Chapter 150: Supportive Care in Cancer

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KEY CONCEPTS

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1. Myelosuppression (low blood counts), a common dose-limiting toxicity for numerous anticancer agents, is managed with blood product transfusions, colony-stimulating factors (CSFs), and/or anticancer therapy dose reduction or delay.

2. Prevention of chemotherapy-induced nausea/vomiting (CINV) throughout the entire risk period is based on emetic risk of regimen, patient risk factors, and response. Management of chemotherapy-induced mucositis and diarrhea uses supportive care measures.

3. Tumor lysis syndrome (TLS) is one of the most common oncologic emergencies and warrants prophylaxis with hydration and either allopurinol or rasburicase depending on risk stratification and TLS management requires ongoing monitoring to correct electrolyte disturbances to prevent clinical sequelae, such as renal impairment, cardiac events, or seizures. Extravasation of intravenous (IV) chemotherapy requires prompt intervention, which may include antidote administration.

4. Immunotherapies are associated with unique immune-related adverse effects (irAEs) managed with immunosuppression (commonly corticosteroids) and dose delay or permanent discontinuation if necessary. Dose reduction is not a strategy used to manage irAEs.

5. Anticancer treatments which capitalize on the immune system, such as chimeric antigen receptor T cell (CAR-T) therapy, can cause cytokine release syndrome (CRS) and neurotoxicity, requiring close monitoring and prompt intervention with the anti-interleukin-6 agent tocilizumab and corticosteroid, respectively.

6. Dermatologic toxicities from cancer treatment are broad in presentation, and accurate identification is important to determine appropriate supportive care interventions. Patients may experience endocrine, cardiovascular, and ocular toxicities as a complication of cancer treatment; prompt identification and management are key to minimizing long-lasting adverse drug reactions (ADRs).

7. Osteopenia or osteoporosis from anticancer treatment or bone fractures and pain from malignancy metastasizing to bone are common. Prevention of skeletal-related complications is important to maintaining patient quality of life.

8. Venous thromboembolisms (VTEs) can be caused by malignancy, treatment, implanted devices (catheters or ports), and comorbidities, and both prevention and treatment are unique in patients with cancer. Routine prophylaxis is recommended in some scenarios, treatment of VTE should continue for at least 3 months or as long as the patient has active cancer or is receiving anticancer therapy, and only certain agents are recommended for prophylaxis and treatment.

9. Patients with cancer may be impacted by pain from various causes, including their disease or complications of cancer treatment and at different time points during their treatment.

10. Numerous long-term physical and psychological complications can occur after cancer treatment. Patients should be educated about potential risk for infertility and secondary malignancies from anticancer treatments.

BEYOND THE BOOK

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Activity

Immune checkpoint inhibitors have revolutionized the treatment of patients with cancer. However, their unique toxicity profile brings a new challenge to the health professional. Oncologic societies have published multiple guidelines to aid in managing immune-related adverse events (irAEs). Please review the *National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology* (NCCN Guidelines) for the "Management of Immunotherapy-Related Toxicities"[1] (https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf). Based on these guidelines and the *National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0* guidelines[2] (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf), please provide your recommendations on the case below.

This activity is helpful to enhance student understanding of the Assess, Plan, Implement, and Follow-up steps in the patient care process.

Patient Case

AD is a 64-year-old patient with metastatic melanoma who presents to the clinic for cycle 5, day 1 of pembrolizumab. The chief complaint is a 3-day history of severe abdominal pain and "profuse diarrhea," which is estimated to be about 10 bowel movements per day (baseline = 1 bowel movement/day). There is tenderness to palpation on examination, but overall, you feel the symptoms are not life-threatening, afebrile and the patient denies blood in their stool. Based on vital signs and laboratory assessments, the patient is admitted to the inpatient oncology service. Workup suggests an inflammatory process in the colon, which you attribute to pembrolizumab.

PMH: Hypertension (HTN) diagnosed 3 years ago, metastatic melanoma diagnosed 5 months ago

Vitals: O_2sat: 98% (0.98) RA; HR 82 bpm; BP 99/51 mm Hg; 37.4°C

Labs: sodium 138 mEq/L (mmol/L; 136-145 mEq/L [mmol/L]); potassium 2.9 mEq/L (mmol/L; 3.4-5.1 mEq/L [mmol/L]); chloride 99 mEq/L (mmol/L; 98-107 mEq/L [mmol/L]); glucose 98 mg/dL (74-99 mg/dL) (5.4 mmol/L [4.1-5.5 mmol/L]); albumin 3.6 g/dL (3.5-5.2 g/dL) 36 g/L [35-52 g/L]); calcium 9.28 mg/dL (8.60-10.2 mg/dL) (2.32 mmol/L [2.15-2.55 mmol/L]); magnesium 1.34 mg/dL (1.61-2.60 mg/dL) (0.55 mmol/L [0.66-1.07 mmol/L]); phosphorous 2.0 mg/dL (2. 5-4.5 mg/dL) (0.65 mmol/L [0.81-1.45 mmol/L]); creatinine 0.94 mg/dL (83 µmol/L; CrCl ~80 mL/min [1.33 mL/s]); ALT 28 U/L (0-33 U/L) (0.47 µkat/L [0-0.55 µkat/L]); ALT 23 U/L (0-32 U/L) (0.38 µkat/L [0-0.53 µkat/L]); T Bili 0.02 mg/dL (0-1.2 mg/dL) (0.3 µmol/L [0-20.5 µmol/L])

Allergies: NKDA

Medication List: lisinopril 10 mg PO once daily; pembrolizumab 200 mg IV every 3 weeks

- Q1. Using NCI CTCAE v5.0, what grade of colitis is AD experiencing?
- Q2. Based on the NCCN guidelines, what is your initial treatment recommendation for this patient? Include any pharmacotherapy interventions and affiliated supportive care measures as well as plan for the current anticancer regimen.
- Q3. After 72 hours of treatment with your initial recommendation, AD's symptoms have not improved. What is your recommendation for the treatment of refractory colitis?

INTRODUCTION

Anticancer treatments can result in numerous adverse drug reactions (ADRs), many of which may be life-threatening if not appropriately managed. ADRs (or toxicities) often relate to the agent's mechanism of action or "off-target" effects. Cytotoxic chemotherapy acts on rapidly dividing cells, often

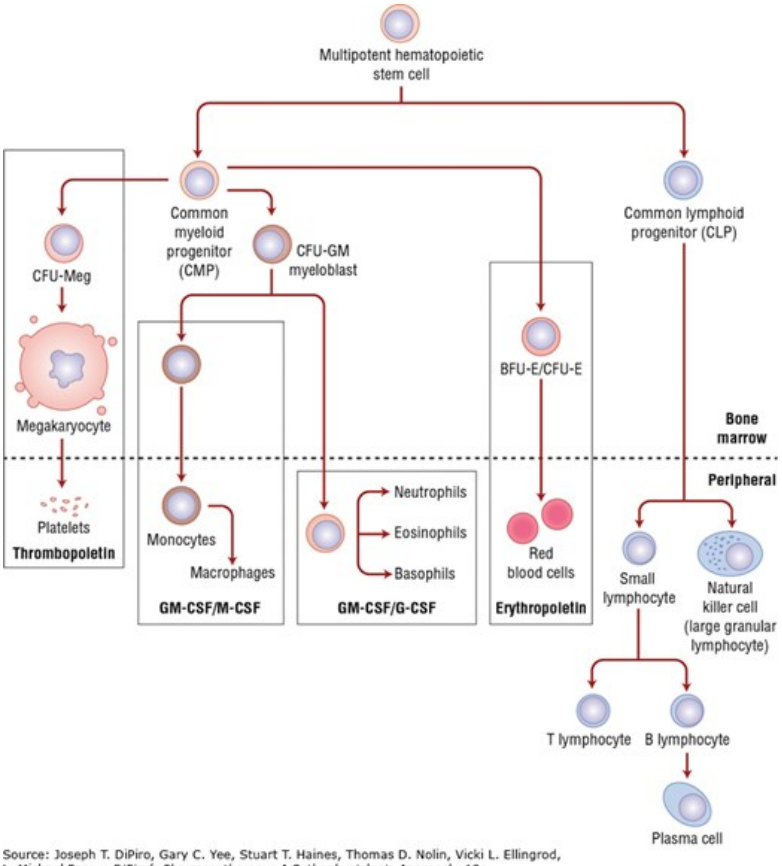
resulting in myelosuppression, gastrointestinal (GI) effects (mucositis, diarrhea, etc.), alopecia, and infertility. Biologic therapies and targeted small molecule agents have various ADRs, depending on the altered intracellular signaling, for example, rash with epidermal growth factor receptor (EGFR) inhibitors and hemorrhage or thrombosis with vascular endothelial growth factor (VEGF) inhibitors. Immunotherapies have a unique ADR profile, including autoimmune toxicities related to the modulation of the immune system. In general, toxicities are commonly graded via the Common Terminology Criteria for Adverse Events (CTCAE) scale from 0 (no toxicity) to 5 (death).[2] The principles of preventing and managing some of the most common and severe ADRs associated with anticancer therapies are detailed below.

HEMATOLOGIC TOXICITIES: ANEMIA, NEUTROPENIA, AND THROMBOCYTOPENIA

Normal hematopoiesis consists of several well-orchestrated steps. Pluripotent stem cells differentiate, proliferate, and maturate to allow the formation of the blood cells seen in the peripheral circulation. Specifically, myeloid stem cells give rise to erythrocytes, platelets, monocytes, basophils, neutrophils, and eosinophils. In contrast, lymphoid stem cells give rise to B-lymphocytes, T-lymphocytes, and natural killer cells (Fig. 150-1).

FIGURE 150-1

Schematic of hematopoiesis with site of action of targetable hematopoietic growth factors. Multipotent hematopoietic stem cells (HSCs) differentiate in the bone marrow into common myeloid or lymphoid progenitors (CMP, CLP) which ultimately generate all mature blood cells. In the lymphoid lineage, the CLP gives rise to B cells, T cells, and natural killer (NK) cells. In the myeloid lineage, the CMP gives rise to several colony forming units (CFUs) and burst forming units (BFUs) that result in the creation of platelets (also called thrombocytes), red blood cells (also called erythrocytes), and myeloblast cells (which further give rise to neutrophils, basophils, eosinophils) as well as monocytes (which become macrophages). Numerous hematopoietic growth factors influence the self-sustaining HSCs to differentiate into these various cells; notably, further differentiation of myeloblasts, megakaryocytes, and erythrocytes can be stimulated by granulocyte colony-stimulating factor (G-CSF) or monocyte/macrophage-stimulating factor (M-CSF), thrombopoietin, and erythropoietin, respectively.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Myelosuppression, depressed bone marrow function resulting in low blood counts—anemia, neutropenia, and thrombocytopenia—can occur due

to cancer invasion in bone marrow or after various anticancer therapies. Myelosuppression is typically not an immediate effect because the circulating blood cells must first be killed by the anticancer treatment or used by the body. For example, neutropenia typically occurs first because white blood cells (WBCs) have a short lifespan of 6 to 12 hours, followed by thrombocytopenia as platelets have a lifespan of 5 to 10 days. Anemia typically occurs late since erythrocytes have a relatively long lifespan of 120 days. The lowest blood cell count (or nadir) typically occurs 10 to 14 days after cytotoxic chemotherapy administration, with a recovery in cell counts occurring by 3 to 4 weeks after administration, or later depending on the agent (eg, nitrosoureas and radiolabeled monoclonal antibodies at 4-6 weeks). Patients with leukemia or receiving a hematopoietic stem cell transplantation (HSCT) typically have a more rapid nadir of approximately 5 to 7 days due to the intensity of therapy utilized in these conditions and the nature of the disease. In many scenarios, subsequent doses should be delayed until minimum suggested blood counts (eg, absolute neutrophil count [ANC] ≥1,000-1,500 cells/mm^3 [1×10^9-1.5×10^9/L], platelets ≥100,000/μL [100×10^9/L]) are achieved to minimize additional toxicity and morbidity. Dose reductions may be considered empirically based on baseline myelosuppression or, more commonly, during treatment based on either prolonged recovery of counts or severe myelosuppression warranting intervention (transfusions/occurrence of neutropenic fever). However, clinicians must balance dose reduction with treatment goals since reduced treatment intensity can compromise efficacy in certain disease states (eg, breast cancer, lymphoma). Clinicians accept some myelosuppression if it is not compromising the patient's quality of life, and the cancer is responding to therapy. In patients where cure is commonly the goal, the empiric use of hematopoietic growth factor products (also called colony-stimulating factors [CSFs]) provides an alternative to dose reduction.

Neutropenia

Neutropenia is associated with an increased risk of infection, the probability of which increases when ANC is <500 cells/mm^3 (0.5×10^9/L) or when the duration of neutropenia is prolonged (>7-10 days). Other risk factors for infection include alteration in the integrity of physical defense barriers and the functional integrity of the leukocytes, which can be affected by underlying cancer, anticancer agent, or radiation therapy (RT).

