of time as the duration of the emetic activity of the chemotherapeutic agent being used. However, daily use of antiemetics is not recommended for some therapeutic agents that are taken long term (eg, imatinib, erlotinib, gefitinib). Antiemetic agents can be administered by the oral, rectal, intravenous, intramuscular, or transdermal route. Oral and intravenous 5-HT3 antagonists have equivalent efficacy when used at the appropriate doses.[8,36] For patients at risk for CINV or unable to swallow or digest tablets because of emesis, intravenous antiemetics should be used. In selected patients who are unable to swallow, transdermal antiemetics may be of value. Although studies may show drugs to be equally effective on a population basis, individual patients may respond differently. Therefore, some drug options may be based on a patient's individual experience.

Serotonin (5-HT3)-Receptor Antagonists

Ondansetron, Granisetron, and Dolasetron

All of the 5-HT3–receptor 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.[43-59] Ondansetron, granisetron, and dolasetron mesylate are first-generation 5-HT3–receptor antagonists. Many clinical trials have compared ondansetron, granisetron, dolasetron mesylate, and palonosetron. These trials have used various doses, routes, and schedules of administration.[60-77] A meta-analysis found no difference in efficacy between the first-generation 5-HT3 antagonists.[78] 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.[79] The most recent meta-analysis of randomized controlled trials comparing palonosetron with the first-generation 5-HT3 antagonists demonstrated that palonosetron was significantly more effective in preventing acute and delayed nausea and vomiting for both HEC and moderately emetogenic chemotherapy (MEC).[80] Based on this meta-analysis and clinical practice, some NCCN Panel Members feel that palonosetron should be the preferred 5-HT3 antagonist for both HEC and MEC. However, the majority of the NCCN Panel recently decided that palonosetron is only preferred for MEC (see *Palonosetron* in this Discussion).[61]

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.[81] Another study found that 5-HT3 antagonists (except palonosetron, which was not studied) were not more effective than prochlorperazine for preventing delayed emesis.[23] A single dose of intravenous palonosetron appears to be effective for preventing both delayed and acute emesis.

The NCCN Guidelines recommend palonosetron as a preferred 5-HT3 antagonist for MEC when used with dexamethasone but without an NK1 receptor antagonist (see *Principles of Managing Multiday Emetogenic*

Chemotherapy Regimens in the NCCN Guidelines for Antiemesis).[61] Several studies[82-85] have evaluated the efficacy of a 3-drug combination regimen with palonosetron, dexamethasone, and NK1 antagonists 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.

Ondansetron and granisetron can be delivered orally or intravenously. 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.[86,87] 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.[86,88,89] 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.[89] Oral administration of ondansetron poses less of a risk of cardiac arrhythmias than intravenous administration.[86]

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.[90,91] A recent phase 4 trial assessed a transdermal granisetron regimen versus a palonosetron regimen for patients receiving MEC; transdermal granisetron was not inferior to palonosetron for preventing nausea and vomiting in the acute stage.[92]

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.[93]

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).[86,87,94-101] However, the palonosetron package insert does not contain this warning. 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.[86] 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.[87,98,102] Routine ECG monitoring during treatment with regimens that include 5-HT3–receptor 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.[86,87]

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.[45] Data suggest that palonosetron is associated with prolonged inhibition of the 5-HT3 receptor and thus differs from ondansetron, granisetron, and dolasetron.[103,104] By suppressing cross talk between 5-HT3 and NK1 signaling pathways, palonosetron may indirectly inhibit substance P.

Several large, multicenter, double-blind, 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.[60-63] In these studies, the primary efficacy endpoint was complete response (CR), defined as having no emesis and no rescue treatments.

