

ONCOLOGY SUPPORTIVE CARE

CHRISTOPHER T. ELDER, PHARM.D., BCOP

LLOYD L. GREGORY SCHOOL OF PHARMACY
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Learning Objectives

1. Identify, assess, and recommend appropriate pharmacotherapy for managing common complications of cancer chemotherapy, including nausea and vomiting, myelosuppression and the appropriate use of growth factors, infection, anemia and fatigue, cardiotoxicity, and extravasation injury.
2. Assess and recommend appropriate pharmacotherapy for managing cancer-related pain.
3. Assess and recommend appropriate pharmacotherapy for managing oncologic emergencies, including hypercalcemia, tumor lysis syndrome, and spinal cord compression.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 50-year-old man is in the clinic to receive his third cycle of R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], prednisone, and rituximab) for non-Hodgkin lymphoma. He is very anxious, with nausea and vomiting lasting for about 12 hours after his previous cycle of chemotherapy. The antiemetic regimen he received for his previous cycle of chemotherapy was granisetron 1 dose plus dexamethasone 1 dose administered 30 minutes before chemotherapy. Which regimen is most appropriate for the patient to receive on day 1 of the next cycle of chemotherapy?
 - A. Granisetron 1 dose plus dexamethasone 1 dose administered 30 minutes before chemotherapy.
 - B. Dolasetron 1 dose plus dexamethasone 1 dose plus aprepitant 1 dose administered 30 minutes before chemotherapy.
 - C. Netupitant/palonosetron 1 dose plus dexamethasone 1 dose plus lorazepam 1 dose administered 30 minutes before chemotherapy.
 - D. Metoclopramide 1 dose plus dexamethasone 1 dose plus aprepitant 1 dose administered 30 minutes before chemotherapy.
2. A 65-year-old man with metastatic non-small cell lung cancer is brought to the clinic by his family because he is lethargic and fatigued. Pertinent laboratory values include serum calcium concentration 12 mg/dL and albumin concentration 2 g/dL. Which therapy is best for this patient's lethargy and fatigue as the result of hypercalcemia of malignancy?
 - A. Calcitonin 4 units/kg every 12 hours.
 - B. Furosemide 20 mg orally.
 - C. Dexamethasone 10 mg orally two times a day.
 - D. Zoledronic acid 4 mg intravenously.
3. A 20-year-old man was recently given a diagnosis of acute myeloid leukemia. He has an elevated white blood cell count (WBC), and he will receive chemotherapy tomorrow. Which is the best prevention strategy for tumor lysis syndrome (TLS)?
 - A. Hydration with 5% dextrose (D₅W), 1 L before chemotherapy, plus allopurinol 300 mg/day.
 - B. Hydration with D₅W, 100 mL/hour starting at least 24 hours before chemotherapy, plus allopurinol 300 mg/day.
 - C. Hydration with normal saline 250 mL/hour starting at least 24 hours before chemotherapy plus allopurinol 300 mg/day.
 - D. Hydration with normal saline 100 mL/hour starting at least 24 hours before chemotherapy plus sodium bicarbonate 500 mg orally every 6 hours.
4. An 18-year-old man is about to begin chemotherapy with curative intent for acute lymphoblastic leukemia. On today's complete blood cell count (CBC), his hemoglobin (Hgb) is 7 g/dL, and he is experiencing fatigue. Which is the best treatment recommendation?
 - A. Initiate epoetin.
 - B. Administer transfusion of packed red blood cells (RBCs).
 - C. Delay chemotherapy treatment until Hgb recovers.
 - D. Reduce chemotherapy dosages to prevent further decreases in Hgb.

Questions 5–7 pertain to the following case.

A patient received her fourth cycle of chemotherapy with paclitaxel/carboplatin for ovarian cancer 12 days ago. She reports to the clinic this morning with a temperature of 103°F. Her CBC is WBC 500 cells/mm³, segmented neutrophils 55%, band neutrophils 5%, basophils 15%, eosinophils 5%, monocytes 15%, and platelet count 99,000 cells/mm³. She denies any signs or symptoms of infection. Her blood pressure is 115/60 mm Hg, heart rate is 80 beats/minute, and respiratory rate is 15 breaths/minute.

5. Which best represents the patient's absolute neutrophil count (ANC)?
 - A. 275 cells/mm³.
 - B. 300 cells/mm³.
 - C. 25 cells/mm³.
 - D. 500 cells/mm³.
6. Which is the best course of action for this patient?
 - A. Admit her to the hospital for intravenous antibiotic drugs.
 - B. Treat her as an outpatient with antibiotic drugs.
 - C. Initiate a colony-stimulating factor (CSF).
 - D. Discontinue chemotherapy.
7. Which statement about this patient is most accurate?
 - A. Given her monocyte count, her neutropenia is expected to last for another week.
 - B. This is a nadir neutrophil count, and neutrophils would be expected to start increasing soon.
 - C. The elevated absolute eosinophil count indicates an allergic reaction to carboplatin.
 - D. It is unusual for the ANC to be this low in the setting of an elevated platelet count.
8. A 60-year-old man has head and neck cancer with extensive involvement of facial nerves. His pain medications include transdermal fentanyl 100 mcg/hour every 72 hours and oral morphine solution 40 mg every 4 hours as needed. He is still having problems with neuropathic pain. Which treatment is best to recommend?
 - A. Begin gabapentin and decrease the dosage of fentanyl.
 - B. Increase the dosages of fentanyl and morphine.
 - C. Begin diazepam and increase the dosage of fentanyl.
 - D. Begin gabapentin and continue fentanyl and morphine at the same dosage.
9. A patient is receiving chemotherapy for limited-stage small cell lung carcinoma. After the third cycle of chemotherapy, she is hospitalized with febrile neutropenia. She recovers, and today she is scheduled to receive the fourth cycle of chemotherapy. Which statement is the best treatment course for this patient?
 - A. The patient should receive filgrastim 250 mcg/m²/day subcutaneously for 10 days, given at least 24 hours after chemotherapy.
 - B. The patient should receive filgrastim 5 mcg/kg/day subcutaneously, starting today.
 - C. The patient should receive pegfilgrastim 1 mg/day subcutaneously for 6 days, given at least 24 hours after chemotherapy.
 - D. The patient should receive filgrastim 5 mcg/kg/day subcutaneously for 7 days, given at least 24 hours after chemotherapy.
10. A 60-year-old woman with breast cancer is to begin chemotherapy with AC (doxorubicin and cyclophosphamide). Laboratory values today include sodium 140 mEq/L, potassium 3.8 mEq/L, glucose 100 mg/dL, serum creatinine 1.1 mg/dL, aspartate aminotransferase 6 IU/L, alanine aminotransferase 35 IU/L, and total bilirubin 2 mg/dL. Which statement is most appropriate?
 - A. The dosage of doxorubicin should be decreased.
 - B. The dosage of cyclophosphamide should be decreased.
 - C. Both chemotherapy drugs should be given at standard dosages.
 - D. Both chemotherapy drugs should be given at decreased dosages.

11. Large cell lymphoma is considered intermediate (between indolent and highly aggressive) in tumor growth and biology. Large cell lymphoma is sensitive to chemotherapy and potentially curable. Metastatic colorectal cancer is considered slow growing. Although responses to chemotherapy commonly occur and chemotherapy can prolong survival (by months), metastatic colorectal cancer is not generally considered curable with chemotherapy. Given these differences between large cell lymphoma and metastatic colorectal cancer, which statement is most accurate?
- A. Patients with large cell lymphoma should receive allopurinol before the first cycle of chemotherapy because they are at an elevated risk of developing TLS.
 - B. Patients with metastatic colorectal cancer should receive allopurinol before the first cycle of chemotherapy because they are at an elevated risk of developing TLS.
 - C. Patients with large cell lymphoma should receive pamidronate before the first cycle of chemotherapy because they are at an elevated risk of developing hypercalcemia.
 - D. Patients with metastatic colorectal cancer should receive pamidronate before the first cycle of chemotherapy because they are at an elevated risk of developing hypercalcemia.
- C. The chemotherapy for patient 1 should be held for now, and he should receive filgrastim after the next time he has chemotherapy.
- D. The chemotherapy for patient 2 should be held for now, and he should receive filgrastim after the next time he has chemotherapy.
13. Sometimes, extravasation is not immediately evident when it occurs. Immediately after patient 1 receives R-CHOP, an extravasation is suspected. Which is the best treatment recommendation for the patient's extravasation?
- A. Application of a warm pack for suspected extravasation of doxorubicin.
 - B. Application of a cold pack for suspected extravasation of vincristine.
 - C. Intravenous dexrazoxane for suspected extravasation of doxorubicin.
 - D. Application of sodium thiosulfate for suspected extravasation of vincristine.

Questions 12 and 13 pertain to the following case.

12. Consider the information provided earlier about large cell lymphoma and metastatic colorectal cancer. Patient 1 with large cell lymphoma is receiving R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], prednisone, and rituximab) chemotherapy. Patient 2 with metastatic colorectal cancer is receiving FOLFIRI (fluorouracil-leucovorin, irinotecan) chemotherapy. On the day cycle 2 is due, both patients have an ANC of 800 cells/mm³. Which statement is most appropriate, given the ANC values?
- A. Patient 1 should receive chemotherapy to keep him on schedule because he has a curable disease.
 - B. Patient 2 should receive chemotherapy to keep him on schedule because he has a curable disease.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
 - a. Tasks 1, 4
 - b. Systems and Patient-Care Problems:
 - i. Antiemetics
 - ii. Pain Management
 - iii. Treatment of Febrile Neutropenia
 - iv. Use of CSFs in Neutropenia and Febrile Neutropenia
 - v. Thrombocytopenia
 - vi. Anemia/Fatigue
 - vii. Chemoprotectants
 - viii. Oncology Emergencies
 - ix. Miscellaneous Antineoplastic Pharmacotherapy
2. Domain 3: System-Based Standards and Population-Based Pharmacotherapy
 - a. Tasks 1, 3, 6

I. ANTIEMETICS

A. Important Definitions Pertaining to Chemotherapy-Induced Nausea and Vomiting (CINV)

1. Nausea is described as an awareness of discomfort that may or may not precede vomiting; nausea is accompanied by decreased gastric tone and decreased peristalsis.
2. Retching is the labored movement of abdominal and thoracic muscles associated with vomiting without the expulsion of vomitus (also called dry heaves).
3. Vomiting (emesis) is the ejection or expulsion of gastric contents through the mouth.
 - a. Acute onset: Occurs 0–24 hours after chemotherapy administration and commonly resolves within 24 hours (intensity peaks after 5–6 hours)
 - b. Delayed onset: Occurs more than 24 hours after chemotherapy administration
 - i. Delayed symptoms are best described with cisplatin, although they are commonly reported in association with other agents (carboplatin or doxorubicin).
 - ii. The distinction between acute and delayed symptoms with respect to time of onset is somewhat arbitrary, and it becomes blurred when chemotherapy is administered for several consecutive days.
 - iii. The importance of the distinction between acute and delayed (and anticipatory) symptoms is that they likely have different mechanisms and therefore different management strategies.
4. Anticipatory vomiting (or nausea) is triggered by sights, smells, or sounds and is a conditioned response; it is more likely to occur in patients whose previous post-chemotherapy nausea and vomiting was not well controlled.
5. Breakthrough emesis occurs despite prophylactic treatment or necessitates additional rescue medications.
6. Refractory emesis is emesis that occurs during treatment cycles when antiemetic prophylaxis or rescue therapy has failed in previous cycles.