Infections are difficult to identify in the neutropenic patient since usual signs and symptoms of infection (eg, purulent drainage) are often absent. Therefore, clinicians heavily rely on fever as an indicator of infection in these patients. Prompt initiation of empiric antibiotics, based on likely organisms from patient presentation and history and local antibiogram, is paramount to prevent mortality. The most common source of infection in these patients is self-infection with body flora, which includes both gram-positive and gram-negative bacteria. Specific treatment of infections in immunocompromised hosts is discussed in Chapter 145, "Infections in Immunocompromised Patients."

CSF products may minimize the severity of neutropenia and subsequently reduce the risk of infection. These products provide proteins essential for the normal growth and maturation of blood cell components (Fig. 150-1). Filgrastim stimulates the production of neutrophilic granulocytes, and sargramostim promotes the proliferation of granulocytes (neutrophils and eosinophils), monocytes, and macrophages. Although sargramostim stimulates megakaryocytes, no consistent effect on platelet production has been observed in trials, and this agent is not commonly used in clinical practice. Both CSFs initially enhance demargination and mobilization of mature cells from the marrow and then provide constant stimulation of stem cell progenitors. Pegfilgrastim is a pegylated form of filgrastim with a substantially longer half-life allowing for single-dose administration compared to daily doses of filgrastim. A pegfilgrastim device is available, which can be placed immediately after the end of chemotherapy to auto-inject the dose of pegfilgrastim 24 hours later. Several biosimilar CSF products are also available and generally considered interchangeable.[3]

For optimal efficacy, CSFs should be started between 24 and 72 hours after chemotherapy. Filgrastim and sargramostim can be stopped the day before chemotherapy, whereas pegfilgrastim should not be administered within 12 days before the next dose of chemotherapy due to its extended half-life.[3] CSFs should not be administered within 14 days of chimeric antigen receptor T cell (CAR-T) due to increased risk of cytokine release syndrome (CRS).[3] Subcutaneous administration is preferred for CSFs. Because of the high cost of these agents, doses of filgrastim are commonly rounded to the nearest product vial size to minimize waste.

CSFs are generally well tolerated, with the most common ADR being bone pain, which can be mitigated with routine concomitant use of an antihistamine, such as loratadine and/or pain medications such as nonsteroidal anti-inflammatory agent naproxen, if no contraindicating factor exists, for the week after CSF administration.[3] Other ADRs include constitutional symptoms (low-grade fever, myalgia, headache, etc.), injection site reactions, and generalized maculopapular rash, with a rare but serious ADR of splenic rupture.

Guidelines exist regarding appropriate use of CSFs for prophylaxis of neutropenia based on the propensity of a regimen to cause febrile neutropenia (FN), which can also be determined from safety results in clinical trial reports.[3,4] Primary prophylaxis, the prevention of neutropenia with the first cycle

of chemotherapy, is recommended for patients receiving a chemotherapy regimen with ≥20% risk of FN.[3,4] Most dose-dense chemotherapy regimens require CSF support to maintain dose intensity and schedule.[3] Additionally, primary prophylaxis can be considered for patients with at least one risk factor who are receiving a chemotherapy regimen with a 10% to 20% risk of FN (intermediate risk). Patient risk factors include age at least 65 years receiving full chemotherapy dose intensity, previous chemotherapy or RT, persistent neutropenia, bone marrow involvement of tumor cells, recent surgery and/or open wounds, liver dysfunction, and renal dysfunction. Secondary prophylaxis refers to the prevention of recurrent neutropenia in patients who had experienced a neutropenic complication (eg, FN) with the prior cycle of chemotherapy. Secondary prophylaxis is generally reserved for patients with chemosensitive cancers where a dose reduction or delay may affect survival. In other scenarios, dose reduction or delay in chemotherapy may be utilized instead of CSFs. Re-evaluation of FN risk is warranted after each cycle and at changes in therapy. CSFs are not recommended for neutropenic patients who are afebrile or routinely for management of FN. However, they may be considered for high-risk patients based on clinical judgment and patient-specific risk factors.[3,4] The use of CSFs in pediatric oncology patients is guided by clinical protocol.

Regarding patients with myeloid malignancies, since myeloid blast cells have receptors for granulocyte CSF and granulocyte-macrophage CSF, some experts were initially concerned that the use of CSFs would stimulate the regrowth of leukemia. Although subsequent studies have addressed these concerns and CSFs can be considered after initial induction therapy (although beneficial impact is deemed to be modest), many clinicians do not initiate filgrastim until an initial remission is achieved. CSFs are used following consolidation therapy in adult patients with acute leukemia. Notably, the use of CSFs can interfere with the interpretation of the day 14 bone marrow examination in this population (ie, may see immature myeloid forms erroneously suggesting residual disease); therefore, CSFs should be discontinued at least 7 days before a bone marrow biopsy.[5] Growth factors are not recommended in patients with acute promyelocytic leukemia during induction therapy due to increased risk of differentiation syndrome.[5]

Other uses for CSFs include peripheral blood stem cell mobilization protocols (notably, higher doses than used for prophylaxis) and the management of congenital or idiopathic neutropenia. In patients undergoing HSCT, CSFs have also proven effective in accelerating engraftment and treating graft failure; therefore, they are recommended postautologous HSCT and can be considered postallogeneic HSCT.[4] CSFs should be used with caution in patients receiving concomitant chemotherapy and RT, especially if the RT involves the mediastinum, as these patients appear to experience more significant thrombocytopenia.

Trilaciclib is a first-in-class myeloprotective agent approved for patients with extensive stage small cell lung cancer with ongoing trials for patients diagnosed with other malignancies. When administered before chemotherapy, trilaciclib arrests hematopoietic stem and progenitor cells in the G1 phase to prevent cellular damage from the cytotoxic chemotherapy. It is administered intravenously on each day of chemotherapy administration. The most common adverse effects are fatigue, hepatotoxicity, and electrolyte imbalances (calcium, potassium, and phosphate). Trilaciclib has several drug-drug interactions, including with cisplatin which may result in increased risk of nephrotoxicity.[6]

Anemia

Anemia is a common complication after cytotoxic chemotherapy and various tyrosine kinase inhibitors (TKIs), such as those targeting EGFR, human epidermal growth factor receptor 2 (HER2), and VEGF. Incidence varies by cancer type and stage as well as dose and duration of therapy. Further, patient-specific factors may contribute to nutritional deficiencies (ie, iron, folate, vitamin B12), receipt of RT, renal dysfunction, and anemia of chronic disease. Fatigue is the most common symptom of anemia, with some patients reporting other symptoms such as shortness of breath. Other causes of fatigue should be considered, such as insomnia, depression, unrelieved pain, and underlying malignancy.

The mainstay of treatment of symptomatic or severe chemotherapy-induced anemia is red blood cell transfusion. Transfusions of packed red blood cells (PRBCs) are generally indicated for hemoglobin <8 g/dL (80 g/L; 4.97 mmol/L) or higher if the patient is experiencing extreme fatigue or dyspnea, tachycardia, or chest pain. Erythropoiesis-stimulating agents (ESAs; epoetin alfa, darbepoetin alfa) may be considered in patients with underlying kidney disease and those receiving palliative treatment who have a hemoglobin <10 g/dL (100 g/L; 6.21 mmol/L). ESAs are restricted to these populations due to serious ADRs, including thrombosis and myocardial infarction, and increased risk of mortality in patients with cancer. Other ADRs of ESAs include injection site reactions, rash, flu-like symptoms, and HTN. Therefore, the risks and benefits of ESA use must be discussed with patients in advance. Generally, these ADRs occurred when the target hemoglobin of 12 g/dL (120 g/L; 7.45 mmol/L) is exceeded or hemoglobin rises too rapidly. Evaluation for iron deficiency is advised before initiating ESA with appropriate ongoing laboratory monitoring. If ESAs are utilized, the goal is to achieve the minimum hemoglobin needed to avoid transfusions. ESAs should not be used for nonchemotherapy-induced anemia, except for select patients with myelodysplastic syndrome. Clinical practice guidelines for cancer and chemotherapy-induced anemia are available.[3,7]

Thrombocytopenia

Thrombocytopenia associated with chemotherapy increases the risk for significant bleeding. The mainstay of management is platelet transfusion which is administered to patients with platelet count <10,000 cells/mm^3 (10×10^9/L) or higher if patient is experiencing active bleeding, undergoing an invasive procedure, has coagulation abnormalities (eg, acute promyelocytic leukemia), or has fever/documented infection.[8] Alloimmunization rarely occurs due to antibodies against human leukocyte antigen (HLA) antigens; in these scenarios, histocompatible donors must be utilized.

GI TOXICITIES: DIARRHEA, MUCOSITIS, AND NAUSEA/VOMITING

Diarrhea

Mucosal damage can occur at any point along the entire length of the GI tract. In the lower portion of the GI tract, this usually manifests as diarrhea and abdominal pain although onset of symptoms varies by inciting agent (eg, generally within a few days of cytotoxic chemotherapy versus delayed after immunotherapy). Monitoring includes stool count per day, electrolytes, and fluid balance since supplementation may be necessary. After infectious causes have been ruled out, mild-to-moderate diarrhea can safely be treated with loperamide (up to 2 mg every 2 hours), with oral antibiotics and/or octreotide for persistent diarrhea (≥48 hours). Adjunctive diphenoxylate/atropine (diphenoxylate 5 mg four times a day; maximum 20 mg per day) can also be used. Nonpharmacologic interventions include cessation of products containing lactose, alcohol, or high-osmolar supplements with addition of clear liquids and small frequent meals; the BRAT diet (banana, rice, applesauce, toast) may also be considered. Severe or complicated diarrhea (dehydration, hypotension, bleeding, fever, neutropenia, severe cramping, unresponsive to intervention, etc.) warrants hospital admission with hydration, antibiotics, and the somatostatin analog octreotide; notably, anticancer treatment often needs to be held.[9]

Certain anticancer agents are known to commonly cause diarrhea. Irinotecan and sacituzumab govitecan can cause both acute diarrhea, occurring in first 24 hours and managed with atropine to counteract the underlying cholinergic mechanism, and delayed diarrhea, which occurs after 24 hours, and is managed supportively as per above. Other agents that commonly induce diarrhea are 5-fluorouracil, capecitabine, certain targeted chemotherapy agents (eg, imatinib and EGFR, HER2, VEGF, phosphoinositide-3 kinase [PI3K], cyclin-dependent kinase, or CDK4/6, inhibitors), and immune checkpoint inhibitors (ICIs); see "Immune-Related Adverse Events" section. Management of diarrhea may vary by agent and its route of administration.

Mucositis

Due to rapid cellular turnover, the GI mucosa is a common site of toxicity associated with anticancer therapy, particularly cytotoxic chemotherapy agents (eg, fluorouracil, methotrexate) and agents, such as multikinase and mammalian target of rapamycin (mTOR) inhibitors. The subsequent inflammation (mucositis) can lead to painful ulcerations and an inability to eat, drink, or swallow. Disruption of the GI mucosal barrier may also provide an avenue for systemic microbial invasion and infection.

Prevention of mucositis is mainly through good oral hygiene. High-risk patients (poor dentition, high-dose chemotherapy, or RT involving the oropharynx) should undergo a dental evaluation before starting therapy and use mouth rinses (baking soda and salt water or plain saline rinses) during therapy.[10] Oral cryotherapy is recommended before certain chemotherapy, such as high-dose melphalan and 5-fluorouracil, to provide vasoconstriction in prevention of drug delivery to mucosal tissue. Prevention with palifermin, a keratinocyte growth factor, can be considered for patients receiving specific HSCT regimens.[11] Dexamethasone mouthwash can be utilized for mTOR-associated mucositis.[12]

After mucositis has developed, treatment is mainly supportive, including use of topical or systemic analgesics. Despite insufficient data, numerous formulations of "magic mouthwash" are commonly used in clinical practice. There are commercially available products, or a compound can be made often including ingredients of viscous lidocaine, diphenhydramine, and liquid antacid. Severe mucositis may lead to dehydration and require IV hydration and opioid analgesics, with prolonged severe cases also warranting evaluation for IV nutrition. Local infections caused by *Candida* species and herpes simplex virus (HSV) can occur; therefore, suspicious lesions should be cultured and appropriate antifungal or antiviral treatment initiated. Mild infections (ie, thrush) may be treated with topical antifungal therapy, such as clotrimazole troches or nystatin oral suspension, whereas more severe oral or esophageal fungal infections require systemic antifungal treatment (see Chapter 144, "Invasive Fungal Infections").