A study in patients receiving MEC (N = 569 evaluable) showed that a single dose of palonosetron (0.25 mg intravenous) was comparable to a single dose of dolasetron (100 mg intravenous) for the prevention of acute CINV (CR rate 63% vs. 53%, respectively). Moreover, intravenous palonosetron was superior to dolasetron in preventing delayed emesis (CR rate 54% vs. 39%; *P* = .004).[62] Approximately 60% of patients in the palonosetron arms and 70% in the dolasetron arm had received anthracycline in combination with cyclophosphamide; only 6% and 5% of patients, respectively, received concomitant corticosteroids.[62] In another 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.[63] 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.[86]

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 antagonists were not used in this trial.[60] 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 antagonists 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).[61] However, the NCCN Panel does not recommend palonosetron as the preferred 5-HT3 antagonist in regimens for HEC, because an NK1 antagonist was not used in this study and it is unknown if a single dose of palonosetron would still be found superior to a single dose of granisetron in the presence of an NK1 antagonist. However, in the absence of an NK1 antagonist, such as in many MEC regimens, the NCCN panel recognizes palonosetron as the preferred 5-HT3 antagonist for the prevention of acute and delayed emesis (see *Moderate Emetic Risk Intravenous Chemotherapy—Acute and Delayed*

Emesis Prevention in the NCCN Guidelines for Antiemesis; also see *Prevention of Acute and Delayed Emesis* in this Discussion). 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 5-HT3 antagonists for preventing delayed nausea.[21,60-63] 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 NCCN Guidelines for Antiemesis).[105]

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 antagonist-containing regimens, which are discussed in this section; and 2) olanzapine-containing regimens. NK1 antagonist regimens include aprepitant, fosaprepitant, rolapitant, or netupitant.

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–receptor antagonists and the corticosteroid dexamethasone to prevent both acute and delayed cisplatin-induced emesis.[106-108] A randomized phase 3 trial compared a standard antiemetic regimen (ondansetron 32 mg intravenous and oral dexamethasone) with or without the addition of aprepitant in patients receiving emetogenic chemotherapy with high-dose cisplatin (N = 521 evaluable). The addition of aprepitant was significantly more effective than the 2-drug regimen in controlling both acute (CR rate 89% vs. 78%; $P < .001$) and delayed emesis (CR rate 75% vs. 56%; $P < .001$).[107] Another similarly designed randomized phase 3 study (N = 523 evaluable) also showed a significant benefit of adding aprepitant to ondansetron and dexamethasone compared with the 2-drug regimen alone for controlling both acute (CR rate 83% vs. 68%; $P < .001$) and delayed emesis (CR rate 68% vs. 47%; $P < .001$).[108] A pooled analysis of data combined from these two phase 3 trials found that the aprepitant regimen was particularly beneficial in improving CR rates for patients receiving concomitant emetogenic therapy with doxorubicin and/or cyclophosphamide, along with high-dose cisplatin therapy.[106]

A meta-analysis (of 7 randomized controlled trials) of patients receiving HEC found that aprepitant used alone or with standard therapy did not significantly increase protection from acute emesis or nausea; however, for delayed emesis and nausea, aprepitant was associated with significantly increased protection compared with control.[109] A larger meta-analysis (of 17 randomized controlled trials) evaluated outcomes with standard antiemetic therapy with or without aprepitant in patients receiving MEC or HEC. The addition of aprepitant was associated with significantly improved CR (no emetic episodes and no rescue medication) rate compared with standard therapy (72% vs. 54%; $P<.001$) during the overall time frame from 0 to 120 hours after starting chemotherapy.[110] The significant increase in CR rate associated with aprepitant was observed for both the acute and delayed periods. Based on data from 3 trials that reported on infectious complications, both aprepitant and standard therapy 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.[110] A randomized phase 3 trial (N = 866) showed that an aprepitant regimen was more effective than a standard regimen for 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.[111] The aprepitant regimen included ondansetron and dexamethasone; the standard regimen included ondansetron and dexamethasone.