B. Risk Factors for CINV

1. Patient-related risk factors
 - a. Patient's age (younger than 50 years)
 - b. Female sex
 - c. History of motion sickness
 - d. History of nausea or vomiting during pregnancy
 - e. Poor control of nausea or vomiting in previous chemotherapy cycles
 - f. History of chronic alcoholism (positive risk factor - decreases incidence of emesis)
2. Emetogenicity of chemotherapy agents: Several schemes for assessing emetogenicity have been proposed.
 - a. Originally, emetogenic risk was classified as “none,” “mild,” “moderate,” or “severe.”
 - b. The Hesketh model, proposed in 1997, classified emetogenic risk as levels ranging from level 1 (less than 10% frequency of emesis) to 5 (more than 90% frequency of emesis).
 - c. Current model includes four levels for intravenous chemotherapy and two levels for oral chemotherapy.
 - d. Levels for intravenous chemotherapy (e.g., minimal, low, moderate, high emetogenic risk) are defined by the percentage of patients expected to experience emesis when not receiving antiemetic prophylaxis.
 - e. Levels for oral chemotherapy (prophylaxis recommended or as needed)

3. Radiation therapy can also cause nausea and vomiting. The incidence and severity of radiation-induced nausea and vomiting vary by site of radiation and size of radiation field.
 - a. Mildly emetogenic: Radiation to the head and neck or to the extremities
 - b. Moderately emetogenic: Radiation to the upper abdomen or pelvis or craniospinal radiation
 - c. Highly emetogenic: Total body irradiation, total nodal irradiation, and upper-half-body irradiation
- C. General Principles for Managing CINV and Radiation-Induced Nausea and Vomiting
 1. Prevention is the key. Prophylactic antiemetics should be administered before moderately or highly emetogenic agents and before moderately and highly emetogenic radiation.
 2. Antiemetics should be scheduled for delayed nausea and vomiting for select chemotherapy regimens (e.g., cisplatin, doxorubicin/cyclophosphamide (AC)), and rescue antiemetics should be available if prolonged acute symptoms or ineffective antiemetic prophylaxis occurs.
 3. Patients need to be protected throughout the full period of risk for nausea/vomiting:
 - a. 3 days for highly emetogenic regimens
 - b. 2 days for moderately emetogenic regimens
 4. Begin with an appropriate antiemetic regimen based on the emetogenicity of the chemotherapy drugs.
 - a. For multidrug regimens, select antiemetic therapy according to the drug with the highest emetic risk.
 - b. The most common antiemetic regimen for highly emetogenic chemotherapy and radiation is the combination of a neurokinin 1 (NK1) receptor antagonist, a serotonin receptor antagonist, and dexamethasone. Adding a corticosteroid to a serotonin receptor antagonist for highly (or moderately) emetogenic anticancer therapy increases efficacy by 10%–20%. Based on randomized clinical trial data, the AC regimen (see Table 1) should always include a three-drug regimen with an NK1 receptor antagonist, a serotonin receptor antagonist, and dexamethasone.
 - c. The new 2017 American Society of Clinical Oncology (ASCO) Antiemetic Guidelines differ from the National Comprehensive Cancer Network (NCCN) Antiemetic Guidelines. ASCO guidelines now recommend a four drug regimen for highly emetogenic chemotherapy to include a neurokinin 1 receptor antagonist, a serotonin receptor antagonist, dexamethasone, and olanzapine. NCCN guidelines recommend either a 3 drug or a 4 drug regimen for highly emetogenic chemotherapy.
 - d. For moderately emetogenic chemotherapy, the most common antiemetic regimen now includes a serotonin receptor antagonist and dexamethasone. Addition of an NK1 receptor antagonist may be considered after risk stratification.
 - e. Single-agent phenothiazine, butyrophenone, or steroids are used for mildly emetogenic regimens and are given on either a scheduled or an as-needed basis for prolonged symptoms (i.e., breakthrough symptoms).
 - f. Consider using a histamine-2 blocker or proton pump inhibitor for dyspepsia (which can mimic nausea).
 - g. Cannabinoids are generally used after other regimens have failed.
 - h. Potential drug interactions between antineoplastic agents or antiemetics and other drugs should always be considered.
 - i. Follow-up is essential. The response to the emetogenic regimen should always guide the choice of antiemetic regimen for subsequent therapy courses.

D. Emetogenic Potential of Intravenous Chemotherapy Agents

Table 1. Emetogenic Potential of Intravenous Chemotherapy Agents

| High Emetic Risk (> 90% frequency of emesis) | |
|---|---|
| AC (combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide) Carboplatin AUC ≥ 4 Carmustine > 250 mg/m ² Cisplatin Cyclophosphamide > 1500 mg/m ² Dacarbazine | Doxorubicin ≥ 60 mg/m ² Epirubicin > 90 mg/m ² Ifosfamide ≥ 2 g/m ² /dose Meclorethamine Streptozocin |
| Moderate Emetic Risk (30%–90% frequency of emesis) | |
| Aldesleukin > 12–15 million IU/m ² Amifostine > 300 mg/m ² Arsenic trioxide Azacitidine Bendamustine Busulfan Carboplatin AUC < 4 Carmustine ≤ 250 mg/m ² Clofarabine Cyclophosphamide ≤ 1500 mg/m ^{2a} Cytarabine > 200 mg/m ² Dactinomycin | Daunorubicin Dinutuximab Doxorubicin < 60 mg/m ² Epirubicin ≤ 90 mg/m ² Idarubicin Ifosfamide < 2 g/m ² /dose Interferon alfa ≥ 10 million IU/m ² Irinotecan Melphalan Methotrexate ≥ 250 mg/m ² Oxaliplatin Temozolomide Trabectedin |
| Low Emetic Risk (10%–30% frequency of emesis) | |
| Ado-trastuzumab emtansine Aldesleukin ≤ 12 million IU/m ² Amifostine ≤ 300 mg/m ² Atezolizumab Belinostat Blinatumomab Brentuximab vedotin Cabazitaxel Carfilzomib Cytarabine (low dose) 100–200 mg/m ² Docetaxel Doxorubicin (liposomal) Eribulin Etoposide Floxuridine Fluorouracil Gemcitabine Interferon alfa > 5 million IU/m ² to < 10 million IU/m ² | Irinotecan (liposomal) Ixabepilone Methotrexate > 50 mg/m ² to < 250 mg/m ² Mitomycin Mitoxantrone Necitumumab Omacetaxine Paclitaxel Paclitaxel/albumin Pemetrexed Pentostatin Pralatrexate Romidepsin Talimogene laherparepvec Thiotepa Topotecan Ziv-aflibercept |

Table 1. Emetogenic Potential of Intravenous Chemotherapy Agents (*Cont'd*)

| Minimal Emetic Risk (< 10% frequency of emesis) | |
|---|-------------------------|
| Alemtuzumab | Obinutuzumab |
| Asparaginase | Ofatumumab |
| Bevacizumab | Panitumumab |
| Bleomycin | Pegaspargase |
| Bortezomib | Peginterferon |
| Cetuximab | Pembrolizumab |
| Cladribine (2-chlorodeoxyadenosine) | Pertuzumab |
| Cytarabine < 100 mg/m ² | Ramucirumab |
| Daratumumab | Rituximab |
| Decitabine | Siltuximab |
| Denileukin diftitox | Temsirolimus |
| Dexrazoxane | Trastuzumab |
| Elotuzumab | Valrubicin |
| Fludarabine | Vinblastine |
| Interferon alfa ≤ 5 million IU/m ² | Vincristine |
| Ipilimumab | Vincristine (liposomal) |
| Methotrexate ≤ 50 mg/m ² | Vinorelbine |
| Nelarabine | |
| Nivolumab | |

E. Emetogenic Potential of Oral Chemotherapy Agents (Table 2)

Table 2. Emetogenic Potential of Oral Chemotherapy Agents

| Moderate to High Emetic Risk (≥ 30% frequency of emesis); Prophylaxis Recommended | |
|--|--|
| Altretamine | Lomustine (single day) |
| Busulfan ≥ 4 mg/day | Mitotane |
| Ceritinib | Olaparib |
| Crizotinib | Panobinostat |
| Cyclophosphamide ≥ 100 mg/m ² /day | Procarbazine |
| Estramustine | Rucaparib |
| Etoposide | Temozolomide > 75 mg/m ² /day |
| Lenvatinib | Trifluridine/tipiracil |

Table 2. Emetogenic Potential of Oral Chemotherapy Agents (*Cont'd*)

| Minimal to Low Emetic Risk (< 30% frequency of emesis); As Needed | |
|---|--|
| Afatinib | Mercaptopurine |
| Alectinib | Methotrexate |
| Axitinib | Nilotinib |
| Bexarotene | Osimertinib |
| Bosutinib | Palbociclib |
| Busulfan < 4 mg/day | Pazopanib |
| Cabozantinib | Pomalidomide |
| Capecitabine | Ponatinib |
| Chlorambucil | Regorafenib |
| Cobimetinib | Ruxolitinib |
| Cyclophosphamide < 100 mg/m ² /day | Sonidegib |
| Dabrafenib | Sorafenib |
| Dasatinib | Sunitinib |
| Erlotinib | Temozolomide ≤ 75 mg/m ² /day |
| Everolimus | Thalidomide |
| Fludarabine | Thioguanine |
| Gefitinib | Topotecan |
| Hydroxyurea | Trametinib |
| Ibrutinib | Tretinoin |
| Idelalisib | Vandetanib |
| Imatinib | Vemurafenib |
| Ixazomib | Venetoclax |
| Lapatinib | Vismodegib |
| Lenalidomide | Vorinostat |
| Melphalan | |

F. Antiemetics

1. Serotonin-3 receptor antagonists (dolasetron, granisetron, ondansetron, and palonosetron)
 - a. Mechanism of action (MOA): Block serotonin receptors peripherally in the gastrointestinal tract and centrally in the medulla
 - b. Adverse events: Headache and constipation, occurring in 10%–15% of patients. May increase liver function tests and cause QT prolongation (especially with high dosages or intravenous push administration).
 - c. Dolasetron, granisetron, ondansetron, and palonosetron are considered equally efficacious at equivalent dosages. Therefore, the antiemetic drug of choice is often based on cost and organizational contract.
 - d. Dosage forms: Granisetron and ondansetron are available in oral and intravenous forms (including an orally disintegrating tablet for ondansetron). Dolasetron is now indicated only in CINV in its oral form. Granisetron is also available in a transdermal patch (34.3 mg applied about 24–48 hours before the first dose of chemotherapy; maximal duration of patch is 7 days) as well as an extended-release subcutaneous formulation (10 mg at least 30 minutes before first dose of chemotherapy; not to be administered more often than every 7 days).
 - e. Palonosetron is indicated to prevent acute CINV for highly emetogenic chemotherapy and acute and delayed CINV for moderately emetogenic chemotherapy.
 - i. Half-life: About 40 hours (longer compared with other serotonin antagonists)
 - ii. Dosage: 0.25 mg intravenous push 30 minutes before chemotherapy administration

- iii. An oral capsule form is available but only as a combination product with an NK1 antagonist (netupitant/palonosetron).
 - iv. One dose may be used before the start of a 3-day chemotherapy regimen instead of several daily doses of oral or intravenous serotonin-3 receptor antagonists.
 - v. Adverse events: Headache and constipation (same as other serotonin antagonists)
2. Corticosteroids (dexamethasone, methylprednisolone)
- a. MOA: Unknown; thought to act by inhibiting prostaglandin synthesis in the cortex
 - b. Adverse effects associated with single doses and short courses of steroids are infrequent; they may include euphoria, anxiety, insomnia, increased appetite, and mild fluid retention; rapid intravenous administration may be associated with transient and intense perineal, vaginal, or anal burning.
 - c. Dexamethasone has been studied more often in clinical trials than methylprednisolone.
3. NK1 receptor antagonists (aprepitant, fosaprepitant, rolapitant)
- a. All NK1 receptor antagonists must be used in combination with a serotonin receptor antagonist and dexamethasone.
 - b. MOA: Aprepitant is a selective high-affinity antagonist of human substance P/NK1.
 - c. Aprepitant is approved for use in combination with other antiemetic drugs for preventing acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy known to cause these problems, including high-dose cisplatin.
 - d. Aprepitant improved the overall complete response (defined as no emetic episodes and no use of rescue therapy) by about 20% when added to a serotonin receptor antagonist and dexamethasone.
 - e. Aprepitant dosage: 125 mg on day 1, then 80 mg on day 2 and 80 mg on day 3
 - f. Fosaprepitant dosage (prodrug): 150 mg intravenously on day 1 only (intravenous formulation)
 - g. Metabolized primarily by cytochrome P450 (CYP) 3A4 with minor metabolism by CYP1A2 and CYP2C19
 - i. Dexamethasone: May increase area under the curve of dexamethasone. Decrease dosage by about 40% on day 2 or 3 if dexamethasone given orally (not necessary if given intravenously because of first-pass metabolism).
 - ii. Oral contraceptives: May reduce the effectiveness of oral contraceptives. Would recommend another form of birth control for women of childbearing age when taking with aprepitant
 - iii. Warfarin: May decrease international normalized ratio (clinically significant). After completing a 3-day course of aprepitant, patients should have their international normalized ratios checked within 7–10 days.
 - iv. Caution use in patients with lymphoma: Studies suggest neuropathy is more common in patients on R-CHOP receiving aprepitant, because of aprepitant's CYP3A4 inhibition.
 - g. Adverse events: Asthenia, dizziness, and hiccups
 - h. MOA: Rolapitant substance P/NK1 receptor antagonist indicated in combination with other antiemetic agents in adults with cancer for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy.
 - i. Rolapitant dosage: 180 mg orally on day 1 only
 - j. Adverse events: Loss of appetite, neutropenia, and hiccups
4. NK1 receptor antagonist/serotonin-3 combination (netupitant/palonosetron)
- a. MOA: Fixed combination of netupitant, a substance P/NK1 receptor antagonist, and palonosetron, a serotonin-3 receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase, and netupitant prevents nausea and vomiting during both the acute and delayed phases after cancer chemotherapy.