Nausea/Vomiting

Introduction

Chemotherapy-induced nausea/vomiting (CINV) is the nausea/vomiting (N/V) associated with the administration of chemotherapy, which is a physiologic and psychological process. The impact of CINV on quality of life is substantial. Unless adequately prevented and managed, CINV can lead to adverse outcomes such as metabolic derangements, nutritional depletion, anorexia, weight loss, premature withdrawal of anticancer treatment, and/or degeneration of self-care and functional ability.[13]

Antiemetic prophylaxis is based on emetogenicity, the likelihood an agent will induce N/V,[14] although this can be tailored by patient risk factors (age <50 years, female, history of motion or morning sickness, prior poor CINV control, and depression or anxiety) and prior lack of response to antiemetics.[13] Guidelines divide IV anticancer therapies into four risk categories: highly emetogenic chemotherapy (HEC), moderately emetogenic chemotherapy (MEC), low emetogenic chemotherapy (LEC), and minimally emetogenic, which causes CINV in >90%, 30% to 90%, 10% to 30%, and <10% of patients, respectively.[13] Oral anticancer therapy is classified as minimal-to-low if <30% risk or moderate-to-high risk if ≥30% risk.[13]

Pathophysiology and Definitions

Chemotherapy damages enterochromaffin cells lining the GI tract which releases serotonin. This process is the peripheral pathway, originating outside the central nervous system (CNS) and occurs within 24 hours of chemotherapy administration (acute CINV). Secondarily, chemotherapy alters the modulation of dopamine and substance P in the CNS. This process is the central pathway that originates within the CNS and occurs within 24 to 72 hours after chemotherapy administration (delayed CINV)[15] (see Chapter 53, "Nausea and Vomiting," Fig. 53-1). CINV can also be classified as anticipatory (conditioned response occurring before chemotherapy begins), breakthrough (occurs within 5 days of prophylactic antiemetics and requires rescue therapy), refractory, or chronic.

Presentation and Evaluation/Monitoring

Clinical presentation of CINV can include more than just emesis and/or nausea. Patients may also present with poor oral intake, malnutrition, weight loss, abdominal discomfort, dehydration, and dizziness. Monitoring should include laboratory markers of serum electrolytes and renal function as well as assessment of fluid status (input and output), blood pressure (BP; orthostatic hypotension), and medication history.

When evaluating CINV, providers must rule out other potential causes of N/V. The differential diagnosis may include fluid and electrolyte abnormalities, volume depletion, hypercalcemia, drug-/opiate-induced, GI obstruction, increased intracranial pressure, brain or meningeal involvement, uremia, and infection.[15] Ongoing monitoring should include emesis count, nausea score (usually a visual analog scale, or VAS), electrolytes, fluid balance, oral intake, and medication use.

Prevention and Treatment

Several antiemetic guidelines exist (American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Network [NCCN]); however, variations exist across guidelines, which may partially be due to the information available at the time of guideline publication. Some examples of differences across guidelines are with respect to the classification of emetic risk (eg, carboplatin AUC ≥4), preference for 5-hydroxytryptamine/serotonin receptor antagonist (5-HT3-RA) agent in MEC doublet, strength of recommendation for four-drug prophylaxis in HEC and HSCT, duration of dexamethasone in certain regimens, olanzapine dose, management of breakthrough CINV, and recommendation for adjunctive agents.[13,14] Therefore, clinicians should consider these variations when implementing recommendations in practice.

1 Antiemetic prophylaxis is determined by risk category: HEC, quadruplet (or triplet, per NCCN); MEC, doublet (or triplet, per NCCN); LEC, monotherapy; minimal, no prophylaxis (Table 150-1). The primary goal of prevention is no vomiting and no nausea throughout the risk period. The duration of emetic risk is 2 days for MEC and 3 days for HEC—antiemetics should be initiated before any chemotherapy with ≥10% risk (generally 30 minutes before) and administered through risk period.

TABLE 150-1

CINV Prophylaxis for IV Chemotherapy Regimens

CINV Prophylaxis Regimen Definitions			
Quadruplet Therapy	**Triple Therapy**	**Doublet Therapy**	**Monotherapy**
5-HT3-RA + steroid +NK1-RA + olanzapine	5-HT3-RA + steroid + NK1-RA *or* olanzapine	5-HT3-RA + steroid Optional: triplet regimen based on patient-specific risk factors (ie, NK1-RA- or olanzapine-based triplet)	5-HT3-RA *or* dexamethasone (per ASCO) *or* metoclopramide *or* prochlorperazine (per NCCN) All ONCE Doses

CINV Prophylaxis Recommendations for IV Chemotherapy[14]		
Risk	**Phase**	**Prophylaxis**
HEC	Acute Phase	Quadruplet: 5-HT3-RA + dexamethasone + NK1-RA + olanzapine
	Delayed Phase	Olanzapine on days 2-4 If used on day 1, oral aprepitant continues days 2-3 If regimen other than AC, dexamethasone continues days 2-3 (dose varies by which NK1 utilized)
MEC	Acute Phase	Doublet: 5-HT3-RA + dexamethasone
	Delayed Phase	Dexamethasone 8 mg PO/IV on days 2-3 only if patients receiving therapies with known potential for delayed CINV
LEC	Acute Phase	Monotherapy: 5-HT3-RA or dexamethasone
	Delayed Phase	None
Minimal	Acute Phase	None
	Delayed	None

AC, anthracycline + cyclophosphamide; NK1-RA, neurokinin-1 receptor antagonist.

Notes: Per ASCO guideline,[14] carboplatin with AUC ≥4 specifically warrants prophylaxis in acute phase with 5-HT3-RA + Dex + NK1-RA and none in delayed phase. When given at equipotent doses, oral and IV serotonin receptor antagonists are equivalent in efficacy.

Patients receiving multiday chemotherapy regimens should be provided antiemetics appropriate for the agent with highest emetogenicity on each day chemotherapy is administered and for the risk period after completion of the regimen, which depends on emetogenicity of last agent(s) administered. For example, a triplet antiemetic therapy is used for 4- to 5-day cisplatin regimens. In patients undergoing HSCT conditioning regimens, triplet or quadruplet antiemetic therapy is recommended.[14]

Oral Anticancer Therapy-Induced N/V

The antiemetic risk of oral anticancer therapies is divided into two categories: moderate-to-high risk (≥30%) versus minimal-to-low risk (<30%). Prophylaxis for moderate-to-high risk is a 5-HT3-RA given 30 minutes before anticancer therapy each day. Prophylaxis for minimal-to-low risk is an as-needed antiemetic agent (5-HT3-RA, prochlorperazine, or metoclopramide). Although if CINV does occur, a scheduled antiemetic before anticancer therapy is recommended.[13] Practical issues must be taken into consideration when choosing a prophylaxis regimen for oral anticancer therapy regimens including setting (inpatient versus outpatient) and available route(s) of administration, overlap with IV regimens, duration of risk period and antiemetic duration of efficacy, tolerability of prolonged antiemetic use, and adherence. Administration of prophylaxis and associated oral anticancer therapy at nighttime may be considered to improve tolerability.

Radiation-Induced N/V

The prevention of radiation-induced N/V is also based on emetogenic risk, which is dependent on the anatomic site of RT.[14] The optimal medication, dosing, and duration of prophylaxis regimen is unknown. Highly emetogenic RT includes total body irradiation (TBI), for which ondansetron or granisetron plus dexamethasone prophylaxis is recommended. For moderate risk, such as RT to the upper abdomen or craniospinalregion, ondansetron or granisetron before each fraction as well as dexamethasone before the first five fractions is recommended. For minimal and low risk RT, rescue therapy is recommended.[14]

Regarding those receiving concomitant RT and chemotherapy, antiemetic prophylaxis is based on the emetogenic risk of the chemotherapy regimen, unless the emetogenic risk level of RT is higher, and continuing prophylaxis appropriate for RT if it continues beyond the end of chemotherapy prophylaxis period.[13,14]

Anticipatory CINV

Anticipatory N/V is often a result of prior negative experience. Patient education is critical: first, educate on what prophylaxis is being offered to alleviate fear; second, educate on specific management strategies for coping with CINV. For example, behavioral therapy can be employed and if benzodiazepine is prescribed; this can be administered 30 minutes before arriving to ambulatory care treatment center or before meals, depending on association of event/food with onset of nausea. Often, lorazepam 0.5 to 2 mg oral (PO)/IV every 4 to 6 hours or pre-meals is utilized in clinical practice.

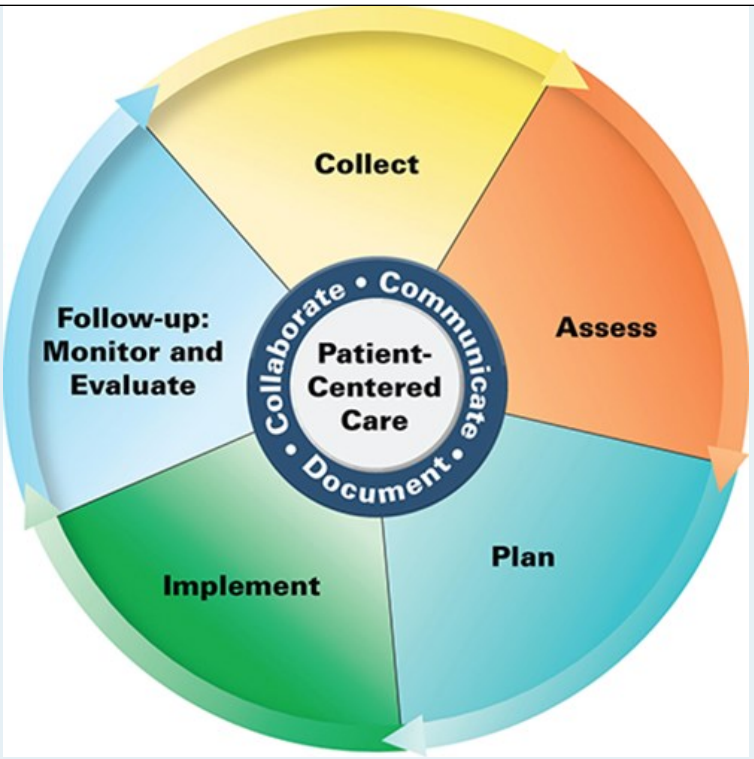
Management of Breakthrough and Refractory CINV

All patients should be provided with breakthrough (PRN) medication and instructed to take as soon as feel nauseated or have emesis. Choice of breakthrough agent may vary in practice, although selecting an agent not previously given as prophylaxis and consideration of toxicities of antiemetics are key considerations. Options include olanzapine, phenothiazine, metoclopramide, dronabinol, scopolamine patch, haloperidol, 5-HT3-RA, dexamethasone, or benzodiazepine.

If breakthrough occurs, future cycles should be adjusted (ie, increase prophylaxis).[13] Specifically, if olanzapine was not previously included in prophylaxis, it should be added.[14]

PATIENT CARE PROCESS

Patient Care Process for Supportive Care in Cancer



The patient care process for tumor lysis syndrome (TLS). See "Oncologic Emergencies: TLS and Extravasation" section and Table 150-2.

Collect

- Patient demographic factors including concomitant medications, cancer diagnosis, and current/impending anticancer treatment intervention(s) along with their affiliated TLS risk category
- Laboratory markers: potassium, SCr, calcium, phosphorus, and uric acid

Assess

- Urine output and hydration status
- Presence of cardiac arrhythmias or seizure activity (ie, obtain ECG and EEG if warranted)
- Presence of symptoms of hyperkalemia (eg, muscle cramps), hypocalcemia (eg, paresthesia), hyperphosphatemia (eg, lethargy), and/or hyperuricemia (eg, oliguria/anuria)

Plan*

- Drug therapy regimen to include hydration with allopurinol for intermediate-risk or rasburicase for high risk. Additionally, add interventions for specific laboratory TLS as indicated (eg, phosphorus binder for hyperphosphatemia)
- Monitoring above laboratory parameters as per risk level

Implement

- Patient education on symptoms of clinical TLS
- Schedule follow-up laboratory monitoring as per risk level

Follow-up: Monitor and Evaluate

- Ongoing laboratory monitoring (at least daily or more frequently if intermediate to high risk or active clinical TLS)
- Resolution of any signs/symptoms and ongoing clinical assessment for renal, cardiac, and/or neurologic changes

Collaborate with patient, caregivers, and other healthcare professionals.