A 3-drug antiemetic regimen with palonosetron, dexamethasone and aprepitant has also been investigated in patients undergoing treatment with HEC. A phase II 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), 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).[84] 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%).[84] A phase II study evaluated a higher dose of palonosetron (0.75 mg intravenous day 1) with 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%.[85] 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.[85]

A phase 3 trial added oral aprepitant to a standard regimen of oral granisetron and oral dexamethasone in patients receiving MEC. The data showed that the addition of aprepitant improved control of nausea, vomiting, and quality of life when compared with granisetron and dexamethasone.[112] A phase II study (N = 58) found that combining palonosetron (0.25 mg intravenous day 1), aprepitant (125 mg day 1; 80 mg days 2, 3), and dexamethasone (12 mg day 1; 8 mg days 2, 3) was effective for 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.[82] A phase II study in patients with breast cancer (N = 41) receiving MEC also found that a single-day regimen of palonosetron (0.25 mg intravenous), 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.[83]

A randomized double-blind phase 3 trial compared the effectiveness of combining ondansetron (8 mg oral twice daily [BID] day 1), aprepitant (125 mg day 1; 80 mg days 2, 3) and dexamethasone (12 mg day 1) versus standard therapy with ondansetron (8 mg oral BID days 1–3) and dexamethasone (20 mg day 1) in patients receiving MEC (N=585).[113] Dexamethasone was only given on day 1 for both treatment groups. A significantly higher proportion of patients in the 3-drug regimen with aprepitant had no vomiting compared with the standard group (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 aprepitant group (69% vs. 56%; *P* < .001) during the overall time period. The significant improvement in antiemetic activity (with regards to no emesis as well as CR rate) in the 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.[113]

Oral aprepitant is approved by the FDA 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).[114] An intravenous version of aprepitant (fosaprepitant dimeglumine), which can be given on day 1 only, is also approved by the FDA. Intravenous fosaprepitant is given 30 minutes before chemotherapy on day 1 only, per the package insert. 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.[115,116] Note that the dexamethasone dosing is slightly different on days 3 and 4 (8 mg oral/intravenous twice daily) 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 standard regimen with 3-day oral aprepitant in a randomized study.[117] There are no studies showing efficacy or safety of chronic dosing with aprepitant. It is possible that the drug-drug interaction profile may change with chronic dosing.

Drug Interactions

Aprepitant is simultaneously a substrate, moderate inducer, and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4); aprepitant also induces CYP2C9.[118] Thus, aprepitant can alter the metabolism of certain drugs and change their plasma concentrations (ie, areas under the curve [AUCs]). These interactions are more significant with orally administered forms of these drugs than with intravenous forms because of first-pass metabolism. Patients should not take aprepitant with pimozide or astemizole; these combinations are contraindicated, because they may cause serious or life-threatening reactions (see the aprepitant package insert). Chemotherapeutic agents known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. In clinical trials, aprepitant was used concurrently with etoposide, vinorelbine, or paclitaxel; although chemotherapy doses were not adjusted for potential drug interactions in phase 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

Netupitant is a highly selective NK1 receptor antagonist 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.[119-122] Similar to aprepitant, fosaprepitant, and rolapitant, netupitant improves control for delayed emesis when compared with traditional antiemetic regimens. For patients receiving HEC and MEC, the NCCN Panel recommends several options for prophylactic antiemetic regimens; NEPA combined with dexamethasone is recommended (category 2A) for acute and delayed emesis prevention based on the FDA approval and randomized trials.

A randomized trial in patients receiving HEC assessed dexamethasone plus 3 varying dose levels of prophylactic oral NEPA compared with oral palonosetron plus dexamethasone.[119] 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 MEC assessed NEPA plus dexamethasone compared with palonosetron plus dexamethasone.[121] More patients in the NEPA arm had CR during the delayed phase when compared with control (76.9% vs. 69.5%; P = .001). In addition, patients in the NEPA arm also had more CR 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). 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.