- b. Netupitant/palonosetron dosage: 1 capsule once on day 1 (capsule contains 300 mg of netupitant/palonosetron 0.5 mg)
 - c. Adverse effects: Headache, asthenia, dyspepsia, fatigue, constipation, and erythema
 - d. Caution in patients with hepatic dysfunction, severe renal impairment, or end-stage renal disease
5. Benzamide analogs (metoclopramide)
- a. MOA: Blockade of dopamine receptors in the chemoreceptor trigger zone; stimulation of cholinergic activity in the gut, increasing (forward) gut motility; and antagonism of peripheral serotonin receptors in the intestines. These effects are dose related.
 - b. Adverse events: Mild sedation and diarrhea, as well as extrapyramidal reactions (e.g., dystonia, akathisia), which may be mitigated by diphenhydramine or benztropine.
 - c. Historically, higher dosages of metoclopramide were used for desired results (1–2 mg/kg intravenously). Guidelines now recommend 10–20 mg every 6 hours, if needed.
6. Phenothiazines (prochlorperazine, chlorpromazine, promethazine)
- a. MOA: Block dopamine receptors in the chemoreceptor trigger zone
 - b. Adverse events: Drowsiness, hypotension, akathisia, and dystonia
 - c. Chlorpromazine is often preferred in children because it is associated with fewer extrapyramidal reactions than prochlorperazine.
7. Butyrophenones (haloperidol, droperidol)
- a. MOA: Similar to phenothiazines
 - b. They are at least as effective as the phenothiazines, and some studies indicate they are superior; they offer a different chemical structure that may bind differently to the dopamine receptor and offer an initial alternative when a phenothiazine fails.
 - c. Adverse events: Sedation; hypotension is less common than with phenothiazines; extrapyramidal symptoms are also seen.
 - d. The use of droperidol as an antiemetic has fallen out of favor because of the risk of QT prolongation or torsades de pointes.
8. Benzodiazepines (lorazepam)
- a. Lorazepam as a single agent has minimal antiemetic activity. However, several properties make lorazepam useful in combination with or as an adjunct to other antiemetics.
 - i. Anterograde amnesia helps prevent anticipatory nausea and vomiting.
 - ii. Relief of anxiety
 - iii. Management of akathisia caused by phenothiazines, butyrophenones, or metoclopramide
 - iv. Adverse events: Amnesia, sedation, hypotension, perceptual disturbances, and urinary incontinence. Note that amnesia and sedation may in fact be desirable.
9. Atypical antipsychotic (olanzapine)
- a. Approved by the U.S. Food and Drug Administration (FDA) to treat schizophrenia and bipolar disorder, this thienobenzodiazepine is used off label as an alternative agent for preventing nausea and vomiting in highly emetogenic regimens and may be used as an option for breakthrough nausea and vomiting.
 - b. MOA: Blocks multiple neurotransmitters, including dopamine, serotonin, catecholamines, acetylcholine, and histamine
 - c. Adverse effects: Sedation, dry mouth, increased appetite, weight gain, postural hypotension, QTc prolongation, and dizziness
 - d. Olanzapine has been associated with an elevated risk of hyperlipidemia, hyperglycemia, and new-onset diabetes. Use with caution in older adults because olanzapine use in this patient population has been associated with an elevated risk of death and an elevated incidence of cerebrovascular adverse events in patients with dementia-related psychosis (black box warning)

- e. Recently, a phase III study was conducted comparing olanzapine with aprepitant in highly emetogenic chemotherapy regimens. Overall response rates were similar in both groups for acute and delayed nausea and vomiting. The proportion of patients without nausea was similar between the two groups in the acute period but was higher in the olanzapine arm in the delay period, resulting in a higher rate of nausea control. As an alternative to, or in combination with, aprepitant, an olanzapine-based regimen may be an option in highly or moderately emetogenic regimens according to the most recent National Comprehensive Cancer Network (NCCN) guidelines.
10. Cannabinoids (dronabinol, nabilone)
- a. MOA: Cannabinoid receptors may mediate at least some of the antiemetic activity of this class of agents. Additional antiemetic mechanisms that have been proposed include inhibition of prostaglandins and blockade of adrenergic activity.
 - b. Adverse events: Drowsiness, dizziness, euphoria, dysphoria, orthostatic hypotension, ataxia, hallucinations, and time disorientation

G. Emesis Prevention Algorithms (Tables 3 and 4)

Table 3. Emesis Prevention Algorithm for Intravenous Chemotherapy (per NCCN Guidelines)

| Level of Emetogenicity | Emesis Treatment Day 1 | Emesis Treatment Days 2, 3, and 4 |
|------------------------|--|--|
| High | NK1 antagonist - Aprepitant 125 mg PO - Fosaprepitant 150 mg IV once - Rolapitant 180 mg PO AND Serotonin-3 antagonist AND Steroid ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor OR Netupitant-containing regimen - Netupitant 300 mg/palonosetron 0.5 mg PO once - Dexamethasone 12 mg PO/IV ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor OR Olanzapine-containing regimen: 1. Olanzapine 10 mg PO 2. Palonosetron 0.25 mg IV once 3. Dexamethasone 20 mg once (12 mg if NK1 antagonist used) ± Aprepitant/fosaprepitant ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor | - If aprepitant PO given day 1, aprepitant 80 mg PO daily on days 2 and 3. Dexamethasone 8 mg PO/IV daily - If fosaprepitant given on day 1, no further fosaprepitant needed on days 2, 3. Dexamethasone 8 mg PO/IV on day 2, 8 mg PO/IV twice daily on days 3, 4 - If rolapitant given day 1, no further NK1 antagonists are needed on days 2, 3. Dexamethasone 8 mg PO/IV twice daily on days 2, 3, 4 OR Dexamethasone 8 mg PO/IV daily on days 2, 3, 4 OR Olanzapine-containing regimen: Olanzapine 10 mg PO days 2–4 ± Dexamethasone 8 mg PO/IV daily (if NK1 antagonist used) - If aprepitant PO given on day 1, give aprepitant 80 mg PO daily on days 2 and 3 |

Table 3. Emesis Prevention Algorithm for Intravenous Chemotherapy (per NCCN Guidelines) (*Cont'd*)

| Level of Emetogenicity | Emesis Treatment Day 1 | Emesis Treatment Days 2, 3, and 4 |
|------------------------|--|---|
| Moderate | <p>Serotonin-3 antagonist AND Steroid Dexamethasone 12 mg PO/IV once WITH/WITHOUT NK1 antagonist ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor</p> <p>OR</p> <p>Netupitant-containing regimen - Netupitant 300 mg/palonosetron 0.5 mg PO once - Dexamethasone 12 mg PO/IV ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor</p> <p>OR</p> <p>Olanzapine-containing regimen: 1. Olanzapine 10 mg PO 2. Palonosetron 0.25 mg IV once 3. Dexamethasone 20 mg IV once ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor</p> | <p>Serotonin-3 antagonist OR Steroid monotherapy Dexamethasone 8 mg PO/IV daily on days 2, 3 OR - If aprepitant PO given day 1, aprepitant 80 mg PO daily on days 2, 3 ± dexamethasone 8 mg PO/IV days 2, 3 - If fosaprepitant given day 1, no further NK1 antagonists needed on days 2 and 3 ± Dexamethasone days 2, 3 - If rolapitant given day 1, no further NK1 antagonists needed on days 2, 3 ± Dexamethasone days 2, 3 OR ± Dexamethasone 8 mg PO/IV days 2, 3</p> <p>OR</p> <p>Olanzapine-containing regimen: Olanzapine 10 mg PO days 2, 3</p> |
| Low | <p>Steroid OR Metoclopramide as needed OR Prochlorperazine as needed OR Serotonin-3 antagonists (oral therapy) ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor</p> | <p>Steroid OR Metoclopramide as needed OR Prochlorperazine as needed OR Serotonin-3 antagonists (oral therapy) ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor</p> |
| Minimal | No routine prophylaxis | No routine prophylaxis |

IV = intravenous(ly); NK1 = neurokinin 1; PO = orally.

Table 4. Emesis Prevention Algorithm for Oral Chemotherapy per NCCN Guidelines

| Level of Emetogenicity | Emesis Treatment (start before chemotherapy and continue daily) |
|------------------------------|--|
| High to moderate emetic risk | Serotonin-3 antagonist (choose one): Dolasetron 100 mg daily Granisetron 1–2 mg (total dose) PO daily or 3.1 mg/24-hr transdermal patch every 7 days Ondansetron 8–16 mg PO daily ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor |
| Low to minimal emetic risk | Metoclopramide 10–20 mg PO and then q6hr PRN OR Prochlorperazine 10 mg PO or IV and then q6hr PRN (maximum 40 mg/day) OR Serotonin-3 antagonist (choose one): Dolasetron 100 mg PO daily PRN Granisetron 1–2 mg (total dose) PO daily PRN Ondansetron 8–16 mg PO daily PRN ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor |

BID = twice daily; PRN = as needed; q = every.

Patient Case

Questions 1 and 2 pertain to the following case.

A 60-year-old woman was recently given a diagnosis of advanced non–small cell lung cancer. She will begin treatment with cisplatin 100 mg/m² plus vinorelbine 30 mg/m².

- Which is the most appropriate antiemetic regimen for preventing acute emesis?
 - Aprepitant plus palonosetron plus dexamethasone.
 - Aprepitant plus prochlorperazine plus dexamethasone.
 - Aprepitant plus granisetron plus ondansetron.
 - Lorazepam plus ondansetron plus metoclopramide.
- If the patient has anticipatory nausea and vomiting with her next cycle, which regimen would be most appropriate?
 - Aprepitant plus palonosetron plus dexamethasone.
 - Aprepitant plus prochlorperazine plus dexamethasone.
 - Aprepitant plus granisetron plus metoclopramide.
 - Aprepitant plus ondansetron plus dexamethasone plus lorazepam.

II. PAIN MANAGEMENT

A. Principles of Cancer Pain Management

1. The most important step in treating pain is the assessment.
2. The oral route is preferred, when available. Although the ratio of oral to parenteral potency of morphine is commonly 6:1, clinical observation of chronic morphine use indicates that this ratio is closer to 3:1.
3. Choose the analgesic drug and dosage to match the patient's degree of pain.
4. For persistent severe pain, use a product with a long duration of action. Pain medications should always be administered on a scheduled basis or around the clock, not as needed.
 - a. It is always easier to prevent pain from recurring than to treat it once it has recurred.
 - b. As-needed dosing should be used for breakthrough pain, which is pain that "breaks through" the regularly scheduled opioid; an immediate-release, short-acting opioid should always accompany a long-acting opioid.
5. Reevaluate pain and pain relief often, especially when initiating pain therapy; if more than two as-needed doses are necessary for breakthrough pain in a 24-hour period, consider modifying the regimen. Before adding or changing to another drug, maximize the dosage and schedule of the current analgesic drug.
6. Provide medications to prevent other potential side effects from opioid therapy (e.g., constipation).
7. Use appropriate adjuvant analgesics and nondrug measures to maximize pain control.
8. Goals of pain management (The "4 A's")
 - a. Optimize analgesia.
 - b. Optimize activities of daily living.
 - c. Minimize adverse effects.
 - d. Avoid aberrant drug taking.

B. Diagnosis and Assessment of Pain

1. Best addressed by proper pain assessment including comprehensive history and physical examination
2. Evaluation of pain management: Pain intensity, pain relief, and medication adverse effects or allergies must be assessed and reassessed.
3. Objective observations such as grimacing, limping, or tachycardia may be helpful in assessment.
4. Clinicians must accept the patient's report of pain.