ONCOLOGIC EMERGENCIES: TLS AND EXTRAVASATION

Oncologic emergencies are a diverse group of acute complications associated with cancer pathophysiology itself and/or the initiation of anticancer treatments. These situations may be the presenting reason for acute hospitalization whereby a diagnosis of cancer is made or may occur at any time during a patient's course of management. Prompt identification and adequate initial treatment are critical to prevent morbidity and mortality. Many complications are considered oncologic emergencies, including TLS and extravasation, which are detailed below. Other oncologic emergencies are beyond the scope of this chapter but include hypersensitivity reaction (see Chapter e108, "Drug Allergy"), FN (see Chapter 145, "Infections in Immunocompromised Patients"), hypercalcemia of malignancy (see Chapter 69, "Calcium and Phosphorus Homeostasis"), malignant spinal cord compression, superior vena cava syndrome, malignant pericardial effusion, malignant airway obstruction, disseminated intravascular coagulopathy, hyponatremia, hyperviscosity syndrome, and leukocytosis.[16,17]

Tumor Lysis Syndrome

TLS is the most common disease-related oncologic emergency. TLS occurs due to the rapid destruction of cells either spontaneously from cancer progression or due to effects of antineoplastic therapy.[18] The lysis of cells releases intracellular contents leading to catabolism of nucleic acids, which results in hyperuricemia while the release of potassium and phosphorus leads to hyperkalemia, hyperphosphatemia, and secondary hypocalcemia. Urate or phosphorus-calcium crystals can cause renal insufficiency, hyperkalemia can cause cardiac disturbances, and hyperphosphatemia can lead to seizures. Laboratory TLS is defined by the Cairo-Bishop Criteria[73] (Table 150-2) while clinical TLS is the presence of laboratory TLS plus at least one of the following: renal impairment (serum creatinine [SCr] ≥1.5 × ULN), cardiac arrhythmias, or seizures. Cairo-Bishop grading scale for TLS evaluates level of renal impairment, cardiac arrhythmia, and seizure activity on a grade 0 to 5 scale.[18] Risk factors are patient-related (preexisting conditions such as dehydration, hypotension, acidosis, renal or cardiac disease) and disease-related (cancer diagnosis, tumor burden – bulky tumor >10 cm or WBC >25 × 10^3/μL (25 × 10^9/L), elevated lactate dehydrogenase, high proliferation rate, chemotherapy sensitivity). While lactate dehydrogenase is a surrogate marker for cell turnover rate and can therefore be a component in risk assessment, it is not part of the diagnosis of TLS.[19] TLS occurs most commonly in patients with aggressive hematologic malignancies, such as high-grade lymphomas or acute leukemias. Incidence varies widely depending on cancer and treatment type. Notably, TLS can occur not just after traditional cytotoxic IV chemotherapy, but also after RT, oral chemotherapy, or targeted therapy (eg, monoclonal antibodies).[20] TLS often occurs within 12 to 72 hours of initiation of antineoplastic therapy, although it can occur later depending on the antineoplastic agent's onset of activity or spontaneously prior to treatment initiation.

TABLE 150-2

Tumor Lysis Syndrome: Definition, Presentation, and Management

Laboratory TLS[a]	Symptoms/Signs	Management Strategies
Uric acid ≥8 mg/dL (476 µmol/L) or >25% ↑ from baseline	• Obstructive uropathy, hematuria, flank pain, lethargy, oliguria, or anuria	• Prevention: hydration, allopurinol (or potentially febuxostat); consider for low risk and optional for intermediate risk • Management: continue hydration; rasburicase optional for intermediate risk and recommended for high risk; allopurinol for those unable to receive rasburicase
Calcium ≤7 mg/dL (1.75 mmol/L) or >25% ↓ from baseline	• Muscle cramp/spasms, tetany, paresthesia, neurologic (confusion, hallucination, seizure), arrhythmia, bradycardia, cardiac failure, death	• First, manage hyperphosphatemia • If symptomatic, IV calcium may be administered
Potassium ≥6 mEq/L (mmol/L) or >25% ↑ from baseline	• GI (nausea, diarrhea, anorexia), muscle weakness/cramps, ECG abnormalities, sudden death	• Loop diuretic • IV insulin + dextrose • Inhaled albuterol • If mild/moderate – oral resin binder • If ECG changes – IV calcium • If acidotic – IV sodium bicarbonate
Phosphorous ≥4.5 mg/dL (1.45 mmol/L) in adults or ≥6.5 mg/dL (2.1 mmol/L) in children (>25% ↑ from baseline)	• GI (nausea, diarrhea), lethargy, seizures	• Reduce phosphorus intake • Phosphorus binders

[a]Two or more of the laboratory changes must be observed within 3 days before or 7 days after cytotoxic therapy.

Data from References 17,73.

TLS Monitoring

TLS Monitoring includes laboratory markers (uric acid, potassium, calcium, phosphorus), renal function, urine output, fluid status, and if needed assessment for arrhythmias (electrocardiogram [ECG]) or seizure activity (electroencephalogram [EEG]). At a minimum, daily assessment during period of risk is required, but more frequent monitoring may be warranted. For example, patients with intermediate risk warrant monitoring every 8 to 12 hours while those classified as high risk and those with active laboratory or clinical TLS may warrant up to every 4- to 8-hour laboratory monitoring.[21] Further, certain cytotoxic therapies have specific guidance regarding required monitoring and management of TLS for patients receiving those agents (eg, venetoclax).[22]

Clinicians should consider trends in laboratory markers (ie, levels and time between any changes in levels), patient risk stratification, and time point around chemotherapy when making recommendations for monitoring and interventions. Adjustment of laboratory monitoring should occur based on patient response to interventions (ie, increase monitoring if optimal response not achieved, reduce frequency of monitoring if not TLS occurring).

Cessation of laboratory monitoring can occur once a patient is outside the period of risk, and all laboratory markers have been stable within normal limits at the discretion of the provider.

TLS Management

Prevention of TLS is paramount. First, in some high-risk patients, the oncologist may opt to "de-bulk" prior to initiating intensive cytotoxic chemotherapy to reduce the risk of severe TLS often with agents, such as cyclophosphamide or hydroxyurea.[23] Second, all patients should be risk stratified, which dictates prophylaxis. Overlap exists between prevention and management of TLS as all patients require ongoing monitoring and adequate hydration (Table 150-2).

Hydration is a mainstay in the prevention of TLS as it enhances urinary excretion of intracellular components via increased intravascular volume and improved renal perfusion enhancing glomerular filtration.[24] Guidelines recommend hydration with approximately 3 L/m^2/day for adult patients at intermediate-to-high risk of TLS[25] while others recommend fluid intake of one to two times maintenance requirements with a goal urine output of 80 to 100 mL/m^2/hr.[24] Although specific fluid types or hydration rates are not standardized, typical fluids are isotonic saline or dextrose containing products as potassium additives or fluids containing potassium (ie, Lactated Ringer's) should be avoided given the risk of hyperkalemia.[25] While diuretics may be used to enhance excretion, caution is warranted, and providers must first ensure no obstruction or hypovolemia exists. No benefit is seen with the addition of alkalinization (ie, sodium bicarbonate); therefore, this strategy is no longer recommended.[25] Hydration should be continued during management of TLS.

Prevention and Management of Hyperuricemia

Hyperuricemia occurs due to the breakdown of nucleic acids released from cells. As uric acid is poorly soluble, it can precipitate leading to obstructive uropathy and acute kidney injury. To prevent and manage hyperuricemia, patients at low risk may receive allopurinol, those with intermediate risk can receive either allopurinol or rasburicase, and those at high risk are recommended to receive rasburicase.

Allopurinol is a xanthine oxidase inhibitor which prevents the conversion of xanthine to uric acid. Therefore, this intervention is preventative with a slow onset of action and should ideally be initiated at least a day before starting chemotherapy. Notably, xanthine itself can accumulate and lead to crystallization, although the precise impact on TLS is not well characterized. Recommended dose of allopurinol is 300 mg/m^2/day PO in one to three divided doses rounded to tablet size (available in 100 mg and 300 mg tablets), with a maximum of 800 mg/day; intravenous (IV) administration is available with different dosing for those unable to take oral medications. Renal dose adjustment is necessary. Allopurinol may cause GI ADRs, rash, as well as hypersensitivity reactions particularly in Asian populations due to a higher frequency of HLA-B*58:01 allele associated with more severe cutaneous drug reaction.[19] Febuxostat is another xanthine oxidase inhibitor which may be used as an alternative to allopurinol.[26] This agent does not require renal dose adjustment and is associated with lower risk of hypersensitivity reactions.

In patients with hyperuricemia before anticancer treatment begins, xanthine oxidase inhibitors are unlikely to be effective. Therefore, rasburicase, a recombinant urate oxidase that converts uric acid into more soluble allantoin, is warranted for the management of hyperuricemia. A fixed dose of rasburicase (6 mg IV once)[27] is recommended for adult patients as a cost-saving measure. Pediatric protocols may require weight-based dosing. Peak activity occurs around 4 hours, and it is generally well tolerated, although GI ADRs, headache, and rash may occur. Notably, pregnant patients and those with glucose-6-phosphate dehydrogenase (G6PD), deficiency are at risk for hemolysis and methemoglobinemia; therefore, assessment in those of certain ethnic background (African American, Mediterranean, or Southeast Asian) who are more likely to exhibit G6PD deficiency is warranted before administration if feasible. Further, blood samples drawn after administration of rasburicase must be immediately placed on ice for transport to laboratory, otherwise the drug continues to act on the blood sample and can lead to falsely low readings.

Management of Electrolyte Disturbances

Rapid treatment of hyperkalemia can be achieved with loop diuretics or intracellular shift of potassium via the administration of 10 units of IV insulin (0.1 unit/kg for pediatric patients) followed by dextrose (generally 25-50 mL of 50% dextrose for adults) or inhalation of albuterol. For mild hyperkalemia not necessitating rapid treatment, cation exchange resins, such as sodium polystyrene sulfate 15 to 30 g PO once, with repeat doses as needed based on repeat potassium levels, can be utilized to remove potassium through the GI tract. Slow infusion of calcium gluconate (1 g IV for adults) can be administered to patients with ECG changes as it can stabilize myocardial membranes, while sodium bicarbonate (50 mEq IV for adults)

can be administered if metabolic acidosis is present. Potassium level of 7 mEq/L (mmol/L) or greater or a widening QRS complex warrants immediate attention with aggressive interventions and close monitoring.[19]

Treatment of hyperphosphatemia includes minimization of dietary phosphorus intake and use of phosphorus binders (ie, sevelamer, calcium acetate, aluminum hydroxide), although caution is warranted for aluminum-based products in patients with renal dysfunction while calcium carbonate products should be avoided in those with hypercalcemia.

Hypocalcemia should not be directly managed unless the patient is symptomatic, due to the risk of furthering the calcium phosphate deposition in renal tubules. First, hyperphosphatemia should be corrected. If hypocalcemia is symptomatic, a slow infusion of calcium gluconate may be administered with ECG monitoring for resolution of symptoms and not necessarily correction to normal value.

Patients with congestive heart failure (HF), renal insufficiency (eg, anuria), calcium-phosphorus product of 70 mg^2/dL^2 (5.6 $mmol^2/L^2$) or more, or TLS refractory to aforementioned interventions may need dialysis to manage electrolyte disturbances.[19] Further details on electrolyte management can be found in Chapter 69, "Calcium and Phosphorous Homeostasis" and Chapter 70, "Potassium and Magnesium Homeostasis."

Extravasation

Extravasation is the unintentional leakage of drug from the injection site into surrounding subcutaneous or subdermal healthy tissue where uptake of the drug may result in cell death. Symptoms and signs of extravasation may include pain, redness, or swelling as well as difficulty with utilization of the IV line such as resistance to infusion or lack of blood return.[28] While fairly infrequent (incidence <7%), it can lead to negative patient outcomes and morbidity.[29] Prevention methods include but are not limited to proper vascular access, the use of a central IV line (eg, port, peripherally inserted central catheter, also known as PICC), and adherence to chemotherapy administration guidelines.[30] Cytotoxic chemotherapy can be classified as exfoliants (cause tissue peeling/inflammation without cell death), inflammitants (cause inflammation/erythema/flare reaction without pain), irritants (cause inflammation/pain without tissue damage), or vesicants (cause tissue necrosis/blisters).[30]

Management of extravasation of a vesicant is specific to the chemotherapy agent and may include administration of a certain antidote (Table 150-3). Dimethyl sulfoxide administered topically neutralizes free radicals and promotes absorption as well as possesses anti-inflammatory, anesthetic, and vasodilatory properties. Hyaluronidase administered subcutaneously (SQ) promotes drug diffusion and absorption by degrading hyaluronic acid, which breaks down subcutaneous tissue bonds. Sodium thiosulfate administered SQ can neutralize mechlorethamine into nontoxic thioesters and neutralizes via the creation of an alkaline-rich environment where the vesicant can bind sodium thiosulfate.[28,30] Dexrazoxane is an IV agent, Food and Drug Administration (FDA) approved for the management of extravasation of anthracyclines due to its proposed mechanism of preventing free radical formation through binding of iron and reduction in oxidative stress. Precise dosing and administration information for each antidote agent can be found in product labeling and tertiary drug information resources.

TABLE 150-3

Management of Extravasation

Chemotherapy Agent/Vesicant	Potential Antidote(s)	Compress Recommendation	
		Cool	Warm
Anthracycline agents	Dexrazoxane	X	
	Dimethyl sulfoxide		
Cisplatin	Sodium thiosulfate	X	
	Dimethyl sulfoxide		
Antitumor antibiotics			
Dactinomycin	--	X	
Mitomycin	Dimethyl sulfoxide	X	
Mitoxantrone	Dimethyl sulfoxide	X	
Docetaxel	Hyaluronidase	X	
Mechlorethamine	Sodium thiosulfate	--	--
Oxaliplatin	Sodium thiosulfate	Controversial/unknown	
Paclitaxel	Hyaluronidase	X	
Vinca alkaloids	Hyaluronidase	Avoid	X

Data from References 28,30.