Rolapitant

Rolapitant is another oral NK1 receptor antagonist 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.[123,124] In the phase 3 trials assessing a prophylactic 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) twice daily on days 2 to 4.[124] More patients receiving the 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 1.6; 95% CI, 1.3–2.1; P = .0001). For patients receiving HEC, the NCCN Panel recommends (category 1) several prophylactic antiemetic regimens; a 5-HT3 antagonist, dexamethasone, and oral rolapitant regimen is recommended for acute and delayed emesis prevention based on the FDA approval and the phase 3 randomized trial.[124]

A phase 3 trial assessed a prophylactic rolapitant-containing regimen for MEC; most patients also received granisetron (2 mg orally) and dexamethasone (20 mg orally) on day 1 and granisetron (2 mg orally) on days 2 to 3.[123] Significantly more patients receiving the rolapitant-containing regimen had CRs in the delayed phase than did those receiving granisetron/dexamethasone alone (475 [71%] vs. 410 [62%]; odds ratio 1.6; 95% CI, 1.2–2.0; P = .0002). For patients receiving MEC, the NCCN Panel recommends several prophylactic antiemetic regimens; a 5-HT3 antagonist/dexamethasone (category 1) with (or without) oral rolapitant (category 1) regimen is recommended for acute and delayed emesis prevention based on the FDA approval and phase 3 randomized trial.[123]

If rolapitant is given on day 1 for either HEC or MEC, no further NK1 antagonist is needed on days 2 and 3. Similar to the other NK1 antagonists, 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 aprepitant, fosaprepitant, and netupitant.

Other Non–5-HT3–Receptor Antagonists

Before the advent of the 5-HT3–receptor antagonists, the available antiemetic agents included phenothiazines,[125] substituted benzamides,[126,127] antihistamines,[128] butyrophenones,[129] corticosteroids,[130-132] benzodiazepines,[133,134] and cannabinoids.[135,136] Most of these non–NK1 antagonists used to prevent chemotherapy-induced emesis are classified as dopamine antagonists, serotonin antagonists, and other antagonists. Based on recent data, the NCCN Panel recently added olanzapine-containing regimens as another option for antiemesis. 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.[137] 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 receptor antagonist–containing regimens and non-5-HT3 receptor antagonist regimens. Although data *suggested* that dexamethasone was superior to 5-HT3–receptor 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.[138,139] The first trial was conducted in chemo-naive patients receiving 50 mg/m^2 or more of cisplatin, which is considered HEC.[138] 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%; 60.9%, 69.1%, and 61.0%; 78.5%; and 66.9%, 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 is considered MEC.[139] 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 should be the preferred 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 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 antagonists. The NCCN Panel felt that all patients would derive optimal benefit from this dose of dexamethasone regardless of use of CYP3A4 inhibitors or not. The studies by the Italian Group were done before the NK1 receptor antagonists were available, and dose finding studies for dexamethasone on day 1 in combination with 5-HT3–receptor antagonists and NK1 receptor antagonists have not been done.[138,139]

Olanzapine

Olanzapine (thienobenzodiazepine) 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.[18] Olanzapine-containing antiemetic regimens were reported as effective for preventing acute and delayed emesis based on phase 3 trials, phase 2 trials and a meta-analysis.[18,140-148] The NCCN Panel recommends (category 2A) an olanzapine-containing regimen for both HEC and MEC based on the phase 3 and phase 2 trials.

A randomized phase 3 study evaluated the effectiveness of an olanzapine (10 mg oral days 1–4) regimen versus an aprepitant (125 mg oral day 1, 80 mg oral days 2, 3) regimen with dexamethasone 8 mg on days 2–4 for preventing acute and delayed emesis in patients (N=251) receiving HEC (cisplatin, or cyclophosphamide plus doxorubicin regimens); both treatment arms included palonosetron (0.25 mg intravenous) and dexamethasone administered on day 1.[147] The CR (no emesis, no rescue) rate was similar between the olanzapine and 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 aprepitant regimen.[147]

A recent systematic review summarized the phase 1 and 2 studies of olanzapine for preventing acute and delayed emesis.[18] Across 4 studies