C. Pain Rating Scales

1. Use pain assessment tools to evaluate pain intensity at baseline and to assess how well a pain medication regimen is working.
 - a. Numeric rating scale of 0–10, with 0 = no pain and 10 = worst pain imaginable
 - b. Pediatric patients: Faces-of-Pain Scale, poker chip method
2. Because pain is subjective, it is best evaluated by the patient (i.e., not a caregiver and not the health professional).

D. Treatment of Pain: The Analgesic Ladder

1. For mild to moderate pain (pain rating of 1–3 on a 10-point scale), the first step is a nonopioid analgesic drug: Nonsteroidal anti-inflammatory drug (NSAID), aspirin, or acetaminophen, or consider slow titration of short-acting opioids either as needed or as scheduled.
2. For persistent or moderate to severe pain (pain rating of 4–6 on a 10-point scale), add a weak opioid: Codeine or hydrocodone, available in combination with nonopioid analgesic drugs. Slow titration of a short-acting opioid may also be considered.

3. For persistent or for severe pain (pain rating of 7–10 on a 10-point scale), replace the weak opioid with a strong opioid: Morphine, oxycodone, or similar drug. In opioid-naïve patients experiencing severe pain, short-acting opioids should be rapidly titrated. Once a patient with persistent pain is taking stable dosages of short-acting opioids, the drug should be changed to an extended-release or long-acting formulation with breakthrough short-acting opioids.
- E. Nonopioid Analgesics: NSAIDs
1. MOA: Act peripherally to inhibit the activity of prostaglandins in the pain pathway
 2. There is a ceiling effect to the analgesia provided by NSAIDs.
 3. Adverse events: Consider inhibition of platelet aggregation and the effects of inhibition of renal prostaglandins. NSAIDs in patients with hematologic disorders are not recommended because of platelet inhibition. In addition, there are concerns about the possibility that NSAIDs will mask fever in a patient with neutropenia who is potentially febrile.
 4. Remember, NSAIDs are generally used in addition to, not instead of, opioids.
 5. NSAIDs are often used for patients with cancer and metastatic bone pain.
- F. Nonopioid/Opioid Combinations
1. Aspirin or acetaminophen or ibuprofen plus codeine or hydrocodone or oxycodone is the most commonly used combination.
 2. Be aware of the risk of acetaminophen overdose with these products. As with any combination product, dosage escalation of one component necessitates escalation of the others. For patients needing high dosages, pure opioids are preferred.
 3. Oxycodone/acetaminophen is available in several strengths; however, use caution when increasing taking multiple tablets per day because of the acetaminophen daily maximum recommendations.
- G. Opioid Analgesics
1. Mechanism: Opioids act centrally in the brain (periaqueductal gray region) and at the level of the spinal cord (dorsal horn) at specific opioid receptors.
 2. The opioids have no analgesic ceiling.
 3. Morphine
 - a. Morphine is the standard with which all other drugs are compared; opioids may differ in duration of action, relative potency, oral effectiveness, and adverse event profiles, but none is clinically superior to morphine.
 - b. Flexibility in dosage forms and administration routes: Oral (sustained release, immediate release), sublingual, intravenous, intrathecal/epidural, subcutaneous, and rectal
 - c. Long duration of action: Sustained-release products last 8–12 hours or, for some preparations, 24 hours.
 - d. Morphine is one of the least expensive opioids, but it should be used with caution in patients with renal dysfunction because of the metabolite.
 4. Oxycodone
 - a. Available in oral formulation only
 - b. Available as a single drug (i.e., not in combination) in both long- and short-acting formulations
 - c. Alternative to morphine in the setting of renal dysfunction
 5. Fentanyl
 - a. Fentanyl is available as an intravenous formulation; a sublingual, intranasal, or transdermal preparation; an oral transmucosal preparation; and a buccal tablet. Transmucosal and buccal fentanyl are used for breakthrough pain.
 - b. Each transdermal patch provides sustained release of drug and can provide pain relief for 48–72 hours. These should not be used in opioid-naïve patients.

- c. Consider the implications for dosing transdermal fentanyl in cachectic patients: Fentanyl initially forms a depot in subcutaneous tissue, and patients with little or no fat may not achieve pain relief.
 - d. Slow onset and long elimination after patch application and removal, respectively
 - e. Bioavailability is greater with buccal tablets than with the transmucosal preparation; thus, equivalent dosages are higher for transmucosal and lower for buccal tablets.
- 6. Hydromorphone
 - a. Available in intravenous and oral formulations (short- and long-acting)
 - b. Considered a semisynthetic compound
 - c. Alternative to morphine with higher potency
 - d. Alternative option in patients with renal dysfunction
- 7. Oxymorphone
 - a. Semisynthetic opioid analgesic
 - b. Most commonly seen as immediate- and extended-release tablets
 - c. Used for moderate to severe pain
 - d. Should not be implemented in patients who are not currently on an opioid regimen
 - e. On June 8, 2017, the FDA has requested that the extended-release formulation of oxymorphone be removed from the market because of risks related to abuse.
- 8. Methadone
 - a. Semisynthetic used in maintenance treatment for opioid-dependent patients and as an effective analgesic in patients taking opioids long term for moderate to severe pain
 - b. Has activity not only at the opioid receptors but also at the *N*-methyl-D-aspartate receptor, which may confer benefit to patients with neuropathic pain
 - c. Complex pharmacokinetics with extended half-life (8–59 hours), which creates difficulties in dosing and transitioning from one opioid to another
 - d. Associated with QT prolongation and torsades de pointes
 - e. Effective long-acting agent also used for neuropathic pain
 - f. Start low and titrate slowly (only escalating after 3–5 days) because of the changing conversion ratios with increasing morphine equivalents.
- 9. Adverse Events
 - a. Sedation: Tolerance usually develops within several days; remember that more sedation may be expected in a patient who has been unable to sleep because of uncontrolled pain. For patients who do not develop tolerance to sedation and have good pain control, a dosage reduction may be considered. If dosage reduction compromises pain control, adding a stimulant (e.g., dextroamphetamine, methylphenidate) may be considered. Other central nervous system adverse events include dysphoria and hallucinations.
 - b. Constipation is very common, and tolerance does not develop to this effect. Decreased intestinal peristalsis is caused by decreased intestinal tone; delayed gastric emptying may also occur. Regular use of stool softeners in addition to a stimulant laxative is imperative to manage constipation.
 - c. Nausea and vomiting are common. As seen with sedation, tolerance develops within about a week. Nausea and vomiting may have a vestibular component, developing as pain relief promotes increased mobility. Agents used in the treatment of vertigo (e.g., meclizine, dimenhydrinate) may be useful in managing the vestibular component, although these agents should be used with caution because combination use with opioids may increase sedation. Nausea and vomiting may also occur because of stimulation of the chemoreceptor trigger zone. Drugs that block dopamine receptors (e.g., phenothiazines) provide relief of this component of nausea and vomiting until tolerance develops.
 - d. Urinary retention and bladder spasm are more common in older adults and in patients taking long-acting formulations.

I. Bisphosphonates

1. Bisphosphonates decrease the worsening of pain by preventing disease progression in the bone and the number of skeletal-related events in patients with breast cancer and multiple myeloma when given for 1 year. Skeletal-related events include pathologic fracture, need for radiation therapy to bone, surgery to bone, and spinal cord compression.
2. In 2000, the American Society of Clinical Oncology published initial guidelines for the use of bisphosphonates in breast cancer (updated in November 2003 and March 2011).
 - a. It is recommended that patients with breast cancer who have evidence of bone metastases on plain radiographs receive either pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3–4 weeks. Dosage adjustments for renal dysfunction are necessary according to package insert recommendations.
 - b. Women with abnormal bone scan and abnormal computed tomographic scan or magnetic resonance imaging showing bone destruction but a normal radiograph should also receive the previously recommended bisphosphonates.
 - c. Therapy should continue until the patient has evidence of a substantial decline in performance status.
 - d. Bisphosphonates may be used in combination with other pain therapies in patients with pain caused by osteolytic disease.
 - e. A new guideline for adjuvant bisphosphonate use in breast cancer by the American Society of Clinical Oncology published in March 2017 recommends that zoledronic acid 4 mg over 15 minutes every 6 months be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy.
3. In 2002, the American Society of Clinical Oncology published guidelines for the use of bisphosphonates in multiple myeloma (updated June 2007).
 - a. Patients with lytic bone destruction seen on plain radiographs should receive either pamidronate 90 mg intravenously over at least 2 hours or zoledronic acid 4 mg over 15 minutes every 3–4 weeks.
 - b. Therapy should continue until there is evidence of substantial decline in a patient's performance status.
 - c. Patients with osteopenia but no radiologic evidence of bone metastases can receive bisphosphonates.
 - d. Bisphosphonates are not recommended for patients with solitary plasmacytoma, smoldering or indolent myeloma, or monoclonal gammopathy of undetermined significance.
 - e. Bisphosphonates may be used in patients with pain caused by osteolytic disease.
4. Adverse events: Low-grade fevers, nausea, anorexia, vomiting, hypomagnesemia, hypocalcemia, hypokalemia, and nephrotoxicity
 - a. Serum creatinine should be monitored before each dose (see package insert for specific recommendations).
 - b. Package insert recommends initiating patients on oral calcium 500 mg plus vitamin D 400 international units/day to prevent hypocalcemia.
 - c. Several reports of osteonecrosis of the jaw occurring in patients receiving bisphosphonates have appeared in the literature. Osteonecrosis of the jaw usually follows a dental or dental disorder. The long half-life of bisphosphonates in bone makes this adverse event difficult to prevent and manage. Patient education and education of dentists are important. Patients should have a dental examination with preventive dentistry before treatment with bisphosphonates.

- J. Receptor Activator of NF- κ B Ligand (RANKL) Inhibitor
1. Denosumab: Fully human monoclonal antibody that targets and inhibits RANKL, a protein that acts as the primary signal to promote bone removal
 2. Indication: Prevention of skeletal-related events in patients with bone metastases from solid tumors
 3. Dosage: 120 mg subcutaneously every 4 weeks
 4. Adverse events: Urinary and respiratory tract infections, cataracts, constipation, rashes, hypocalcemia (especially in patients with CrCl less than 30 mL/minute), and joint pain
 5. Contraindications: Hypocalcemia. Patients should be taking calcium and vitamin D.
 6. No adjustment for hepatic or renal dysfunction is needed.
- K. Adjuvant analgesics are drugs whose primary indication is other than pain; they are used to manage specific pain syndromes. Most often, adjuvant analgesics are used in addition to, rather than instead of, opioids.
1. Antidepressants (e.g., amitriptyline, duloxetine) and anticonvulsants (e.g., gabapentin, carbamazepine, pregabalin) are used for neuropathic pain (e.g., phantom limb pain, nerve compression caused by tumor).
 2. Transdermal lidocaine is useful in localized neuropathic pain.
 3. Corticosteroids are useful in pain caused by nerve compression or inflammation, lymphedema, bone pain, or elevated intracranial pressure.
 4. Benzodiazepines: Diazepam, lorazepam. Useful for muscle spasms; baclofen is another alternative for intractable muscle spasms
 5. Strontium-89: Radionuclide for treatment of bone pain caused by osteoblastic lesions; a single dose may provide relief for several weeks or even months; however, it is myelosuppressive.
 6. NSAIDs are recommended for treating pain caused by bone metastases. Prostaglandins sensitize nociceptors (pain receptors) to painful stimuli, thus providing a rationale for using NSAIDs.
- L. Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release/Long-Acting Opioid Analgesics
1. On June 9, 2012, the FDA announced it would require manufacturers of extended-release and long-acting opioid analgesics to provide training for health care professionals who prescribe these agents.
 2. Components of the REMS program
 - a. Prescriber education: Information on extended-release or long-acting opioid analgesics; information on assessing patients for treatment with these drugs; initiating therapy, modifying dosing, and discontinuing use of extended-release or long-acting opioid analgesics; managing therapy and monitoring patients; and counseling patients and caregivers about the safe use of these drugs. Prescribers will also learn how to recognize evidence of potential opioid misuse, abuse, and addiction.
 - b. Patient counseling: Patient counseling documents for providers will be developed to assist prescribers in counseling patients about their responsibilities for using these medications safely. Patients will receive an updated medication guide, together with their prescription, that contains information on the safe use and disposal of extended-release or long-acting opioid analgesics from their pharmacist. Guide will include instructions for patients to consult their health care professional before changing dosages, signs of potential overdose and emergency contact instructions, and advice on safe storage to prevent accidental exposure of family members.
 - c. Short-acting opioid products are not included in this program.