Nonpharmacologic interventions are standard for any extravasation and include immediate cessation of the chemotherapy agent, aspiration, avoidance of flushing the IV line as this may further potentiate the extravasation, and elevation of the limb for ~48 hours to promote drainage.[28,30] Compresses generally applied for ~20 minutes four times a day for 24 to 48 hours are recommended. While a cool compress is recommended for extravasation of most agents to localize the vesicant by providing vasoconstriction to avoid further spread of the drug, only warm compresses should be used for the extravasation of vinca alkaloids to avoid further tissue damage and promote drug absorption and redistribution.[28,30] Moist compresses and occlusive dressings should be avoided.[31]

IMMUNE-RELATED ADVERSE EVENTS

The use of ICIs (ie, cytotoxic T-lymphocyte-associated protein 4 [CTLA4], programmed cell death protein 1 [PD-1], and programmed death-ligand 1 [PD-L1] inhibitors) in cancer care has exploded at a rapid pace. These agents work by activating the immune system, but ICIs can also attack healthy cells causing a unique group of toxicities called irAEs. Although irAEs are the most notable toxicities seen with ICIs, fatigue is the most common ADR. The most commonly affected organ systems are skin, gut, endocrine, lung, and musculoskeletal system, whereas cardiovascular, hematologic, renal, neurologic, and ocular irAEs are rare. The onset of irAEs is delayed and varies by organ system affected and specific ICI administered. Rash/dermatitis

presents first, about 2 to 3 weeks following first ICI dose, while diarrhea/colitis typically presents around week 5, and hepatotoxicity and hypophysitis around week 7.[32] The incidence rate of any grade irAEs ranges from 15% to 90%.[1] CTLA4 inhibitors are associated with a higher rate of irAEs than PD-1/PD-L1 inhibitors, and severe irAEs result in treatment delay or discontinuation in 0.5% to 13% of patients. Combination treatment of ipilimumab and nivolumab is associated with the highest rate of severe irAEs and often requires treatment delay or discontinuation. Fortunately, irAEs are typically reversible, with the exception of endocrine-related irAEs.

4 The prompt recognition and management of irAEs is key to keeping patients on therapy. Several clinical practice guidelines to manage irAEs have been published by various professional organizations including the Society for Immunotherapy of Cancer,[33] the European Society for Medical Oncology,[34] the NCCN,[1] and ASCO.[32] The majority of irAEs that occur are mild to moderate, and patients may typically continue on ICI therapy. Notably, ICI therapy is not dose-reduced for toxicities, only held/delayed. Management varies slightly by the organ system affected, but first-line therapy is commonly systemic corticosteroids with doses ranging from 0.5 to 2 mg/kg/day of oral prednisone. If corticosteroids are indicated for irAE management, ICI therapy should be held until the irAE is grade ≤1 and the patient has tapered off corticosteroids. Patients who present with severe irAEs are treated with IV methylprednisolone at 1 to 2 mg/kg/day initially and typically require ICIs to be held or permanently discontinued. If no response to corticosteroids within 48 to 72 hours, occurs additional immunosuppression is recommended based on evidence for treating autoimmune diseases for the respective organ system affected. Commonly employed immunosuppressive agents include tumor necrosis factor (TNF) inhibitors (ie, infliximab, etanercept), vedolizumab, mycophenolate, IV immunoglobulin, or IVIG, and rituximab.

Patients on prolonged corticosteroid require additional interventions, including monitoring for hyperglycemia, H2-receptor antagonists or proton pump inhibitors to prevent gastritis, anti-infective prophylaxis (eg, consider prophylaxis against herpes zoster), and vitamin D and calcium supplementation (see "Bone Health" section). Patients receiving prednisone equivalent of ≥20 mg for ≥4 weeks require PJP (*Pneumocystis jirovecci pneumonia*) prophylaxis as well as fungal prophylaxis (eg, fluconazole) if it is continued for ≥6 weeks. In patients requiring anti-TNF therapy, testing for hepatitis B and C virus should be conducted prior to administration if possible, but should not delay initiation of TNF inhibitor treatment. TNF inhibitors should be avoided in patients with immune-related hepatitis due to the risk for hepatotoxicity.

Patients at higher risk of developing irAEs or experiencing an exacerbation of underlying comorbidities include those with autoimmune diseases. These patients may experience a flare of their underlying condition; therefore, immunosuppression for their pre-existing autoimmune condition should be optimized prior to ICI initiation. Ideally, patients who are on prednisone for their autoimmune condition would be controlled on <10 mg of prednisone daily (or equivalent) prior to starting ICI. Caution is also utilized in patients who were prior organ transplant recipients as they are at risk for graft failure and transplant organ loss. In patients who received an allogeneic stem cell transplant, graft-versus-host disease (GVHD) is a risk.

ICIs are a significant advancement in the treatment of cancer; however, they are associated with unique toxicities called irAEs. These toxicities are delayed in presentation and have a prolonged duration. irAEs may occur months and even years after ICI discontinuation requiring clinicians to remain vigilant in monitoring patients. irAEs are commonly managed with immunosuppression, typically corticosteroids. Patients with mild-to-moderate irAEs can often remain on therapy, but patients who require corticosteroids or have severe irAEs often need to have treatment held or permanently discontinued. Additional supportive care interventions are required in patients on prolonged courses of corticosteroids or who require additional immunosuppressive therapy beyond corticosteroids.

CELLULAR IMMUNOTHERAPY ADRs: CRS AND NEUROTOXICITY

5 While immune activation directly leads to the efficacy of therapies that engage T cells, the subsequent massive release of various cytokines can lead to clinically significant ADRs, namely CRS and neurotoxicity. These events can occur after infusions of any cellular immunotherapy product, such as CAR-T therapy (eg, tisagenlecleucel and axicabtagene ciloleucel) or bispecific T-cell engaging therapy (BiTE; eg, blinatumomab). These ADRs require prompt identification and accurate grading to provide optimal management. However, their grading and management may differ by product as delineated below. Ongoing studies are evaluating optimal prevention and management of these ADRs.

CAR-T

CRS is caused by endogenous or infused immune effector cells, such as T cells, leading to a supraphysiologic and rapid release of cytokines.[35] CRS grading is based on symptoms, which includes fever at onset and may also include hypotension and/or hypoxia.[35] Symptoms can be progressive, and end-organ damage may occur. CRS typically presents in the first 2 weeks with median onset of approximately 3 days after CAR-T infusion and median

duration of about 1 week necessitating monitoring of vital signs (temperature, BP, and oxygen saturation) twice daily during this time.[1] Treatment of CRS includes antipyretics for fever with fluid and/or oxygen supplementation as clinically necessary. Tocilizumab, an anti-interleukin-6 agent, is FDA-approved for moderate to severe cases (eg, grade 2 and higher CRS) dosed as 8 mg/kg IV (maximum dose: 800 mg) with up to three repeat doses in 24 hours. Dexamethasone 10 mg IV up to every 6 hours is recommended for persistent refractory grade 2 (eg, nonresponse to 1-2 doses of tocilizumab) and for grade 3-4 CRS. For refractory grade 4, methylprednisolone 1,000 mg/day for up to three doses IV can be utilized with escalation to every 12 hours if refractory.[1,36]

Neurotoxicity after cellular immunotherapy was specifically termed immune effector cell-associated neurotoxicity syndrome (ICANS).[35] ICANS is thought to be due to diffusion of either the immune effector cells and/or cytokines through blood-brain barrier into the CNS. ICANS typically occurs within the first 4 weeks of cellular infusion with median onset of approximately 7 days and duration of about 14 days.[1] Signs and symptoms of ICANS can vary among patients and may include aphasia, impairment in cognition, reduced level of consciousness, seizures, motor weakness, or cerebral edema. ICANS grading requires the assessment of five domains: level of consciousness, seizure activity, motor findings, cerebral edema/elevated intracranial pressure, as well as the 10-point Immune Effector Cell-Associated Encephalopathy, or ICE Score, which should all be assessed twice daily during the at-risk period.[1] Notably, the Cornell Assessment of Pediatric Delirium (CAPD) is used instead of ICE Score for pediatric patients under the age of 12 years with further specific guidance available for interpreting actions in patients under 2 years.[35] Management of ICANS includes supportive care with aspiration precautions as well as anti-epileptics and interventions to manage elevated intracranial pressure as needed. Further, corticosteroids are the mainstay of management of ICANS of grade 2 or higher[36] with dexamethasone (grade 2: 10 mg IV and may repeat; grade 3: 10 mg IV q 6 hours or methylprednisolone 1 mg/kg IV q12 hours; grade 4: high-dose steroid regimen such as methylprednisolone 1,000 mg/day or twice daily × 3 days with a rapid taper over approximately 1 week).[1]

Bispecific T-Cell Engaging (BiTE)—Blinatumomab

Blinatumomab is a BiTE antibody construct that links CD3 T cells to the targeted malignant cells (CD19 B cells) for destruction in patients with B-cell acute lymphoblastic leukemia, or ALL. Unlike CAR-T therapy, which once infused is active within the body, due to short half-life blinatumomab is administered as a continuous infusion which allows for the management of ADRs via holding drug or discontinuation.

CRS is less common and often less severe after blinatumomab than CAR-T, most often low grade and occurring in the first cycle or at dose escalation.[37,38] Prevention of CRS includes cytoreduction for high-risk patients, initiation of blinatumomab with dose escalation inpatient for monitoring, and routine prophylactic dexamethasone.[38,39] The CTCAE is utilized for grading CRS after blinatumomab. Management of CRS from blinatumomab includes utilization of dexamethasone, dose interruption, or discontinuation[38] and potentially off-label use of tocilizumab for severe CRS.[37] Notably, the use of corticosteroids has not been shown to impact efficacy.[40]

Neurotologic events are common after blinatumomab (~50%-65% of patients), most frequently occurring within 1 to 2 weeks of the first cycle.[37] Severe (grade 3 or higher) events occur in approximately 10% to 20% of patients which necessitates holding therapy and resumption at a lower rate with permanent discontinuation for grade 4 neurotoxicity, if >1 seizure, or if recurs when a patient is receiving reduced infusion rate.[38] Precise management may vary by institution or research protocol,[41] including the use of dexamethasone or tocilizumab for severe symptoms (encephalopathy, aphasia).[37,39,41] Anti-epileptics are warranted for patients with seizure activity, although prophylaxis is not routinely utilized.[39]

DERMATOLOGIC TOXICITIES

6 Anticancer treatment can cause a variety of dermatologic toxicities affecting a patient's skin, hair, and nails. These toxicities may result in dose reductions or treatment discontinuation, which affects patient outcomes. It is important to be able to accurately recognize, prevent, and manage these ADRs.

Skin

Dry Skin (Xerosis) and Pruritus

Dry skin is reported in up to 84% of patients on anticancer treatment and can negatively impact their quality of life and lead to infections, sensitization to allergens and pruritus.[42-44] Dry skin and pruritus are reported more commonly with targeted therapies. Skin can be more sensitive to ultraviolet radiation and more prone to skin pigmentation. Counseling points on prevention measures include avoiding alcohol-containing lotions and irritating products, limiting shower time, using gentle cleansers, routinely applying emollients and sun-protective measures. Treatment of mild-to-moderate pruritis can include a topical antipruritic agent containing menthol 0.5% or a topical corticosteroid (mometasone furoate 0.1% ointment or betamethasone valerate 0.1% ointment) and oral antihistamines, in particular nonsedating second-generation agents. Second-line options include antiepileptic agents (pregabalin and gabapentin), doxepin, aprepitant, and short-term, systemic corticosteroids (0.5-2 mg/kg/day).

Acneiform RASH

Acneiform rash or papulopustular eruption is characterized by an eruption of papules and pustules commonly appearing on the face, scalp, upper chest, and back.[43] It is the most common ADR in patients treated with EGFR inhibitors (all grade: 75%-90%, grade 3/4: 10%-20%) and commonly seen in patients on MEK (mitogen-activated protein kinase) inhibitors (all grade: 74%-85%, grade 3/4: 5%-10%). It begins within the first few days to weeks following treatment initiation, and patients report pruritus, stinging, and pain. Prevention and management strategies for this rash are detailed in Table 150-4 and commonly include a good skin care routine, avoidance of sun exposure, topical corticosteroids, and oral antibiotics.