(201 patients), the CR was 97.2%, 83.1%, and 82.8 % for the acute, delayed, and overall phases, respectively. An olanzapine-containing regimen was reported as effective for preventing acute and delayed emesis in a phase II trial in patients (N = 30) who received cyclophosphamide, doxorubicin, and/or cisplatin.[141] Other studies have also showed the value of olanzapine for delayed, refractory, and breakthrough emesis and nausea.[142-145,149] Several studies have demonstrated the activity of olanzapine combined with a 5-HT3 receptor antagonist and dexamethasone in controlling emesis in patients receiving emetogenic chemotherapy regimens.[146-148] A phase II study evaluated the combination of olanzapine with palonosetron and dexamethasone in patients receiving HEC and MEC regimens (N=40).[146] Among patients undergoing HEC (n = 8), the CR rate was 75% during the overall study period (0–120 hours); the CR rates for the acute phase (0–24 hours) and delayed phase (24–120 hours) were 100% and 75%, respectively. The corresponding CR rates among the patients receiving MEC (n = 32) were 72%, 97%, and 75%, respectively.[146]

Common side effects with olanzapine included 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).[150] Parenteral olanzapine use combined with parenteral benzodiazepine use is contraindicated. To avoid excessive dopamine blockade, olanzapine should not be administered concurrently with metoclopramide or haloperidol. In 100 patients receiving concurrent chemoradiation, preliminary data suggested that an olanzapine antiemetic regimen may be equivalent to a fosaprepitant regimen for controlling emesis and appeared to be better than a fosaprepitant regimen (71% overall had no nausea for olanzapine vs. 41% overall for fosaprepitant).[151]

Treatment Issues

As new data on the use of antiemetics in patients receiving chemotherapy 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. For the 2016 update, the NCCN Panel added a new section to the algorithm on pharmacologic considerations 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.[10] 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 chemotherapy.

In addition to using antiemetic regimens, patients can adjust their eating habits and adopt other lifestyle measures that may alleviate nausea and vomiting (see *Eating Hints: Before, During, and After Cancer Treatment* from the National Cancer Institute).[152] Suggestions include eating small frequent meals, food that is easy on the stomach, full liquid foods, and food at room temperature; patients can also avoid foods that make them feel nauseous.

Prevention of Acute and Delayed Emesis

To prevent acute emesis, antiemetic therapy should start before the administration of chemotherapy and 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 chemotherapy of different emetogenic potential (ie, high, moderate, low, and minimal). Prophylactic antiemetics should be administered before chemotherapy. The recommendations for prophylactic antiemetic treatment include drug dosages. The guidelines reflect accumulating experience with the 5-HT3 antagonists, 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 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 anthracycline plus cyclophosphamide (AC) combinations at any dose (eg, doxorubicin or epirubicin with cyclophosphamide). Although most of these drugs are also considered highly emetogenic by the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) guidelines,[8] the NCCN Guidelines for highly, moderately, low, and minimally emetogenic agents differ slightly based on the experience and expertise of the panel members.[153,154]

The NCCN Guidelines recommend several different antiemetic regimen options for patients receiving highly emetogenic drugs. Recommended antiemetic regimens contain 5-HT3 antagonists, dexamethasone, NK1 antagonists (such as aprepitant [or fosaprepitant], rolapitant, or netupitant), and olanzapine. Lorazepam and an H2 blocker or a proton pump inhibitor may also be added to all of these regimens.[32,36,107] Category 1 regimens for day 1 therapy include those containing dexamethasone, a 5-HT3 antagonist, and one of the following: aprepitant, fosaprepitant, or rolapitant. Alternative antiemetic regimens for highly emetogenic agents on day 1 include: 1) NEPA and dexamethasone; or 2) olanzapine, palonosetron, and dexamethasone. Note that the regimens and doses are often modified on days 2 to 4 after chemotherapy.

Although it is not recommended as a single agent, lorazepam is a useful adjuvant because it decreases anxiety.[36,134] Lorazepam is also recommended for patients who are at risk for anticipatory nausea and/or vomiting (see *Anticipatory Emesis Prevention/Treatment* in the NCCN Guidelines for Antiemesis). Antacid therapy (eg, proton pump inhibitors,

H2 blockers) should be considered if patients have dyspepsia, because patients sometimes have difficulty discriminating heartburn from nausea. If appropriate, lorazepam (0.5–2 mg every 6 hours on days 1–4; either oral, 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 dose can be oral or intravenous. Note that 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.[61] 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).[147]

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.[155] Palonosetron was not assessed in these studies. The NCCN Guidelines do not recommend a 5-HT3 antagonist on days 2 to 4 for HEC, although some feel this may be useful if palonosetron or a granisetron patch was not used.