Patient Case

Questions 3 and 4 pertain to the following case.

A 75-year-old man has metastatic prostate cancer. The main sites of metastatic disease are regional lymph nodes and bone (several hip lesions). He has aching pain with occasional shooting pains. The latter are thought to be the result of nerve compression by enlarged lymph nodes. He has been taking oxycodone/acetaminophen 5 mg/325 mg 2 tablets every 4 hours and ibuprofen 400 mg every 8 hours. His current pain rating is 8/10, and he states that his pain cannot be controlled.

3. Which is the best recommendation to manage his pain at this time?
 - A. Increase oxycodone/acetaminophen to 7.5 mg/325 mg, 2 tablets every 4 hours.
 - B. Increase oxycodone/acetaminophen to 10 mg/325 mg, 2 tablets every 4 hours.
 - C. Discontinue oxycodone/acetaminophen, discontinue ibuprofen, and add morphine sustained release every 12 hours.
 - D. Discontinue oxycodone/acetaminophen and add morphine sustained release every 12 hours.
4. Which is the most appropriate adjunctive medication for this patient's pain?
 - A. Naproxen.
 - B. Single-agent (single ingredient) acetaminophen.
 - C. Gabapentin.
 - D. Baclofen.

III. TREATMENT OF FEBRILE NEUTROPENIA

- A. Principles of Chemotherapy-Induced Bone Marrow Suppression
 1. Bone marrow suppression is the most common dose-limiting toxicity associated with traditional cytotoxic chemotherapy.
 2. WBC = a normal range of $4.8\text{--}10.8 \times 100 \text{ cells/mm}^3$ with a circulating life span of 6–12 hours; decreased WBC = neutropenia, leucopenia, or granulocytopenia; the risk is life-threatening infections; the risk increases with absolute neutrophil count (ANC) less than 500 cells/mm^3 , and the risk is greatest with ANC less than 100 cells/mm^3 . Because neutrophils have the fastest turnover, the effects of cytotoxic chemotherapy are greatest on neutrophils (compared with platelets or red blood cells [RBCs]).
 - a. The nadir (usually described as the ANC) is the lowest value to which the blood count falls after cytotoxic chemotherapy. Usually occurs 10–14 days after chemotherapy administration, with counts usually recovering by 3–4 weeks after chemotherapy; exceptions include mitomycin, decitabine, and nitrosoureas (carmustine and lomustine), which have nadirs of 28–42 days after chemotherapy and recovery of neutrophils 6–8 weeks after treatment
 - b. $\text{ANC} = \text{WBC} \times \text{percentage granulocytes or neutrophils}$ (segmented neutrophils plus band neutrophils). Example: A patient's WBC = 4500 cells/mm^3 with 10% segmented neutrophils and 5% band neutrophils. What is the ANC? $4500 \times (0.1 + 0.05) = 675 \text{ cells/mm}^3$.
 - c. To receive chemotherapy, a patient should have a WBC greater than 3000 cells/mm^3 or an ANC greater than 1500 cells/mm^3 and a platelet count of $100,000 \text{ cells/mm}^3$ or more. These are general guidelines; some protocols and FDA labels or package inserts specify different (lower) thresholds for administering chemotherapy; if cytopenia is attributable to disease in the bone marrow, chemotherapy (full dose) may cause improvement; some drugs are nonmyelosuppressive (e.g., vincristine, bleomycin, monoclonal antibodies).

- d. The potential curability of the disease influences what action will be taken during the next cycle of chemotherapy, either dosage reduction of myelosuppressive chemotherapy or support with a CSF.
3. Other factors affecting myelosuppression include previous chemotherapy, previous radiation therapy, and direct bone marrow involvement by tumor.

B. Neutropenia and Febrile Neutropenia

1. Infectious Diseases Society of America guidelines for antibiotic use were updated in 2010.
2. Neutropenia is defined as an ANC of 500 cells/mm³ or less or a count of less than 1000 cells/mm³, with a predicted decrease to less than 500 cells/mm³ during the next 48 hours.
3. Febrile neutropenia is defined as neutropenia and a single oral temperature of 101°F or more or a temperature of 100.4°F or more for at least 1 hour.
4. Neutropenic patients are at an elevated risk of developing serious and life-threatening infections.
5. The usual signs and symptoms of infection (e.g., abscess, pus, infiltrates on chest radiograph) are absent, with fever often being the only indicator. In addition, cultures are negative more often than not. Therefore, prompt investigation and treatment of febrile neutropenia are essential.
6. The initial assessment of patients with febrile neutropenia includes a risk assessment for complications and severe infection.
 - a. Characteristics of low-risk neutropenia include the following: ANC of 100 cells/mm³ or more and absolute monocyte count of 100 cells/mm³ or more, normal chest radiograph, almost normal renal and hepatic function, neutropenia for less than 7 days and resolution expected in less than 10 days, no intravenous access site or catheter site infection, early evidence of bone marrow recovery, malignancy in remission, peak oral temperature of less than 102°F, no neurologic or mental status changes, no appearance of illness, absence of abdominal pain, and no comorbid complications (e.g., shock, hypoxia, pneumonia, other deep organ infection, vomiting, diarrhea).
 - b. The Multinational Association for Supportive Care in Cancer has developed a scoring index to help identify patients with low-risk febrile neutropenia. Scores are assessed on the basis of factors such as those listed previously.
 - c. Febrile neutropenia that is considered to carry a low risk of complications may be treated with either oral or intravenous antibiotics in an outpatient or inpatient setting.
 - d. Patients with high-risk febrile neutropenia (i.e., patients who do not have low-risk characteristics, as noted earlier) should receive intravenous antibiotics in the hospital.
7. Considerations in the initial selection of an antibiotic include the potential infecting organism, potential sites and source of infection, local antimicrobial susceptibilities, and organ dysfunction potentially affecting antibiotic clearance or toxicity, and drug allergy. The most common source of infection is endogenous flora, which could be gram-negative or gram-positive bacteria; the more prolonged the neutropenia (and the more prolonged the administration of antibacterial antibiotics), the greater chance of fungi playing a role in the infection.
8. Recommendations for initial empiric treatment for patients with high-risk febrile neutropenia include broad-spectrum monotherapy with cefepime, a carbapenem, or piperacillin/tazobactam.
9. Intravenous combination therapy can be considered, especially for management of complications (e.g., hypotension and pneumonia) or if antimicrobial resistance is expected.
10. All patients should be reassessed after 3–5 days of antibiotic therapy, and antibiotics should be adjusted accordingly.
11. Prophylactic antibiotics (fluoroquinolones, trimethoprim/sulfamethoxazole) may be considered for patients who are receiving chemotherapy who are expected to be profoundly neutropenic for more than 7 days.

IV. USE OF COLONY-STIMULATING FACTORS FOR PREVENTION OF FEBRILE NEUTROPENIA

- A. CSFs improve both the production and the function of their target cells. Four products and one biosimilar are currently available in the United States: Granulocyte colony-stimulating factor (G-CSF, or filgrastim [Neupogen]) or tbo-filgrastim (Granix), pegylated granulocyte colony-stimulating factor (PEG-G-CSF, pegfilgrastim [Neulasta]) granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]), and filgrastim-sndz (Zarxio).
- B. Pegfilgrastim, the long-acting agent, is approved for use in patients with nonmyeloid malignancies who are receiving myelosuppressive chemotherapy associated with a high incidence of febrile neutropenia.
- C. Studies have shown that G-CSF and GM-CSF reduce the incidence, magnitude, and duration of neutropenia after chemotherapy and bone marrow transplantation.
- D. Guidelines for the use of CSFs were established by the American Society of Clinical Oncology in 1994; the most recent update was published in 2015.
- E. CSFs are recommended for primary prophylaxis with chemotherapy regimens associated with a 20% or greater risk of febrile neutropenia.
 - 1. G-CSF, tbo-filgrastim, GM-CSF, and filgrastim-sndz are given by daily subcutaneous injection.
 - 2. To date, no large trials have compared G-CSF and GM-CSF. Therefore, although it cannot be stated unequivocally that the two are therapeutically equivalent, they are often used interchangeably. However, they have varying adverse effect profiles (increased in fluid retention and fevers with GM-CSF).
 - 3. A meta-analysis of tbo-filgrastim and filgrastim resulted in tbo-filgrastim being noninferior to filgrastim for reducing the incidence of febrile neutropenia. Toxicities are considered similar between the two agents.
 - 4. Pegfilgrastim is given as a single 6-mg subcutaneous dose, generally administered 24–72 hours after chemotherapy. Pegfilgrastim on-body injector is also available for administration in the outpatient setting. The on-body single use injector can be applied on the same day of chemotherapy, but it is designed to deliver the actual dose the next day about 27 hours later.
 - 5. A single dose of pegfilgrastim is as effective as 11 daily doses of G-CSF 5 mcg/kg in reducing the frequency and duration of severe neutropenia, promoting neutrophil recovery, and reducing the frequency of febrile neutropenia.
 - 6. Tbo-filgrastim was approved in an original biologics license application by the FDA in 2012. The FDA has not approved tbo-filgrastim as a biosimilar to Neupogen (filgrastim). Tbo-filgrastim is administered at 5 mcg/kg daily.
 - 7. Filgrastim-sndz was the first biosimilar approved by the FDA (March 2015). Filgrastim-sndz is also administered at 5 mcg/kg daily.
 - 8. The choice of CSF (pegfilgrastim vs. filgrastim) should be based on the expected duration of neutropenia and the specific anticancer regimen (e.g., short courses of a daily CSF rather than one dose of pegfilgrastim) with chemotherapy administration on a weekly schedule.
 - 9. Adverse events associated with all three preparations appear similar; they include bone pain (most common) and fever.
 - 10. The CSF should be initiated 24–72 hours after the completion of chemotherapy.
 - 11. The package literature recommends continued administration of G-CSF until the post-nadir ANC is greater than 10,000 cells/mm³; however, both G-CSF and GM-CSF are usually discontinued when adequate neutrophil recovery is evident. To decrease cost without compromising patient outcome, many centers continue the CSF until ANC is greater than 2000–5000 cells/mm³. Note that the ANC will decrease about 50% per day after the CSF is discontinued if the marrow has not recovered (i.e., if the CSF is discontinued before the ANC nadir is reached).

12. Avoid the concomitant use of CSF in patients receiving chemotherapy and radiation therapy; the potential exists for worsening myelosuppression.
- F. See the American Society of Clinical Oncology guidelines for the following indications: increasing chemotherapy dosage intensity, using as adjuncts to progenitor cell transplantation, administering to patients with myeloid malignancies, and using in pediatric populations.
- G. American Society of Clinical Oncology Guidelines for Secondary CSF Administration (secondary prophylaxis)
1. If chemotherapy administration has been delayed or the dosage reduced because of prolonged neutropenia, then CSF use can be considered for subsequent chemotherapy cycles; administering CSF in this setting is considered secondary prophylaxis.
 2. Dosage reduction of chemotherapy should be considered the first option (i.e., instead of a CSF) after an episode of neutropenia in patients being treated with the intent to palliate (i.e., not a curative intent).
- H. Use of CSFs for Treatment of Established Neutropenia
1. Administering CSFs in patients who are neutropenic but not febrile is not recommended.
 2. Administering CSFs in patients who are neutropenic and febrile may be considered in the presence of risk factors for complications (e.g., ANC less than 100 cells/mm³, pneumonia, hypotension, multiorgan dysfunction, invasive fungal infection); CSFs may be used in addition to antibiotics to treat neutropenia in patients with these risk factors.
 3. Pegfilgrastim is not approved for the treatment of established neutropenia.

Patient Case

Questions 5 and 6 pertain to the following case.

A 50-year-old woman is receiving adjuvant chemotherapy for stage II breast cancer. She received her third cycle of AC 10 days ago. Her CBC today includes WBC 600 cells/mm³, segmented neutrophils 60%, band neutrophils 10%, monocytes 12%, basophils 8%, and eosinophils 10%. She is afebrile.

5. Which best represents this patient's ANC?
 - A. 600 cells/mm³.
 - B. 360 cells/mm³.
 - C. 240 cells/mm³.
 - D. 420 cells/mm³.
6. Given this ANC, which statement is most appropriate?
 - A. The patient should be initiated on a CSF.
 - B. The patient should begin prophylactic treatment with either a quinolone antibiotic or trimethoprim/sulfamethoxazole.
 - C. The patient, who is neutropenic, should be monitored closely for signs and symptoms of infection.
 - D. Decrease the dosages of AC with the next cycle of treatment.