TABLE 150-4

Acneiform Rash/HFS/HFSR

Toxicity	Prevention	Treatment
Acneiform rash (Papulopustular exanthema)	• Avoid frequent washing with hot water • Avoid skin irritants, including OTC anti-acne medications containing benzoyl peroxide, solvents, or disinfectants • Use alcohol-free[a] OTC moisturizing creams or ointments BID, preferably with urea-containing (5%-10%) moisturizers to the body • Avoid excessive sun exposure • Apply sunscreen (SPF) ≥15 to exposed areas of body and reapply every 2 hours when outside • Oral antibiotics for 6 weeks at start of therapy (doxycycline 100 mg PO BID or minocycline 100 mg PO daily; if unable to tolerate/allergy cephadroxil 500 mg PO BID or trimethoprim-sulfamethoxazole 160/80 mg PO BID), with or without topical low/moderate-strength steroid to face and chest BID	Grade 1/2: ◦ Continue anticancer treatment ◦ Continue or initiate: oral antibiotic for 6 weeks AND topical low/moderate steroid ◦ Reassess after 2 weeks; if no improvement or worsening escalate therapy Grade ≥3: ◦ Interrupt anticancer treatment until grade 0/1 ◦ Obtain bacterial/viral/fungal cultures if infection is suspected ◦ Continue or initiate: oral antibiotic for 6 weeks AND topical low/moderate steroid, systemic corticosteroids (eg, prednisone 0.5-1 mg/kg × 7 days) ◦ Reassess after 2 weeks; if no improvement or worsening may need to discontinue treatment
HFS and HFSR	• Avoid irritation to hands and feet; long walks, heavy carrying without protection • Avoid chemical stress; skin irritants, solvents, or disinfectants • Treat predisposing factors before anticancer therapy • Apply 10% urea cream TID • For taxane-based therapy: use skin cooling gloves or socks • For capecitabine-based therapy: may consider celecoxib 200 mg PO BID	• Anticancer treatment interruption and dose reduction commonly required; initiation of topical agents (HFS and HFSR) or cooling (HFS) may allow for continued dosing • Hyperkeratosis: treat with keratolytics (topical creams or ointments with 5%-10% salicylic acid or 10%-40% urea) • Inflammation: high-potency topical corticosteroids (eg, clobetasol proprionate 0.05%) • Erosions and ulcerations: antiseptic solutions (eg, silver sulfadiazine 1%, polyhexanide 0.02%-0.04%) • Pain: lidocaine 5% cream or patches • Reassess after 2 weeks; if no improvement or worsening escalate therapy

BID, two times daily; OTC, over the counter; SPF, sun protection factor; TID, three times daily.

[a]Avoid SD alcohol 40, denatured alcohol, ethanol, and isopropyl alcohol.

Data from Reference 43.

Hand-Foot Syndrome and Hand-Foot Skin Reaction

Hand-foot syndrome (HFS) also known as palmar-plantar erythrodysesthesia syndrome, acral erythema, or toxic erythema, is characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands and soles of the feet.[43] Common chemotherapy causes include 5-fluorouracil, capecitabine, doxorubicin, pegylated liposomal doxorubicin, docetaxel, and cytarabine. It may be severe (grade 3/4) in 5% to 10% of patients, and the incidence increases with the use of multiple causative agents. Hand-foot skin reaction (HFSR) differs from HFS in presentation with well-defined painful hyperkeratosis. Multikinase VEGFR inhibitors such as sorafenib, cabozantinib, sunitinib, and regorafenib are a common cause. HFSR is less common with lenvatinib, pazopanib, and sunitinib and is grade 3/4 in 5% to 20% of patients.

The onset of this reaction is usually within days to weeks, but may take up to 6 months to appear. With HFS, the first symptoms are dysesthesia of the palms and soles with a tingling that develops into burning pain, swelling, and erythema followed by hyperkeratosis. Lesions can progress to blisters, desquamation, erosions, ulcerations, and bleeding associated with discomfort and moderate to severe pain. HFSR more commonly affects the soles, and blisters occur followed by callus-like hyperkeratosis at pressure-bearing areas. Table 150-4 includes prevention and management strategies for HFS and HFSR.

Pigmentary Changes

Hyperpigmentation may occur at different sites and in different patterns.[42] It can present within days to months after treatment and usually fades months after therapy discontinuation. Some of the agents associated with hyperpigmentation include busulfan, bleomycin, methotrexate, capecitabine, 5-fluourouracil, docetaxel, doxorubicin, ifosfamide, and thiotepa. C-kit inhibitors (eg, imatinib) can cause diffuse or localized hypopigmentation, as c-kit is involved in the regulation of melanocyte function. It is usually reversible with dose reductions or discontinuation. Patients, especially those with melanoma, on immunotherapy may experience vitiligo-like lesions.

Other Rashes

Many treatments may cause a nonspecific maculopapular rash or morbilliform eruption that starts gradually with mild symptoms including pruritus weeks after treatment.[42] Management includes antihistamines and when localized topical corticosteroids or when more diffuse short-term oral corticosteroids. Up to 50% of patients on rapidly accelerated fibrosarcoma (RAF)/v-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors may experience a maculopapular rash that appears early and spreads quickly.[45] Approximately 20% of patients on these therapies also develop nonmelanoma skin cancer that should be excised. Less commonly, rash occurs in patients treated with gemcitabine, pemetrexed, and liposomal doxorubicin.[45] Up to 95% of patients may experience acute or chronic RT dermatitis, and patients receiving concurrent chemotherapy are at higher risk.[46] A delayed recall reaction may occur weeks to years following RT and present as a new rash that appears after treatment with a precipitating drug. Common offending agents include taxanes, doxorubicin, and gemcitabine. Prevention and management strategies include instructing the patient to wear loose fitting clothing to avoid friction, avoid sun exposure and exposure to extremes of temperature, and not use cosmetic or irritating products to the radiated skin. Patients should use a good emollient during treatment, and topical corticosteroids may be added. Anticancer treatment can cause photosensitivity, phototoxic, or photoallergic reactions. Inflammatory rashes occur on photo-exposed areas in patients treated with 5-fluorouracil and taxanes. Vemurafenib and vandetanib are associated with ultraviolet A (UVA) sensitivity, and preventive sun measures are required.[42]

Hair

Alopecia

Alopecia is one of the more distressing and well-known dermatologic toxicities mainly caused by chemotherapy but is also reported with targeted agents and hormone therapy.[42,43] Chemotherapy-induced alopecia (CIA) typically results in diffuse complete hair loss on the entire scalp, but patients may have diffuse partial alopecia, or patchy, unevenly distributed alopecia. It may also involve eyebrows, eyelashes, and body hair. CIA typically begins 1 to 3 weeks after treatment, and hair will start regrowing 2 to 3 months after completion. Hair loss severity is dependent upon the type, dose, method of administration, and time between treatments. Cyclophosphamide, doxorubicin, irinotecan, and taxanes are associated with a high risk of CIA.

Endocrine therapy-induced alopecia usually does not result in complete hair loss and is located primarily on the crown of the scalp, with recession of the frontal and bitemporal hairline. It is more common in postmenopausal women receiving aromatase inhibitors and is most noticeable between 6 and 18 months after treatment initiation. Scalp cooling is the only proven method to prevent CIA, but efficacy is only 50% to 80%. Scalp cooling causes vasoconstriction and reduced biochemical activity in the scalp and hair follicles. These techniques are contraindicated in patients whose cancer can metastasize to the scalp, such as leukemia and lymphoma. To treat alopecia following anticancer treatment, patients may use topical minoxidil 5%. Patients may also consider taking biotin to stimulate hair growth. Patients are informed about potential alopecia prior to initiating treatment, and a discussion regarding hats, scarfs, or wigs to protect the scalp should occur.

Other Hair Changes

Patients on targeted therapies may report changes in hair quality, texture, and growth pattern starting months 2 or 3 of treatment.[42] Excessive hair growth in androgen-dependent areas of the body may occur in women on endocrine therapies. Trichomegaly, or longer, thicker, and often curled eyelashes and hypertrichosis are associated with EGFR inhibitors. Patients may need to trim their eyelashes to prevent eye irritation. The hypopigmentation associated with c-KIT inhibitors, such as pazopanib, also impacts the hair presenting as white hair growth.

Nails

Nail changes are common during treatment and usually disappear following the completion of therapy.[42] Cytotoxic chemotherapy usually results in melanonychia (black or brown discoloration that is diffuse, transverse, or longitudinal), leukonychia (white spots), onycholysis (nail detachment from the nail bed), Beau's lines (indentations across the nail), onychomadesis (proximal separation of the nail plate from the nail matrix), and onychorrhexis (brittle nails). Patients receiving a taxane may experience painful subungual hemorrhage followed by onycholysis and occasional abscess. Chemotherapy and targeted therapy may cause brittle nails, nail cracking, and splitting. Preventive strategies include decreased exposure to water, use of cotton gloves, and nail hydration with thick emollients. Patients may consider oral biotin to help with nail growth and nail lacquers. Asymptomatic splinter subungual hemorrhages of black, red, or brown are common in patients treated with VEGFR inhibitors. EGFR inhibitors are associated with the risk of paronychia occurring two or more months after treatment initiation on finger and toenails. Similar lesions are reported less frequently with MEK inhibitors and mTOR inhibitors.[43] Additional prevention methods include the use of comfortable shoes, adequate nail trimming, and use of antiseptic solutions. If fissuring occurs, protective covering should be applied.

ENDOCRINE TOXICITIES

The endocrine system is complex and composed of a series of glands that produce and secrete hormones used by the body for a variety of functions. Anticancer treatment can impact these glands resulting in dysfunction in hormone production.

Hypothalamic-Pituitary Dysfunction

RT is a common cause of hypothalamic-pituitary dysfunction in patients with cancer. The onset and severity are dose-dependent and may occur years later. Symptoms are nonspecific and include fatigue and weakness. Management includes hormone replacement as necessary.[47] Although rare, ICI can cause hypophysitis, inflammation of the pituitary gland which is delayed in onset and also managed with hormone replacement as well as ICI dose delays and discontinuation if necessary[1] (see Chapter e98, "Pituitary Gland Disorders").

Thyroid Dysfunction

Thyroid function can be affected by a variety of anticancer treatments including RT, targeted therapy, and cytokines.[48] Hypothyroidism is more common than hyperthyroidism. Patients on multitargeted TKIs and ICIs should have their thyroid function (thyroid-stimulating hormone [TSH] and free thyroxine or T4) monitored at baseline and periodically while on treatment. Hypothyroidism is common in patients on sunitinib, with a variable onset, most commonly 4 weeks. Other TKIs associated with hypothyroidism include sorafenib, imatinib, dasatinib, nilotinib, and axitinib. Drug-induced hypothyroidism can persist following TKI discontinuation. Patients on thyroid hormones prior to treatment initiation often need dose increases while on TKI treatment. ICIs are associated with both hyper- and hypothyroidism, with hypothyroidism being more common. Hyperthyroidism also often transitions into hypothyroidism. Patients can typically continue on ICI but need lifelong thyroid supplementation.[1] RT to the neck is associated with primary hypothyroidism, especially when treated during childhood. Five years after treatment nearly half of patients develop hypothyroidism, with a

median onset of 1.5 years posttreatment[48] (see Chapter 96, "Thyroid Disorders").

Hyperglycemia

Hyperglycemia is a common toxicity seen in patients with cancer. Glucocorticoids are likely the most common cause of hyperglycemia. They are used as an antiemetic, for edema from brain metastasis, prevention of transplant rejection, treatment of GVHD, and irAEs, and even in some anticancer treatment regimens.[49] Agents that inhibit the phosphoinositide-3 kinase (PI3:K)/protein kinase B (also known as AKT)/mTOR pathway are associated with hyperglycemia due to the interruption of intracellular response to insulin, resulting in decreased glucose transport, decreased glycogen synthesis, and increased glycolysis.[50] The PI3K inhibitors (eg, alpelisib) and mTOR inhibitors (eg, everolimus) are associated with grade 3 to 4 hyperglycemia in approximately 10% of patients. ICIs can rarely cause hyperglycemia, pancreatitis, and new-onset type I diabetes. L-asparaginase can induce hyperglycemia through both direct and indirect effects inhibition of insulin production and release, and pancreatitis, respectively.[49]

Patients should be periodically screened for diabetes by fasting plasma glucose, oral glucose test, hemoglobin A1c, random plasma glucose levels, or pre- or postprandial glucose testing. Management of hyperglycemia should consider glycemic variability of the agent administered, and commonly includes oral anti-hyperglycemic agents and insulin. Patients may require treatment interruption or discontinuation if hyperglycemia cannot be controlled[49,50] (see Chapter 94, "Diabetes Mellitus").

BONE HEALTH

7 Cancer and its treatment can have a significant impact on bone health. Patients may be at risk for osteoporosis and metastatic bone disease, which can significantly affect quality of life.

Osteoporosis

Osteoporosis is a common complication of anticancer treatment, especially hormonal therapy.[51] Additionally, chronic inflammation associated with cancer can promote increased bone loss via altered systemic bone remodeling, increased bone resorption, and impaired bone formation. Rates of bone loss from anticancer treatment can be more than sevenfold greater than that of normal aging. Patients with the following conditions may be considered for bone-modifying treatment: premenopausal women receiving gonadotropin-releasing hormone (GnRH) therapies causing ovarian suppression, premenopausal women with chemotherapy-induced ovarian failure or who have had an oophorectomy, postmenopausal women who are receiving aromatase inhibitors, men who have received or are receiving androgen deprivation therapy, patients undergoing or with a history of bone marrow transplantation, or patients with chronic (>3-6 months) glucocorticoid treatment. Assessment and treatment of bone loss is similar to other patients at risk for osteoporosis (see Chapter 112, "Osteoporosis" for more detail).