The NCCN Guidelines recommend several antiemetic regimens for intravenous MEC, including: 1) dexamethasone and a 5-HT3 antagonist with or without NK1 antagonists such as aprepitant, fosaprepitant, netupitant or rolapitant; or 2) olanzapine, palonosetron, and dexamethasone. If needed, lorazepam and either an H2 blocker or a proton pump inhibitor may be added to these regimens.[5] As per high emetic risk prevention, an NK1 antagonist 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 + 5-HT3 antagonist alone. Intravenous fosaprepitant 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, palonosetron is preferred when an NK1 antagonist is not included, as previously mentioned.[61] Similar to the setting of HEC regimens, an alternative antiemetic regimen for patients receiving MEC includes: 1) olanzapine (10 mg oral days 1–3); 2) palonosetron (0.25 mg intravenous day 1 only); and 3) dexamethasone (20 mg intravenous day 1 only).[146,147]

The antiemetic regimen for low emetogenic intravenous drugs includes orally administered 5-HT3–receptor antagonists or agents such as dexamethasone, prochlorperazine, or metoclopramide (see the NCCN Guidelines for Antiemesis). Lorazepam and an H2 blocker or a proton pump inhibitor may also be added to all of these regimens. When using prochlorperazine or metoclopramide, patients should be monitored for dystonic reactions.[156-158] Diphenhydramine can be used for the treatment of dystonic reactions.[159,160] Benztropine may be used in patients who are allergic to diphenhydramine.[157]

The emetogenic potential of oral chemotherapeutic agents is shown in the NCCN Guidelines. Oral antiemetic prophylaxis is recommended for

the following oral agents: altretamine, busulfan (≥ 4 mg/d), ceritinib, crizotinib, cyclophosphamide (≥ 100 mg/m^2/d), estramustine, etoposide, lenvatinib, lomustine (single day), mitotane, olaparib, panobinostat, procarbazine, 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 agents, recommended prophylaxis includes oral 5-HT3 antagonists (such as granisetron, ondansetron, dolasetron); lorazepam and an H2 blocker or a proton pump inhibitor may also be added.. For low or minimal emetic risk oral agents, recommended oral agents are given on an as-needed basis only (ie, PRN) and include oral 5-HT3 antagonists, metoclopramide, prochlorperazine, or haloperidol. Lorazepam and an H2 blocker or a proton pump inhibitor may also be added to all of these regimens.

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.[9,19,20,24] Patients rank nausea as more of a problem than vomiting.[9] Data suggest that rolapitant and netupitant are effective at decreasing delayed nausea.[119,121,123,124] Palonosetron is the preferred 5-HT3 antagonist for preventing delayed nausea associated with MEC as previously discussed.

Delayed Emesis

The best management for delayed emesis is prevention.[161] For chemotherapeutic agents with high emetogenic potential, the prophylactic treatment on days 2 to 4 depends on which antiemetics were used before chemotherapy. Fosaprepitant, rolapitant, or netupitant are used on day 1 only. If aprepitant was used on day 1, then aprepitant is continued on days 2 and 3. Dexamethasone is continued on days 2 to 4 for all regimens, except for the olanzapine-containing regimen; the dexamethasone dose varies slightly among the regimens. However, 5-HT3 antagonists are given on day 1 only.

The antiemetic regimens in the NCCN Guidelines include different options on days 2 to 3 for MEC.[32,36,161] Postchemotherapy prevention depends on which antiemetics were used before chemotherapy. If aprepitant was used on day 1, then aprepitant is continued on days 2 and 3; however, fosaprepitant, rolapitant, or netupitant are not given on days 2 and 3. Palonosetron is only administered on day 1.[63] Antiemetic therapy on days 2 and 3 may just be single agents. There are several possible regimens on days 2 to 3, including: 1) aprepitant (if used on day 1) with or without dexamethasone; 2) dexamethasone only; 3) ondansetron, granisetron, or dolasetron only (if no NK1 antagonist was given on day 1); or 4) olanzapine only.[161] Each of these regimens may also include lorazepam and an H2 blocker or a proton pump. It is important to note that the doses of both aprepitant (80 mg oral) and dexamethasone (8 mg oral or intravenous) are decreased when used on days 2 to 3 (when compared with the doses given on day 1).