V. THROMBOCYTOPENIA

- A. Megakaryocytes (platelets) = a normal range of 140,000–440,000 cells/mm³ with a circulating life span of 5–10 days.
- B. Thrombocytopenia is defined as a platelet count less than 100,000 cells/mm³; however, the risk of bleeding is not substantially elevated until the platelet count is 20,000 cells/mm³ or less. Practices for platelet transfusion vary widely from institution to institution. Many institutions do not transfuse platelets until the patient becomes symptomatic (ecchymosis, petechiae, hemoptysis, or hematemesis). Other institutions transfuse when the platelet count is 10,000 cells/mm³ or less, even in the absence of bleeding.

VI. ANEMIA AND FATIGUE

- A. Overview of Anemia
 - 1. Occurs in 3.4 million Americans each year and most common in women, African Americans, and older adults
 - 2. Defined as hemoglobin (Hgb) less than 13 g/dL in men or 12 g/dL in women
 - 3. Anemia defined as a reduction of RBC mass, number of RBCs, and Hgb concentration of RBCs
 - 4. Caused by a deficiency, impaired bone marrow function, and peripheral causes.
 - 5. Signs and symptoms of anemia include weakness and fatigue, irritability, tachycardia and palpitations, shortness of breath, chest pain, pale appearance, dizziness, decreased mental acuity, ecchymoses, blood in urine or stool, and hematomas.
 - 6. There are several types of anemia, including microcytic (iron deficiency anemia), macrocytic/megaloblastic anemia (vitamin B₁₂ deficiency, folic acid deficiency), anemia of chronic disease (including chemotherapy-induced anemia), anemia of critical illness, hemolytic anemias, and drug-induced anemias.
 - 7. Hematologic laboratory values:

Table 5. Hematologic Laboratory Values

| Test | Reference Range | Definition |
|------------------------|------------------------------------|---|
| Hgb | M 13.5–17.5 g/dL F 12–16 g/dL | Hgb per volume of whole blood |
| Hct | M 41–53% F 36%–46% | Percentage of total blood volume composed of RBCs (3 - Hgb) |
| MCV | 80-96 fL | Average volume of RBCs (Hct/RBC) |
| MCHC | 31%–37% | Weight of Hgb per volume (Hgb/Hct) |
| MCH | 26-34pg | Percentage volume of Hgb in RBC (Hgb/RBC) |
| RBC | 4.5-5.9 million/m ³ | RBCs per unit blood |
| Reticulocyte count | 0.5%-1.5% | Immature RBCs |
| RDW | 11%-16% | RBC distribution width |
| EPO | 0-19 mU/mL | Endogenous erythropoietin |
| Serum iron | M 50-160 mcg/dL F 12-150 mcg/dL | Concentration of iron bound to transferrin |
| TIBC | 250-400 mcg/dL | Iron binding capacity of transferrin |
| Ferritin | M 15-200 ng/mL F 12-150 ng/mL | Stored iron concentration |
| Folate | 1.8-1.6 ng/mL | Serum folic acid |
| Vitamin B12 | 100-900 pg/mL | Serum vitamin B ₁₂ |
| Transferrin saturation | >30% | Serum iron divided by TIBC |

EPO = erythropoietin; F = female; Hct = hematocrit; Hgb = hemoglobin; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cells; RDW = RBC distribution width; TIBC = iron binding capacity of transferrin.

B. Microcytic Anemia

1. Iron deficiency is the most common nutritional deficiency, with laboratory values reflecting a decreased RBC, Hgb/Hct, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), iron, ferritin, and transferrin. Total iron binding capacity (TIBC) and RBC distribution width (RDW) are increased.
2. Treatment includes oral iron supplementation: 200 mg elemental iron divided twice daily or three times daily for 3–6 months.
3. Available oral iron products (multiple branded agents):

Table 6. Available Oral Iron Products (multiple branded agents)

| Product | % Elemental | Elemental Iron (mg) |
|--|-------------|---------------------|
| Ferrous sulfate 325-mg tablet | 20 | 65 |
| Ferrous gluconate 325-mg tablet | 12 | 39 |
| Ferrous fumarate 100-mg tablet | 33 | 33 |
| Polysaccharide iron complex 150-mg capsule | 100 | 150 |
| Carbonyl iron 50 mg caplet | 100 | 50 |

4. Iron adverse effects include constipation and nausea or vomiting.
5. Iron products should be taken with food to avoid gastrointestinal discomfort (but absorption will be decreased). Vitamin C may increase the absorption of iron and is often used to increase the efficacy of iron products. Iron therapy may cause dark stools.
6. Parental iron products:

Table 7. Parental Iron Products

| | Iron Dextran | Sodium Ferric Gluconate | Iron Sucrose | Ferumoxytol |
|-----------------------|--|---|--|--|
| Elemental iron | 50 mg/mL | 62.5 mg/5 mL | 20 mg/mL | 30 mg/mL |
| Preservative | None | Benzyl alcohol 9 mg/5 mL 20% | None | None |
| Indication | IDA where PO not an option | IDA in patients on chronic HD receiving EPO | IDA in patients on chronic HD receiving EPO | IDA with CKD |
| Warning | Boxed warning: anaphylactic type reactions | Hypersensitivity reactions | Boxed warning: anaphylactic type reactions | Hypersensitivity reactions |
| IM injection | Yes | No | Yes | No |
| Usual dosage | 100 mg IV push (no faster than 50 mg/min) | 125 mg diluted in 100 mL NS over 60 min (IV injection at 12.5 mg/min) | 100 mg at 1 mL undiluted solution/min into dialysis line | 510 mg IV injection repeated 3–8 days later |
| Test dose | Yes | No | No | No |
| Common adverse events | Pain, stinging at injection site (brown), hypotension, flushing, chills, fever, myalgia, anaphylaxis | Cramps, nausea or vomiting, flushing, hypotension, rash, pruritus | Leg cramps and hypotension | Diarrhea, constipation, nausea, dizziness, hypotension, peripheral edema |

CKD = chronic kidney disease; EPO = erythropoietin; HD = hemodialysis; IDA = iron deficiency anemia; IM = intramuscular; IV = intravenous; NS = normal saline; PO = by mouth.

C. Macrocytic Anemia

1. Vitamin B₁₂ and folate deficiency are the most common causes of macrocytic anemia. Causes of B₁₂ deficiency include inadequate intake, malabsorption, and inadequate utilization. Folate deficiency is caused by inadequate intake, decreased absorption, hyperutilization, and inadequate utilization.
2. In B₁₂ deficiency RBC, Hgb and Hct, and serum B₁₂ are decreased, with an increase in MCV, MCH, methylmalonic acid, and homocysteine. Hypersegmented polymorphonuclear leukocytes may also be present on the peripheral smear.
3. In folate deficiency, RBC, Hgb and Hct, and serum folic acid are decreased, with an increase in MCV and MCH. B₁₂ will be normal (will need to rule out this deficiency).
4. In B₁₂ deficiency, patients may experience neurological changes, glossitis, weakness, loss of appetite, and possibly thrombocytopenia, leucopenia, and pancytopenia. Folate deficiency also presents with glossitis and other central nervous system symptoms including weakness, forgetfulness, headache, syncope, and loss of appetite.

5. Treatment options for vitamin B₁₂ deficiency include oral replacement daily or intramuscular replacement weekly for 1 month, then monthly.
 6. Folate deficiency anemia should be treated with 1 mg of folate daily for 4 months. Pregnant women should take supplements to prevent neural tube defects in the fetus.
- D. Anemia of Chronic Disease (Specifically Chemotherapy-Induced Anemia): Causes of Anemia and Fatigue in Adult Patients with Cancer
1. Unmanaged pain or other symptoms can increase fatigue.
 2. Decreased RBC production because of anticancer therapy, either radiation or chemotherapy
 3. Decreased or inappropriate endogenous erythropoietin production or decreased responsiveness to endogenous erythropoietin
 4. Decreased body stores of vitamin B₁₂, iron, or folic acid
 5. Increased destruction of RBCs
 6. Blood loss
 7. Although anemia can certainly contribute to or worsen fatigue, there are probably other (perhaps many) mechanisms of fatigue (e.g., cytokines) that are independent of Hgb concentration.
- E. Principles of Anemia and Fatigue
1. Fatigue is estimated to affect 60%–80% of all patients with cancer.
 2. Fatigue may be caused by the disease or treatment.
 3. Fatigue can be assessed with a numeric rating scale, 0 = no fatigue and 10 = worst fatigue imaginable, or with any of several questionnaires (e.g., FACT-An).
 4. Drugs used in the treatment of anemia and fatigue
 - a. Epoetin and darbepoetin alfa (erythropoiesis-stimulating agents [ESAs]) are approved for treating chemotherapy-induced anemia, the end point of treatment being a decreased need for transfusion. Darbepoetin has additional carboxy chains, resulting in a longer half-life compared with epoetin.
 - b. Reports of a detrimental effect of ESAs (e.g., increased deaths, reduced chemotherapy outcomes) have led to changes in practice guidelines and reimbursement for these agents. Hgb targets are lower than they were previously, and Hgb is carefully monitored. According to the most recent guidelines, ESAs are initiated once a patient's Hgb drops below 10 g/dL.
 - c. It is important to distinguish between the use of these agents for chemotherapy-associated anemia and cancer-associated anemia. The latter is not an approved use. These agents should be used only in the noncurative setting.
 - d. Adverse events: Hypertension and seizures, venous thromboembolism, and pure red cell aplasia (rare)
 - e. The use of these agents requires baseline and follow-up monitoring to determine whether agents need titration or discontinuation.
 5. Transfusions are an option if patients are symptomatic. Transfusion goal is to maintain Hgb at 8–10 g/dL.

F. Dosing of Erythropoiesis-Stimulating Agents

Table 8. Dosing of Erythropoiesis-Stimulating Agents

| Agent | Starting Dosage | Dosage Increase | Dosing Parameters |
|----------------------------------|---|---|--|
| Erythropoietin (Procrit, Epogen) | 150 units/kg subcutaneously 3 times/wk 40,000 units subcutaneously weekly | 300 units/kg subcutaneously 3 times/wk 60,000 units subcutaneously weekly | Hgb must be < 10 to initiate and continue therapy Evaluate after 4 wk and increase dosage if rise is < 1 g/dL Decrease by ~25% if rapid rise in Hgb Discontinue therapy if no response after 8 wk |
| Darbepoetin (Aranesp) | 2.25 mcg/kg subcutaneously weekly 500 mcg every 3 wk | 4.5 mcg/kg subcutaneously weekly Not applicable | Hgb must be < 10 to initiate and continue therapy Evaluate after 6 wk and increase dosage if rise is < 1 g/dL Decrease by ~40% if rapid rise in Hgb Discontinue therapy if no response after 8 wk |

G. REMS for ESAs

1. Historically the FDA required these agents to be prescribed and monitored under a risk management program to ensure their safety.
2. In 2017, the FDA determined that the ESA REMS, which was limited to the use of erythropoietin (Procrit, Epogen) and darbepoetin (Aranesp) to treat patients with anemia caused by chemotherapy, is no longer required.
3. Although the ESA REMS may no longer be required, clinicians should keep these risks in mind and continue to discuss the risk-benefit of using ESAs with each patient before initiating therapy.

Patient Case

7. A 45-year-old woman is beginning her third cycle of chemotherapy for the adjuvant treatment of breast cancer. At diagnosis, her Hgb was 10 g/dL; however, today, it is less than 10 g/dL. The patient has fatigue that is interfering with her activities of daily living. Which is the most appropriate treatment option?
 - A. Treatment with epoetin should be considered.
 - B. Treatment with darbepoetin should be considered when Hgb decreases to less than 9 g/dL.
 - C. The patient is being treated in the curative setting and therefore is not eligible to receive an ESA.
 - D. The patient should not receive RBC transfusions because she is symptomatic.

VII. CHEMOPROTECTANTS

- A. Properties of an Ideal Protectant Drug for Chemotherapy- and Radiation-Induced Toxicities
 1. Easy to administer
 2. No adverse events
 3. Prevents all toxicities, including non-life-threatening (e.g., alopecia) toxicities, irreversible morbidities (e.g., neuropathies, ototoxicity), and mortality (e.g., severe myelosuppression, cardiotoxicity)
 4. Does not interfere with the efficacy of the cancer treatment
 5. To date, no such drug has been identified.