Bone Metastases

Metastatic bone disease is common in multiple myeloma, prostate, breast, lung, and kidney cancer.[52] Bone metastases commonly affect the axial skeleton and lead to skeletal-related events (SREs): pathological fracture, need for RT to the bone, surgery to bone, spinal cord compression, and hypercalcemia of malignancy. Bone pain is the result of structural damage and will be discussed in more detail (see "Bone Pain (Not Oncologic Emergency)" section). Preventing SREs is important as they are associated with loss of mobility, decreased social functioning, reduced quality of life, increased health care expenditure, and poor survival.

The pathophysiology of bone metastases is not completely understood.[52] Disseminated tumor cells enter the bone marrow microenvironment and may stay dormant for years before causing damage. Proliferating tumor cells can produce a variety of cytokines and growth factors, which increase osteoblast production of receptor activator of nuclear factor kappa-B ligand, or RANKL, that then leads to the activation of osteoclasts and disruption of normal bone formation and bone resorption. Multiple skeletal sites are typically involved. Patients report pain and boney tenderness. Imaging modalities (eg, computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan, positron emission tomography [PET]) are used for diagnosis and monitoring every 3 to 6 months.

The goal of treatment is to prevent disease progression and palliate symptoms.[52] Treatment varies by the underlying malignancy. Local external beam RT is effective at relieving painful bone metastasis with overall response rates of 70% to 80%. Approximately one-third of patients report complete pain

relief. Targeted RT with systemic radioisotopes may be used to spare normal tissues in patients will multiple metastatic sites in some malignancies. Radium-223 (^{223}Ra) is a bone-seeking alpha particle-emitting radiopharmaceutical approved for use in bone-predominant metastatic castration-resistant prostate cancer (see Chapter 154, "Prostate Cancer"). Surgical intervention may be recommended to maintain patient function and mobility by relieving pain, preventing impending fractures and/or neural compression, or stabilizing a pathological fracture.

Bone-modifying agents (BMA; eg, zoledronic acid, pamidronate, and denosumab; Table 150-5), potent inhibitors of bone resorption, are also used to relieve pain and reduce the risk of and time to the development of SREs. Patient factors including the risk for an SRE and overall disease control help to determine which BMA is used. Denosumab is preferred when considering efficacy, convenience, and renal health. However, generic bisphosphonates are more cost-effective and not associated with a risk of rebound osteolysis. Once a patient develops bone metastases, it is common to initiate therapy and continue indefinitely. Use in specific cancers will be discussed in their respective chapters (see Chapter 151, "Breast Cancer"; Chapter 154, "Prostate Cancer"; and Chapter 159, "Multiple Myeloma"). BMAs are generally well tolerated; however, they may cause hypocalcemia due to the inhibition of bone resorption. Calcium and vitamin D levels should be monitored at baseline and throughout treatment.[52,53] Patients who are vitamin D deficient should be repleted and then maintained with daily supplements of 800 to 2,000 units/day. To maintain an adequate daily calcium intake, supplementation of 1,000 to 1,200 mg/day should be recommended. With prolonged BMA administration, it is important to monitor for osteonecrosis of the jaw and for patients to have a thorough dental exam prior to initiation if possible.

TABLE 150-5

BMA Dosing for Bone Metastases

Medication	Brand Name[a]	Dose
Denosumab	Xgeva	120 mg SQ every 4 weeks
Pamidronate	Aredia	90 mg IV over 2 hours every 3-4 weeks
Zoledronic acid	Zometa	4 mg IV over 15 minutes every 3-4 weeks[b]

[a]Note: unique brand names, dosing, and schedule for this indication.

[b]May be dosed every 12 weeks after treatment for 3-6 months.

Data from Reference 52.

Spinal cord compression is a medical emergency that requireds an urgent MRI to confirm the diagnosis.[52] Patients with spinal cord compression should receive 16 to 24 mg of dexamethasone/day to decrease inflammation and preserve function. This should be tapered over 2 weeks if possible. Patients with a single are a of compression and good performance status may be amenable to surgery followed by RT. Patients unable to tolerate surgery should receive RT alone.

OTHER TOXICITIES

Ocular Toxicities

A broad spectrum of ocular toxicities may be seen with anticancer treatment. Common ocular toxicities reported include blurred vision, photophobia, conjunctivitis, cataracts, abnormal lacrimation, dry eye, keratitis, optic neuropathy, and retinopathy.[54-56] Ocular toxicities are typically mild (grade 1-2) but may progress to severe and result in blindness. For agents associated with more severe toxicities, routine ophthalmic surveillance and baseline assessment are recommended. Follow-up appointments with the cancer care team should include an assessment of eye pain, redness, and changes in vision. Some specific management strategies for ocular toxicities include artificial tears and lubricants for dry eyes and keratitis, steroid eye drops for conjunctivitis (especially from high-dose cytarabine), and systemic diuretics to manage periorbital edema (that is common with BCR-ABL TKIs like imatinib). Patients who experience photophobia and flashing lights from anaplastic lymphoma kinase (ALK) inhibitors tend to have symptoms improve

over time.

Cardiovascular Toxicities

Patient-related and treatment-related factors contribute to cardiovascular toxicities experienced by patients with cancer.[57] Cardiovascular toxicity may be a short- or long-term complication, asymptomatic or symptomatic, as well as reversible or irreversible. Patients may experience HF, HTN, QT prolongation, arrhythmias, myocarditis, and other cardiac abnormalities from systemic treatment, RT, CAR-T therapy, or HSCT. A thorough cardiac workup should be conducted before initiating any potential cardiotoxic treatment, and any conditions identified should be well controlled according to current cardiovascular guidelines before treatment. A baseline risk assessment should include cardiac history, anticancer treatment history, cardiovascular risk factors, BP, hemoglobin A1c, cholesterol profile, cardiac biomarkers (troponin and natriuretic peptides), ECG, and echocardiogram (ECHO).

Left Ventricular Dysfunction/Heart Failure

Anthracyclines, HER2-targeted therapy, VEGFR inhibitors, and some proteasome inhibitors (eg, carfilzomib) may cause left ventricular dysfunction (LVD).[58] Anthracyclines are associated with type I LVD, which is a result of cellular loss, and is irreversible.[59] Anthracycline-induced cardiotoxicity can be categorized as acute, occurring immediately after the infusion (<1% of patients); early-onset progressive, occurring during therapy or within the first year of treatment (~2%); or late-onset chronic, occurring at least 1 year after therapy (1.6%-5%). Risk factors include cumulative dose, IV bolus administration, higher single dose, history of prior RT, use of other concomitant cardiotoxic drugs (cyclophosphamide, trastuzumab, paclitaxel), female gender, underlying cardiovascular disease, age (young and older adult), increased time since completion of chemotherapy, and increase in cardiac biomarkers (troponin, natriuretic peptides) during and after treatment. The risk of cardiotoxicity is cumulative, whereby patients are at risk for cardiotoxicity when they have reached the cumulative lifetime doses of anthracyclines. Patients who have received more than one type of anthracycline should have their cumulative lifetime dose converted to doxorubicin equivalents (Table 150-6).[60] Type II cardiotoxicity results from cellular dysfunction (mitochondrial and protein alterations) and is usually temporary, without injury marker release, and cardiac function returns to baseline. HER2-targeted agents and VEGF inhibitors are common examples of agents that cause type II LVD. When these agents are given in combination with anthracyclines, the risk of cardiovascular toxicity increases; therefore, trastuzumab should not be given in combination with anthracyclines. Type II LVD is not dose-related or cumulative.

TABLE 150-6

Lifetime Cumulative Anthracycline Dose Conversion and Maximums

Anthracycline	Conversion Factor	Maximum Recommended Cumulative Dose (mg/m^2)
Doxorubicin	1	550
Daunorubicin	1	550 (no CV risk factors)
	0.7	400 (chest irradiation or CV risk factors)
Epirubicin	1.6	900
Idarubicin	0.3	150
Mitoxantrone	0.25	140

CV, cardiovascular.

Data from Reference 60.

Quantitative assessment with an ECHO or multigated acquisition (MUGA) of LV ejection fraction (LVEF) and diastolic function prior to cardiotoxic

treatment may help to identify patients at high risk of cardiovascular complications.[58] It also serves to establish a baseline should symptoms occur during treatment. Patients should have routine monitoring with an ECHO or MUGA while on therapy (for HER2 therapy every 3 months; for anthracyclines after cumulative doxorubicin dose of 250 mg/m^2 or its equivalent, or after each additional 100 mg/m^2) and following treatment completion to evaluate for delayed onset cardiovascular toxicity.

Patients receiving treatment known to cause cardiotoxicity should be considered to have stage A HF (see Chapter 36, "Chronic Heart Failure"). Patients may be considered for prophylactic angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or selected beta-blockers (BBs) to decrease the risk of cardiotoxicity. Dexrazoxane may be used as a cardioprotectant in certain patients receiving >300 mg/m^2 cumulative anthracycline-based treatment, or at anthracycline treatment initiation in patients with preexisting cardiomyopathy. Because dexrazoxane has the potential to decrease anthracycline efficacy due to its free radical scavenging activity, it is not widely used.

Asymptomatic patients treated with anthracyclines who have a decrease in LVEF of ≥10% from baseline to 50% or a decrease to ≥40% and <50%, initiation of cardioprotective agents (ACEIs, ARBs, or BBs), if not already prescribed, and a cardiology (cardio-oncology specialist) consultation should occur. A benefit-risk discussion for continued anthracycline use versus changing to nonanthracycline treatment should occur. Patients may benefit from the use of dexrazoxane or liposomal doxorubicin, if appropriate. Patients on trastuzumab who experience the same impact in LVEF should also have a cardiology consultation and cardioprotective treatments started. If mild asymptomatic reductions in LVEF occur, trastuzumab therapy may be continued. If trastuzumab is stopped, LVEF can be reassessed within 3 to 6 weeks and restarted if LVEF is >50%. In patients on other therapy associated with LVD, if LVEF decreases, cardioprotective treatment and repeat LVEF assessment should occur every 3 months. Patients who have LVD and are diagnosed with HF should be managed according to the American College of Cardiology/American Heart Association guidelines.

Hypertension

HTN is a risk factor for chemotherapy-induced cardiotoxicity. Several cancer treatments are associated with the risk of HTN, most notably the VEGF inhibitors. BP increases usually occur within 1 day of treatment initiation and stabilizes within 6 to 10 days. Possible predictors of HTN include age ≥ 60 years, body mass index ≥25 kg/m^2, and pre-HTN. Resting BP should be monitored daily during the first cycle of VEGF inhibitor treatment, and once BPs are stabilized, it can be extended to every 2 to 3 weeks while on treatment. More frequent monitoring is recommended in patients with preexisting HTN and those at a higher cardiac risk. Potential contributors to BP elevation include obstructive sleep apnea, excessive alcohol consumption, nonsteroidal anti-inflammatory drugs (NSAIDs), adrenal steroids, erythropoietin, oral contraceptives, and sympathomimetics (methylphenidate). Management of HTN should follow the American College of Cardiology/American Heart Association guidelines (see Chapter 30, "Hypertension"). It is important to be mindful of potential drug-anticancer treatment interactions when selecting antihypertensive therapy. Once VEGF inhibitor therapy is stopped, HTN management should be modified and stopping antihypertensive therapy may be necessary to avoid hypotension.

QT Prolongation

Several anticancer therapies have a known potential to cause QT prolongation including arsenic trioxide, midostaurin, histone deacetylase inhibitors, TKIs and cyclin-dependent kinase 4/6 inhibitors.[58] Some agents with warnings for serious or life-threatening risks for QT interval prolongation include sunitinib, sorafenib, vandetanib, crizotinib, vemurafenib, dasatinib, lapatinib, and nilotinib. Agents associated with QT interval prolongation should be used with caution in patients with hypokalemia or hypomagnesemia, genetic long QT syndrome, and those on other QT prolonging medications. Electrolyte abnormalities should be corrected prior to initiation and during therapy. ECGs should be conducted at baseline and periodically to assess for QT prolongation and arrhythmia.

Others

Atrial fibrillation (AF) can also occur with some anticancer agents (eg, ibrutinib, anthracyclines, immunomodulatory agents).[61] Management of AF from anticancer treatment considers rhythm versus rate control and thromboembolic prophylaxis. There is no valid risk assessment in patients with active cancer, so several cardiovascular and oncology-related factors are considered, including the CHADS-VASC score; HAS_BLED score; thromboembolic and bleeding risk of the malignancy; platelet count; and life expectancy (see Chapter 40, "Arrhythmias"). Anticoagulant selection should consider potential drug interactions with anticancer therapy. Rate control is typically preferred over rhythm control, particularly if the agent causing AF is continued. BB is commonly used due to the lack of drug-drug interactions. Cardiac ischemia is a rare cardiovascular toxicity from anticancer treatment.[59] Anti-microtubule agents (ie, taxanes and vinca alkaloids), anti-metabolites (ie, fluorouracil, capecitabine), platinum compounds (ie,

cisplatin), and some VEGF inhibitors have been linked to ischemic events.[62] Baseline ECG and frequent vital sign monitoring are recommended for early detection.