Breakthrough Treatment

Breakthrough nausea or emesis presents a difficult situation, because refractory ongoing nausea and/or vomiting is often challenging to reverse (see *Principles for Managing Breakthrough Emesis* in the NCCN Guidelines for Antiemesis). Generally, it is much easier to prevent nausea and/or vomiting than to treat it. 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.[32] 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 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 an NK1-containing regimen to an olanzapine-containing prophylactic regimen, or vice versa, prior to the next cycle of chemotherapy. Olanzapine is possibly more effective than standard NK1-antagonist–containing regimens for preventing nausea.[18,147,148]

Miscellaneous agents (eg, haloperidol, metoclopramide, olanzapine, scopolamine transdermal patch), corticosteroids, and agents such as lorazepam may be incorporated for breakthrough treatment. In a randomized double-blind 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).[162,163] 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.[163] Thus, olanzapine was more effective in controlling breakthrough emesis and nausea compared with metoclopramide in this patient population.

Dronabinol and nabilone (which are cannabinoids) are approved by the FDA for nausea and vomiting in patients who have not responded to conventional antiemetic agents. Before administering the next cycle of chemotherapy, the patient should be reassessed for other possible non-chemotherapy-related reasons for breakthrough emesis with the current cycle (eg, brain metastases, electrolyte abnormalities, tumor infiltration of the bowel or other GI abnormality, and other comorbidities; see *Principles for Managing Breakthrough Emesis* and *Principles of Emesis Control for the Cancer Patient* in the NCCN Guidelines for Antiemesis). Adequate hydration or fluid repletion should be ensured, and any possible electrolyte abnormalities should be assessed and corrected.

In addition, before the next cycle of chemotherapy, the antiemetic regimen (both the day 1 and postchemotherapeutic) that did not protect the patient during the present cycle should be assessed and alternatives should be considered (see *Principles for Managing Breakthrough Emesis* in the NCCN Guidelines for Antiemesis). Because patients sometimes have difficulty discriminating heartburn from nausea, use 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 chemotherapy.[34,164,165] When RT is combined with chemotherapy, prophylaxis is dictated by the emetogenic potential of the chemotherapy regimen. 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.[34] A meta-analysis suggests that 5-HT3 antagonists are the preferred agents for preventing RT -induced vomiting.[166]

Patients undergoing RT to the upper abdomen may receive antiemetic prophylaxis with oral ondansetron or oral granisetron, with or without oral dexamethasone.[8,34] A randomized study compared oral ondansetron with placebo in patients receiving daily fractionated radiotherapy including the abdomen. In this study, 67% of patients given ondansetron had complete control of emesis compared with 45% of patients who received placebo (*P* < .05).[167] A study showed that the

addition of oral dexamethasone (4 mg daily) to the ondansetron regimen decreases emesis and nausea, although the effect is modest.[168] Another randomized study in patients receiving radiotherapy to the upper abdomen found that oral granisetron decreased emesis and nausea when compared with placebo.[169]

Patients undergoing total body irradiation may receive antiemetic prophylaxis with either ondansetron or granisetron; either agent can be given with or without oral dexamethasone.[8,34,170] 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 NCCN Guidelines for Antiemesis).

Anticipatory Nausea and/or Vomiting

About 20% of patients develop anticipatory nausea and/or vomiting. 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.[8] 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.[32,171,172] Behavioral therapy has been used in patients with anticipatory nausea and/or vomiting.[173-178] Systematic desensitization may also be helpful.[174] Hypnosis with guided imagery is another behavioral technique that has shown some success in treating this condition.[175]

The antianxiety agents, lorazepam and alprazolam, have been combined with antiemetics for anticipatory nausea and/or vomiting.[172,179,180] The usual starting dose of alprazolam for anxiety is 0.5 to 1 mg orally (or lorazepam 0.5–2 mg orally), beginning on the night before treatment and then repeated the next day 1 to 2 hours before chemotherapy begins. In elderly patients, patients with debilitating disease, and patients with advanced liver disease, the usual starting dose of alprazolam or lorazepam is 0.5 mg orally for treatment of anxiety (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 alprazolam therapy.