B. Dexrazoxane

1. The anthracyclines (daunorubicin, doxorubicin, idarubicin, and epirubicin) and anthracenedione (i.e., mitoxantrone) can cause cardiomyopathy that is related to the total lifetime cumulative dosage.
2. Dexrazoxane acts as an intracellular chelating agent; iron chelation leads to a decrease in anthracycline-induced free radical damage.
 - a. Dexrazoxane may be considered for patients who have received doxorubicin 300 mg/m² or more and who may benefit from continued doxorubicin, considering the patient's risk of cardiotoxicity with continued doxorubicin use.
 - b. Dexrazoxane may increase the hematologic toxicity of chemotherapy at high doses (greater than 750 mg).
 - c. An early study suggested that dexrazoxane decreases the response rate to chemotherapy. More recent data suggest this is not the case, but dexrazoxane is still not indicated for patients with early (curable) breast cancer.
3. Dexrazoxane is also approved for use as an antidote for the extravasation of anthracycline chemotherapy.

C. Amifostine

1. Amifostine is used to prevent nephrotoxicity from cisplatin.
2. It is also used to decrease the incidence of both acute and late xerostomia in patients with head and neck cancer who are undergoing fractionated radiation therapy.
3. Adverse events associated with amifostine include sneezing, allergic reactions, warm or flushed feeling, metallic taste in mouth during infusion, nausea and vomiting, and hypotension. The latter two are the most clinically significant toxicities. Prevention of hypotension includes withholding antihypertensive medications, using hydration, and close blood pressure monitoring. Because of the problems with nausea and vomiting (30%–60%) and the incidence of hypotension, this agent is not often used in clinical practice.

D. Mesna (sodium-2-mercaptoethane sulfonate)

1. The metabolite acrolein is produced from metabolism of both cyclophosphamide and ifosfamide, and it has been implicated in sterile hemorrhagic cystitis.
2. Mesna inactivates acrolein by binding to the urotoxic metabolite and preventing its interaction with host cells.
3. Mesna is always used with ifosfamide and may be used with cyclophosphamide (in dosages of 1500 mg/m² or greater), although this is not a label indication.
4. Mesna may be given intravenously or orally and is usually 60%-100% of the ifosfamide dose. The oral dose is twice the intravenous dose. Several dosing schedules may be used. With any schedule, mesna must begin concurrently with or before ifosfamide or cyclophosphamide and end after ifosfamide or cyclophosphamide because of its short half-life (i.e., mesna must be present in the bladder when acrolein is present in the bladder).

Patient Cases

8. A 38-year-old woman has a history of Hodgkin lymphoma. Two years ago, she completed six cycles of ABVD chemotherapy (i.e., doxorubicin, bleomycin, vinblastine, and dacarbazine). Each cycle included doxorubicin 50 mg/m². Recently, she was given a diagnosis of stage IV breast cancer. She will be initiated on doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² for four cycles. Which statement is most applicable?
- A. The patient has not reached the appropriate cumulative dosage of doxorubicin to consider dexrazoxane.
 - B. The patient has reached the appropriate cumulative dosage of doxorubicin to consider dexrazoxane.
 - C. The patient should not receive any more doxorubicin because she is at an elevated risk of cardiotoxicity.
 - D. The patient should not receive dexrazoxane because of the possibility of increased myelosuppression.
9. Which is the best sequence for administering mesna and ifosfamide?
- A. Mesna before ifosfamide and then at 4 and 8 hours after ifosfamide.
 - B. Ifosfamide before mesna and then at 4 and 8 hours after mesna.
 - C. Mesna and ifosfamide beginning and ending at the same time.
 - D. Mesna on day 1 and ifosfamide on days 2–5.

VIII. ONCOLOGIC EMERGENCIES**A. Hypercalcemia**

1. The most common tumors associated with hypercalcemia are lung (metastatic non–small cell lung cancer more than small cell lung cancer), breast, multiple myeloma, head and neck, renal cell, and non-Hodgkin lymphoma.
2. Cancer-associated hypercalcemia results from increased bone resorption with calcium release into the extracellular fluid; in addition, renal clearance of calcium is decreased.
 - a. Some tumors cause direct bone destruction, resulting in osteolytic hypercalcemia.
 - b. Other tumors release parathyroid hormone–related protein (i.e., humoral hypercalcemia).
 - c. Immobile patients are also at an elevated risk of hypercalcemia because of increased resorption of calcium.
 - d. Medications (e.g., hormonal therapy, thiazide diuretics) may precipitate or exacerbate hypercalcemia.
 - e. Corrected Ca (mg/dL) = $(4 - \text{plasma albumin in g/dL}) \times 0.8 + \text{serum calcium}$.
 - f. Symptoms of hypercalcemia: Lethargy, confusion, anorexia, nausea, constipation, polyuria, and polydipsia.
3. Management of hypercalcemia
 - a. Mild hypercalcemia (corrected calcium less than 12 mg/dL) may not warrant aggressive treatment. Hydration with normal saline followed by observation is an option in asymptomatic patients with chemotherapy-sensitive tumors (e.g., lymphoma, breast cancer).
 - b. Moderate hypercalcemia (corrected calcium 12–14 mg/dL) requires basic treatment of clinical symptoms with aggressive hydration.
 - c. Severe hypercalcemia (corrected calcium greater than 14 mg/dL; symptomatic) requires aggressive inpatient treatment.
 - i. Hydration with normal saline about 3–6 L in 24 hours
 - ii. Loop diuretics may be administered after volume status has been corrected or to prevent fluid overload during hydration.
 - iii. Thiazide diuretics are contraindicated in hypercalcemia because of the increase in renal tubular calcium absorption.

- iv. Bisphosphonates bind to hydroxyapatite in calcified bone, which prevents dissolution by phosphatases and inhibits both normal and abnormal bone resorption. The onset of action is 3–4 days.
- v. Calcitonin (intramuscular formulation) inhibits the effects of parathyroid hormone and has a rapid-onset (though short-lived) hypocalcemic effect. May cause tachyphylaxis
- vi. Steroids may be used to lower calcium in patients with steroid-responsive tumors (lymphoma and myeloma).
- vii. Phosphate is reserved for patients who are both hypophosphatemic and hypercalcemic. Phosphate is seldom used because of the possibility of calcium and phosphate precipitation in soft tissue.
- viii. Dialysis may be needed in patients with hypercalcemia and renal failure.

B. Spinal Cord Compression

- 1. Signs and symptoms include back pain, weakness, paresthesias, and loss of bowel and bladder function.
- 2. Treatment consists of dexamethasone and radiation therapy or surgery.

C. Tumor Lysis Syndrome

- 1. Occurs secondary to the rapid cell death that follows the administration of chemotherapy in patients with leukemia or lymphoma or in patients with high tumor burdens from other diseases that are also highly chemosensitive. Tumor lysis syndrome (TLS) can occur spontaneously in hematologic malignancies, without being triggered by the administration of chemotherapy (i.e., some patients present in tumor lysis).
- 2. Manifestations include hyperuricemia, hyperkalemia, hyperphosphatemia, and secondary hypocalcemia. Uric acid and calcium/phosphorus may precipitate in the kidney and can lead to renal failure.
- 3. The primary management strategy is prevention with intravenous hydration (with normal saline) and allopurinol.
- 4. Rasburicase is a recombinant urate oxidase that converts uric acid into allantoin, which is 5–10 times more soluble in urine than uric acid. Rasburicase should be considered for patients at high risk of developing TLS, such as those with a serum uric acid concentration greater than 8 mg/dL, a large tumor burden, preexisting renal dysfunction, or an inability to take allopurinol. The drug is expensive, and currently it is not recommended for prophylaxis in all patients but may be used together with hydration for treatment of TLS. The approved dosage is 0.2 mg/kg intravenously for five doses. There is now increasing evidence for the use of an off-label, low, fixed, single dose of rasburicase for chemotherapy-induced hyperuricemia in adults. The FDA indication is management of uric acid concentrations. Rasburicase causes enzymatic degradation of the uric acid in blood, plasma, and serum samples, potentially resulting in spuriously low plasma uric acid assay readings. Blood must be collected in pre-chilled tubes containing heparin anticoagulant; immediately immerse plasma samples for uric acid measurement in an ice water bath.

IX. MISCELLANEOUS ANTINEOPLASTIC PHARMACOTHERAPY

- A. Leucovorin rescue may be used after methotrexate doses greater than 100 mg/m²; in general, methotrexate doses greater than 500 mg/m² require leucovorin rescue.

- B. Factors that increase the likelihood of methotrexate toxicity include renal dysfunction (causing delayed elimination), third-space fluid (e.g., pleural effusion, ascites), and administration of other drugs that may delay methotrexate elimination (penicillin, NSAIDs, proton pump inhibitors). Toxic reactions include mucous membrane toxicity (e.g., oral mucositis), renal and hepatic toxicity, central nervous system toxicity, and myelosuppression.
- C. The dosage of leucovorin depends on the methotrexate dosage or concentration and the time since completing methotrexate. Methotrexate concentrations are usually obtained 24–48 hours after intermediate- or high-dose methotrexate, and leucovorin is continued until the methotrexate concentration falls to less than 0.1 mM (less than 1×10^{-7} M). This regimen is typically protocol driven.
- D. In contrast to its use with methotrexate, leucovorin is given in combination with fluorouracil in colorectal cancer to improve activity, not to rescue normal cells.
- E. Glucarpidase, a carboxypeptidase enzyme, is now approved and indicated for treating toxic methotrexate concentrations (greater than 1 micromole/L) in patients with delayed methotrexate clearance because of renal dysfunction. Administered as a single intravenous dose of 50 units/kg. Continue leucovorin until the methotrexate concentration has been maintained below the leucovorin treatment threshold for a minimum of 3 days. However, caution must be used with administering leucovorin in conjunction with glucarpidase. Leucovorin should not be administered within 2 hours before or after a dose of glucarpidase.
- F. Extravasation Injuries
 1. A vesicant is an agent that, on extravasation, can cause tissue necrosis. Vesicant antineoplastic drugs include doxorubicin, daunorubicin, epirubicin, mechlorethamine, mitomycin, vincristine, vinblastine, vinorelbine, and streptozocin.
 2. Anthracyclines cause the most severe tissue damage on extravasation.
 3. The literature generally recommends administering vesicants by intravenous injection rather than infusion, but some exceptions exist.
 - a. Some institutional policies require infusions for every drug or approved protocols.
 - b. Vincristine has been incorrectly administered by intrathecal injection, with fatal consequences. Dilution of vincristine for administration as a short intravenous infusion has been recommended to prevent this error from occurring.
 - c. Paclitaxel is administered as an infusion (1, 3, or 24 hours, depending on the protocol).
 4. Management of extravasation
 - a. Cold for doxorubicin, daunorubicin, and epirubicin
 - b. Heat for vincristine, vinblastine, and vinorelbine
 - c. Sodium thiosulfate for mechlorethamine
 - d. Topical dimethyl sulfoxide has been recommended for anthracyclines. Its use is not as well established as that of the antidotes given earlier. Hyaluronidase is recommended for vinca alkaloids, but hyaluronidase is of limited availability. Antidotes for mitomycin, streptozocin, paclitaxel, and oxaliplatin are not well documented in the literature.
 - e. Dexrazoxane (Totect) for doxorubicin, daunorubicin, idarubicin, and epirubicin. Cold compress should be removed 15 minutes before dexrazoxane treatment.
 - f. Many institutions do not allow the administration of vesicants through a peripheral vein but instead require that vesicants be administered through a central line with a venous access device. Although administering vesicants through a central line minimizes the likelihood of an extravasation injury, extravasation may still occur. Management of extravasation is intended for suspected or actual extravasation from a peripheral or central vein.

G. Management of Diarrhea

1. Intensive loperamide therapy using dosages higher than recommended is sometimes necessary for irinotecan-induced diarrhea. Atropine is used to prevent cholinergic activity of acute irinotecan-induced diarrhea (given during administration of chemotherapy). There is no maximal dosage of loperamide when used for delayed diarrhea in this setting (greater than 24 hours after irinotecan administration). The recommended dosing regimen of loperamide is 4 mg by mouth, followed by 2 mg every 2 hours until diarrhea free.
2. Intensive antidiarrhea treatment is also used for other agents (e.g., fluorouracil, epidermal growth factor receptor inhibitors).
3. Diarrhea/colitis caused by immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab) may require steroid treatment to resolve symptoms.

H. Dosage Adjustment for Organ Dysfunction

1. Conflicting recommendations for dosage adjustment have been reported. Many drugs have not been studied in patients with organ dysfunction. Consultation of oncology-specific drug information resources may be useful.
2. Dosage adjustment for renal dysfunction may be considered for methotrexate, carboplatin, cisplatin, etoposide, bleomycin, topotecan, capecitabine, and lenalidomide.
3. Dosage adjustment for hepatic dysfunction is often based on total bilirubin concentrations.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This highly emetogenic regimen is associated with delayed nausea and vomiting. The best choice is a serotonin receptor antagonist with dexamethasone and aprepitant for prophylaxis against nausea and vomiting per NCCN guidelines (Answer A is correct). Prochlorperazine is not effective against a highly emetogenic stimulus (Answer B is not correct). Granisetron and ondansetron are both serotonin receptor antagonists, and no rationale exists for combining them (Answer C is not correct). Lorazepam may be a useful addition, but the combination of ondansetron and metoclopramide is not recommended per NCCN guidelines (Answer D is not correct).

2. Answer: D

Lorazepam is recommended for use in combination with the standard antiemetic regimen based on chemotherapy emetogenicity to prevent anticipatory nausea and vomiting (Answer D is correct). Aprepitant plus palonosetron plus dexamethasone alone has no effects on anticipatory nausea/vomiting, but the combination can be useful for acute and delayed nausea/vomiting (Answer A is not correct). The aprepitant plus prochlorperazine plus dexamethasone regimen does not provide any additional benefit to treat the sensory symptoms (Answer B is not correct). Metoclopramide added to an aprepitant/granisetron regimen would not be appropriate for anticipatory nausea and vomiting (Answer C is not correct).

3. Answer: D

The patient is taking oxycodone/acetaminophen 5 mg/325 mg, which provides 60 mg of oxycodone per day and 3900 mg of acetaminophen. His current drugs should not be increased because of concerns about acetaminophen toxicity. If he were changed to a higher strength of the combination product, acetaminophen toxicity would still be a concern, which eliminates the choices of increasing to oxycodone/acetaminophen the dose to 7.5mg or 10mg (Answer A and B are not correct). Adding sustained-release morphine is a good option and continuing ibuprofen might be helpful for bone pain (Answer D is correct, Answer C is not correct). Oxycodone/acetaminophen, which is short acting, could be continued for breakthrough pain, but he is already receiving high dosages of acetaminophen without good pain relief.

4. Answer: C

Gabapentin might help the neuropathic component (i.e., the shooting pains) of his pain (Answer C is correct). He is already receiving an NSAID, so there is no need to add naproxen (Answer A is not correct). There is no reason to add acetaminophen as it will not provide additional benefit (Answer B). The case does not mention muscle spasms and therefore Baclofen will likely not be effective (Answer D is not correct).

5. Answer: D

To calculate the ANC, multiply the WBC by the segmented neutrophils and the band neutrophils: $600 \text{ cells/mm}^3 \times (0.6 + 0.1) = 420 \text{ cells/mm}^3$ (Answer D is correct). Other options available will not produce the appropriate ANC count due to miscalculation (Answer A, B, and C are not correct).

6. Answer: C

The patient is neutropenic; however, she should not begin a CSF. Her ANC is greater than 100 cells/mm^3 , and she has no signs or symptoms of active infection (Answer A is not correct). Prophylactic treatment with antibiotic drugs is not necessary and can increase the risk of resistant organisms (Answer B is not correct). At this time, the patient should be monitored for evidence of infection (e.g., she should be instructed to take her temperature and return to the clinic or emergency department if she has a single oral temperature of 101°F or more or of 100.4°F or more for at least 1 hour or if she develops any signs or symptoms of infection) (Answer C is correct). Because the disease is potentially curable, dosages should not be reduced on the next cycle (Answer D is not correct).

7. Answer: C

Recent literature and subsequent changes in guidelines and Centers for Medicare & Medicaid Services reimbursement suggest that an erythropoiesis-stimulating protein should be considered when Hgb is less than 10 g/dL. However, this patient is being treated potentially for a cure; therefore, she would not be eligible for an ESA (Answer A and B are not correct, Answer C is correct). Transfusions are an option if patients are symptomatic (Answer D is not correct). The transfusion goal is to maintain Hgb at 8–10 g/dL.

8. Answer: B

The patient has received a cumulative dose of 300 mg/m² of doxorubicin (50 mg/m² × 6 cycles). This is the appropriate cumulative dosage of doxorubicin for dexrazoxane to be considered (Answer A is not correct, Answer B is correct). She is at an elevated risk of cardiotoxicity; however, dexrazoxane protects the heart from this toxicity (Answer C is not correct). Dexrazoxane may increase the myelosuppression from chemotherapy, but that does not represent a contraindication (Answer D is not correct).

9. Answer: A

Several different schedules of ifosfamide and mesna administration exist (e.g., ifosfamide short infusion, followed by intermittent infusions of mesna and continuous infusion of both ifosfamide and mesna). Most schedules recommend the administration of mesna prior to ifosofamide to prevent hemorrhagic cystitis (Answer A is correct, Answer B is not correct). Mesna should always be continued longer than ifosfamide (Answer C and D are not correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

According to the NCCN guidelines, this regimen would likely be considered highly emetogenic. According to these guidelines, an NK1-based regimen with a serotonin-3 antagonist and dexamethasone combination would be recommended (Answer C is correct). However, the patient is likely having some anticipatory nausea/vomiting. Patients who have had poor control of nausea and vomiting on previous cycles of chemotherapy are at an elevated risk of anticipatory emesis. Anxious patients are also at an elevated risk of CINV. Benzodiazepines help decrease anxiety and, by causing anterograde amnesia, may minimize anticipatory symptoms (Answer C is correct). Although it is unclear whether patients who do not respond to one serotonin receptor antagonist will respond to another, a change in regimen is needed (Answer A is not correct). Substituting dolasetron for granisetron would be acceptable, but adding lorazepam is essential (Answer B is not correct). Metoclopramide is another option, but an effective dose might be difficult to administer orally (especially as tablets), and again, adding lorazepam would be preferred to adding aprepitant in this patient (Answer D is not correct).

2. Answer: D

The corrected calcium is 13.6 mg/dL. Corrected calcium concentrations greater than 12 g/dL should be treated with a bisphosphonate (either pamidronate or zoledronic acid) in addition to hydration with normal saline (Answer D is correct). Furosemide may be needed during hydration, but not before hydration because the patient is probably dehydrated (Answer B is not correct). This patient does not need rapid reversal of hypercalcemia; therefore, calcitonin is not needed (Answer A is not correct). Dexamethasone may be used in patients with lymphoma or myeloma, but it has no effect on metastatic non-small cell lung cancer (Answer C is not correct).

3. Answer: C

The patient is at risk of TLS because he has a chemosensitive tumor and a high tumor burden (elevated WBC). Prevention is key in TLS, which includes adequate saline hydration and the use of allopurinol (Answer C is correct). Dextrose 5% is an inappropriate

intravenous fluid for hydration because it does not contain saline (Answer A and B are not correct). The value of alkalization with sodium bicarbonate is somewhat controversial, but alkalization is not a replacement for allopurinol (Answer D is not correct).

4. Answer: B

This anemia is not attributable to treatment because chemotherapy has not yet begun. Epoetin and darbepoetin are indicated only for noncurative chemotherapy-associated anemia in non-myeloid tumors (answer A is not correct). Chemotherapy should not be delayed, nor should chemotherapy dosages be reduced in the setting of a potentially curable malignancy (Answer C and D are not correct). Therefore, the patient should receive a transfusion of packed RBCs because his hemoglobin is less than 8 g/dL and he is fatigued (Answer B is correct).

5. Answer: B

$(55\% \text{ segmented neutrophils} + 5\% \text{ band neutrophils}) \times 500 = 300 \text{ cells/mm}^3$ (Answer B is correct). Other options available will not produce the appropriate ANC count due to miscalculation (Answer A, C and D are not correct).

6. Answer: A

The patient is neutropenic (ANC 300 cells/mm³). A temperature of 103°F places the febrile neutropenia outside the definition of low-risk febrile neutropenia (Answer B is not correct). Therefore, the patient should be hospitalized for intravenous antibiotics and an infection workup (Answer A is correct). She has none of the appropriate reasons to administer CSFs (i.e., documented pneumonia, hypotension, sepsis syndrome, or fungal infection) (answer C is not correct). Her chemotherapy may need to be delayed, but it should be continued on count recovery (Answer D is not correct). She should receive a CSF with the next cycle of chemotherapy.

7. Answer: B

In this patient, febrile neutropenia developed at the time of the expected neutrophil nadir, 12 days after chemotherapy (Answer B is correct). Marrow recovery would be expected to follow (Answer A is not correct). The percentage of eosinophils may be slightly elevated, but

the absolute count is low (Answer C is not correct). The platelet count is also low, not elevated. Neutrophils are often affected by myelosuppressive chemotherapy to a greater degree than are platelets (Answer D is not correct).

8. Answer: D

Opioids may provide some relief from neuropathic pain, but often, the response to opioids is less than optimal. In general, higher opioid dosages provide greater pain relief; therefore, increasing the dosage of fentanyl and morphine is an option for this patient but will likely not be effective because of the descriptions of neuropathic pain (Answer B is not correct). Adjuvant analgesic drugs, including tricyclic antidepressants and anticonvulsants, are used to help manage neuropathic pain. Gabapentin, with a good adverse event profile, is a reasonable option. However, adjuvant analgesic drugs should not be given to decrease the opioid dosage or discontinue the use of opioid drugs (Answer A is not correct). Adding gabapentin to the current medication profile is the best choice (Answer D is correct). It may be possible to decrease the dosages of opioids later if gabapentin provides adequate pain relief. Diazepam is more effective for muscle spasms than for neuropathic pain, and this option includes decreasing the fentanyl dosage at the same time as the new drug is initiated (Answer C is not correct).

9. Answer: D

Limited-stage small cell lung cancer is potentially curable; therefore, the patient should continue on the planned chemotherapy dosages. The correct dosage of filgrastim is 5 mcg/kg/day subcutaneously, not 250 mcg/m² (this is the dose for sargramostim) (Answer A is not correct). The correct dosage for pegfilgrastim is a single 6-mg injection (Answer C is not correct). Filgrastim should not be given on the same day as chemotherapy (Answer B is not correct, Answer D is correct).

10. Answer: A

Doxorubicin undergoes hepatic clearance (by the biliary tract), and there are recommendations for dosage reduction based on bilirubin (Answer A is correct). There is no reason to reduce the cyclophosphamide dosage (Answer B is not correct). Because only doxorubicin requires reduction, both agents should not be adjusted based on the laboratory values given (Answer

D is not correct). Both agents shouldn't be continued at the current dose as doxorubicin must be adjusted in patients with elevated total bilirubin (Answer D is not correct).

11. Answer: A

Large cell lymphoma is faster growing and more chemosensitive than metastatic colorectal cancer (Answer B is not correct). Therefore, patients with large cell lymphoma are more likely to develop hyperuricemia or TLS from rapid cell turnover, both before treatment and after chemotherapy (Answer A is correct). Hypercalcemia is not a common complication of either of these diseases. Some aggressive lymphomas may be associated with hypercalcemia, but pamidronate is used to treat, not prevent, this complication (Answer C and D are not correct).

12. Answer: C

Neither patient should undergo chemotherapy with an ANC of 800 cells/mm³ (Answer A and B are not correct). Both can be treated when neutropenia resolves (probably within 1 week). It is important to keep patient 1 on schedule because his disease is potentially curable; therefore, patient 1 should receive filgrastim after the next chemotherapy treatment to prevent another dose delay (answer C is correct). When patient 2 resumes chemotherapy, his dosages can be decreased to prevent a recurrence of neutropenia (Answer D is not correct).

13. Answer: C

Injury after extravasation of an anthracycline is potentially the most severe. Therefore, when the recommended antidotes for different vesicants conflict (e.g., heat vs. cold), treatment should be directed at the anthracycline (Answer B is not correct). Dexrazoxane is now indicated for doxorubicin extravasation (Answer C is correct). Cold, rather than heat, would also be appropriate (Answer A is not correct). Although vincristine is considered a vesicant, sodium thiosulfate is not the recommended antidote (Answer D is not correct).