Principles of Managing Multiday Emetogenic Chemotherapy Regimens

Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea and/or vomiting based on the emetogenic potential of the individual chemotherapy agents and their sequence.[32,181-185] 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. General principles for managing multiday emetogenic chemotherapy regimens recommended by the NCCN Panel are described in the algorithm (see *Principles of Managing Multiday Emetogenic Chemotherapy Regimens* in the NCCN Guidelines for Antiemesis).

5-HT3–Receptor Antagonists

For antiemetic prophylaxis of multiday emetogenic chemotherapy regimens (eg, cisplatin-containing regimens), the combination of a 5-HT3 antagonist with dexamethasone has been the standard

treatment.[8,32] 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 an antiemetic is not recommended when using treatment regimens containing drugs that elicit an immune response such as aldesleukin, interferon, ipilimumab, nivolumab, or pembrolizumab.[186]

A 5-HT3 receptor antagonist should be administered each day before the first dose of MEC or HEC. Intravenous palonosetron may be used before the start of a 3-day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT3–receptor antagonists.[187,188] Repeat dosing of palonosetron (0.25 mg intravenous) is likely to be safe, based on the dose ranging phase II trial and the 3 phase 3 trials using palonosetron as a single fixed dose (0.75 mg intravenous).[60,62,63,189] 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.[190] 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).[105] 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.[187] A recent review also cited the value of palonosetron for patients receiving multiday chemotherapy.[191] Further studies are needed to define whether a need exists for repeat dosing of palonosetron in the setting of multiday chemotherapy.

NK1 Antagonists

The potential role of NK1 antagonists in the antiemetic management of multiday chemotherapy regimens has been investigated in several studies.[124] In one study, the addition of 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, and aprepitant and dexamethasone were given for an additional 2 days following chemotherapy.[192] 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.[192] In a multicenter phase II study, an extended 7-day regimen with aprepitant (125 mg oral day 1, 80 mg oral days 2–7) combined with a 5-HT3 receptor antagonist (days 1–5) and dexamethasone (8 mg oral days 1–8) was evaluated in patients with germ line tumors undergoing chemotherapy cycles with 5-day cisplatin-based regimens (N = 50).[193] 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. Over 80% of patients had no emesis on any given day of any given chemotherapy cycle. No unexpected or serious adverse events were reported.[193]

In a randomized phase 3 trial (double-blind, placebo-controlled cross-over), the efficacy of adding aprepitant (vs. placebo) to an antiemetic regimen with 5-HT3 receptor antagonist and dexamethasone was evaluated in patients with testicular cancer undergoing 2 cycles of a 5-day cisplatin combination chemotherapy regimen (n = 69 evaluable).[194] Patients were randomized to receive 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 aprepitant or placebo for cycle 1. Palonosetron was excluded from the options for 5-HT3 antagonists due to its longer half-life.[194] 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 aprepitant compared with placebo (42% vs. 13%; $P < .001$). The CR rates were also higher with aprepitant during the acute phase (days 1–5; 47% vs. 15%; $P<.001$) and delayed phase (days 6–8; 63% vs. 35%; $P<.001$).[194] 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 aprepitant compared with placebo was reported.[194]

Aprepitant 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, aprepitant should be administered 125 mg orally 1 hour prior to chemotherapy on day 1, along with a 5-HT3 receptor antagonist and dexamethasone. Aprepitant 80 mg should be administered daily on days 2 and 3 after the start of chemotherapy along with dexamethasone.[181] Repeated dosing of 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.[181,194] Based on smaller studies, aprepitant 80 mg may be safely administered beyond day 3 of initiating chemotherapy.[114,193] Alternatively, for HEC regimens, 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, netupitant, or rolapitant.

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