SPECIAL CONSIDERATIONS

VTE Prevention and Management

8 VTE, which includes deep VTE (DVT) and pulmonary embolism (PE), is a common cause of cancer-associated morbidity and mortality. Potential pathophysiological causes for VTE in patients with cancer include known hypercoagulability (pro-coagulants expressed by cancer cells), vessel wall damage, and vessel stasis from direct tumor compression.[62] Several factors place patients at a higher risk of VTE, including the malignancy type and stage, systemic treatment used, surgery, RT, and use of indwelling catheters. Patient factors such as advanced age, comorbidities, previous VTE, hereditary thrombophilia, and immobilization and hospitalization also contribute to VTE risk. The risk of a patient with cancer developing a VTE is four- to sevenfold greater than the general population and is reported in up to 15% of patients each year.[63] Patients with cancer are also more likely to have higher rates of VTE recurrence and bleeding complications during VTE treatment.[63]

Prophylaxis

Routine prophylaxis is not recommended in all patients with cancer but is indicated in certain scenarios.[62,63] Patients with an active malignancy who are hospitalized should be offered thromboprophylaxis with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) in the absence of bleeding or other contraindications. Patients who have major surgery for their cancer should receive thromboprophylaxis for at least 7 to 10 days. Patients who have a high-risk abdominal or pelvic cancer surgery should have VTE prophylaxis continued for up to 4 weeks postoperatively. Patients who are ambulatory receiving chemotherapy should be assessed for VTE risk utilizing the Khorana prediction model. Patients identified to have a high risk (Khorana score ≥2; see NCCN guidelines for score calculation) should be offered prophylaxis with apixaban, rivaroxaban, or LMWH for up to 6 months or longer if the risk persists. Patients diagnosed with multiple myeloma who are receiving treatment with immunomodulatory drugs may be indicated to receive VTE prophylaxis based upon their SAVED and IMPEDE VTE Score (see NCCN guidelines for score algorithms). Patients determined to be high risk should be offered enoxaparin, dalteparin, warfarin, or apixaban prophylaxis, while low risk patients may be offered no intervention or aspirin prophylaxis. Refer to the NCCN and ASCO guidelines for specific drug dosing recommendations.

Treatment

Once a patient is diagnosed with a VTE, treatment should be continued for at least 3 months or as long as the patient has active cancer or is receiving anticancer therapy.[62] For noncatheter associated clots, patients should be on anticoagulation indefinitely while the cancer is active, while they are receiving treatment, or if risk factors for recurrence persist. For a catheter-associated clot, patients should be on anticoagulation as long as the catheter is in place. The agent used for VTE treatment should be selected based upon a variety of factors: renal failure, hepatic disease, inpatient or outpatient status, FDA approval, cost, patient preference, ease of administration, monitoring, bleeding risk, and ability to reverse anticoagulation, if needed. Direct oral anticoagulants (DOACs), LMWHs, fondaparinux, and UFH are available options for initial treatment. Warfarin is not recommended as first-line therapy in patients with cancer, as LMWHs have been associated with a lower risk of recurrent VTE without an increased risk of major bleeding, but may be used for long-term anticoagulation in certain circumstances. DOACs are absorbed primarily in the stomach and proximal bowel (apixaban is partially absorbed in the colon) and may not be good options for patients who have had significant resections of these areas. DOACs should be used with caution in patients with genitourinary or GI tract lesions, pathology or instrumentation, since they have been associated with an increased risk of GI bleeding and possibly genitourinary tract bleeding. LMWH is preferred in these patients. Refer to the NCCN and ASCO guidelines for specific drug dosing recommendations.

Unique Considerations

Thrombocytopenia is a common complication of anticancer treatment and can place patients on anticoagulation at an increased risk of bleeding. Generally, anticoagulation is considered safe to use in patients with a platelet count of 50×10^9/L (50,000/mm^3) or more. The NCCN guidelines provide guidance for prophylactic and treatment dosing of anticoagulation in patients who are thrombocytopenic.[62] Some additional contraindications to anticoagulation include active bleeding, indwelling neuraxial catheters, neuraxial anesthesia/lumbar puncture, interventional spine, and pain

procedures. The NCCN guidelines also offer further guidance on potential relative contraindications to anticoagulation and recommendations for holding anticoagulation around surgeries and procedures, including lumbar punctures. Patients with cancer are at risk for recurrent VTE and anticoagulation failure. Patients may require a change in dose, schedule, or agent. The NCCN guidelines also provide recommendations if this occurs.

Pain Management

9 Pain is one of the most common symptoms experienced by patients with cancer. It can be acute or chronic, and has multiple possible etiologies such as the disease itself (eg, tumor invasion, organ obstruction), treatment (eg, chemotherapy, RT, and surgical incisions), or diagnostic procedures (eg, biopsy). Nociceptive and neuropathic are the two most predominant mechanisms of pain pathophysiology. To ensure proper management, a comprehensive pain assessment should be completed at the initial evaluation, at each subsequent contact, and at the start of a new therapy. The goals of pain management are to optimize patient treatment outcomes in five dimensions, also known as the 5A's of pain management outcomes: analgesia (optimize, analgesia), activities (optimize activities of daily living), adverse effects (minimize ADRs), aberrant drug-taking (avoid aberrant drug-taking), and affect (relationship between pain and mood). Treatment must be individualized considering clinical circumstances and patient wishes, with the goal of maximizing function and quality of life (see Chapter 79, "Pain Management" for more information).

It is important to determine if pain is related to an oncologic emergency, which is a life-threatening event directly or indirectly related to a patient's cancer or anticancer treatment. This includes pain due to bone fracture or impending fracture of weight-bearing bone, epidural or leptomeningeal metastases, pain associated with infection, or obstructed or perforated viscus. Oncologic emergency-related pain should be treated immediately while concurrently treating the underlying condition. Patients with pain not related to an oncologic emergency may be treated with a combination of pharmacologic analgesics; nonopioids (eg, NSAIDs or acetaminophen), opioids, and adjuvant analgesics (eg, antidepressants, anticonvulsants, topical agents, and corticosteroids) or nonpharmacologic integrative interventions (eg, physical, cognitive modalities, spiritual).

Adult cancer pain can be categorized by level of pain intensity (0-no pain, 10-worst pain; mild [1-3], moderate [4-7], and severe [8-10]) which can be used to help guide treatment decisions (Table 150-7). For patients with severe pain, pain crisis, or uncontrolled pain, hospital or inpatient hospice may be required for treatment due to the frequent need to reassess and adjust opioid dosing to achieve adequate pain control (Fig. 150-2). See Chapter 79, "Pain Management" and NCCN Adult Cancer Pain guidelines[64] for medication dosing, ADRs, drug interaction, and contraindication information. Patients may experience inadequate pain relief despite pharmacologic therapy or may not tolerate opioid titration due to ADRs. In these scenarios, interventional therapies may be appropriate to eliminate or significantly reduce pain levels, and/or may allow a significant decrease in systemic analgesics. Some useful interventional therapies include nerve blocks, vertebral augmentation, regional infusion of analgesics, radiofrequency ablation, and others.[64]

TABLE 150-7

Cancer-Related Pain Treatment Recommendations

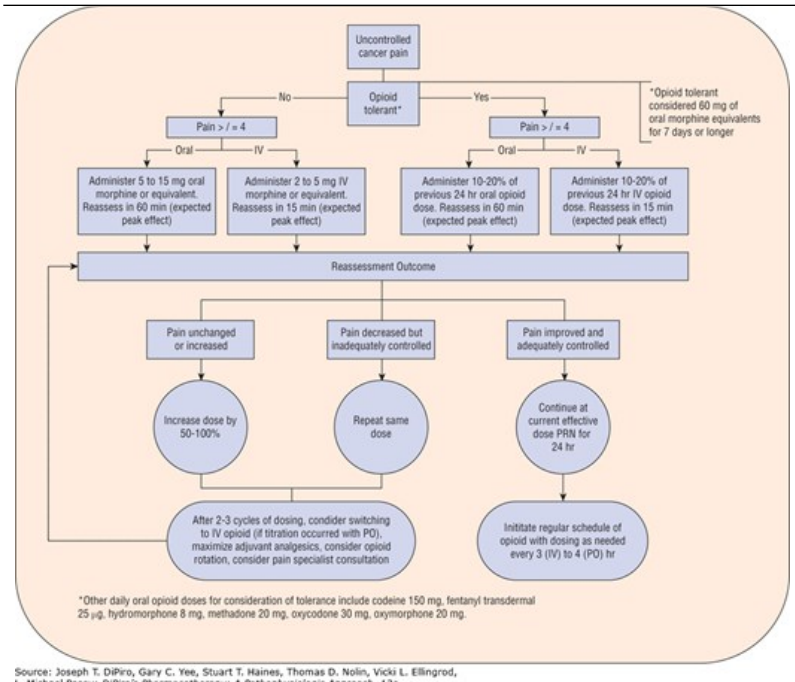
Pain Intensity (Numerical Rating Score)	Opioid-naïve	Opioid-tolerant
Mild (1-3)	• Nonopioid analgesics + adjuvant analgesics	• Nonopioid analgesics + adjuvant analgesics • Re-evaluate need for opioid analgesics and initiate gradual dose reductions if indicated
Moderate (4-6)	• Nonopioid analgesics + adjuvant analgesics + short-acting opioids as needed • Titrate every 3-4 hours • If ≥4 doses are needed/day, consider addition of long-acting opioid based on TDD	• Nonopioid analgesics + adjuvant analgesics + short-acting opioids as needed • Titrate short-acting opioids with goal of increasing TDD by 30%-50% until pain relief is achieved • If ≥4 doses are needed/day, consider addition or increase in dose of long-acting opioid based on TDD
Severe (7-10)	• Consider hospital or inpatient hospice admission • IV or oral short-acting opioids	

TDD, total daily dose.

Data from Reference 64.

FIGURE 150-2

Treatment algorithm for cancer pain crisis. Patients should first be assessed for opioid tolerance and then managed according to their pain score on the 0-10 numeric rating scale. Patients in pain crisis require frequent monitoring and reassessment of their pain score to determine if redosing of opioids are needed to achieve adequate pain control. (Data from NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines®]. Adult Cancer Pain V.2.2021 National Comprehensive Cancer Network, Inc. Accessed July 29, 2021.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Additional interventions may be needed for treatment in specific scenarios. Some specific cancer pain syndromes with unique treatment considerations include neuropathic pain, bone pain (not associated with an oncologic emergency), and pain from mucositis, pharyngitis and esophagitis (see "GI Toxicities: Diarrhea, Mucositis, and Nausea/Vomiting" section).

Neuropathic Pain

Cancer-related neuropathic pain can be caused by the cancer itself, or the acute or chronic effects of anticancer treatment.[64] Many chemotherapy agents including taxanes, platinums, vinca alkaloids, epothilones, eribulin, and bortezomib cause treatment-related neuropathy.[65] No agents are recommended for the prevention of chemotherapy-induced peripheral neuropathy (CIPN). Patients who develop intolerable neuropathy and/or functional impairment may require dose delays, reductions, substitutions of treatment, or discontinuations. Adjuvant analgesics commonly used to manage neuropathic pain include anticonvulsants (eg, pregabalin, gabapentin), antidepressants (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors), and topical treatments (eg, gel or patch lidocaine).[64] The ASCO CIPN guidelines support the use of duloxetine for patients with established painful CIPN[65]; however, the NCCN guidelines recommend antidepressants and anticonvulsants first-line.[64] Corticosteroids may also be used, particularly in the setting of radiculopathies from vertebral body compression fractures (see "Bone Health" section for more information). See Chapter 79, "Pain Management" and NCCN Adult Cancer Pain guidelines for medication dosing, ADRs, and interaction and contraindication information.

Bone Pain (Not Oncologic Emergency)

Patients with bone metastases may also experience bone pain. Bone pain may be treated with NSAIDs, acetaminophen, or steroids in combination with opioids.[64] Topical diclofenac (gel or patch) may be considered to provide pain relief with minimal systemic effects. BMAs are used in patients with bone metastases for their role in reducing overall SREs, but they also provide modest pain relief and may be recommended in conjunction with other therapies (eg, systemic analgesics, surgery, RT).

LONG-TERM EFFECTS/SURVIVORSHIP

10 Anticancer agents pose a risk for a variety of long-term effects, including but not limited to organ damage, impact on reproductive organs, as well as immunologic and psychological effects. Advances in screening and early diagnosis of cancer as well as improvements in treatments have led to a higher number of survivors of cancer. Many institutions have multidisciplinary clinics for long-term survivors of cancer focused on monitoring and

management of long-term complications of cancer and its treatments. Survivors should be assessed for long-term physical and psychosocial effects, including but not limited to organ dysfunction (eg, anthracycline-induced cardiotoxicity), pain or neuropathy, depression, cognitive dysfunction, as well as infertility and secondary malignancies.[66] Various consensus-based guidelines exist regarding long-term screening and follow-up for patients with cancer, often specific to initial disease and treatment regimens, which is beyond the scope of this chapter.[67]

Anticancer treatments may be affiliated with the risk of embryo-fetal toxicity and the risk of infertility due to gonadotoxicity. Before initiating regimens with the risk of embryo-fetal toxicity, pregnancy testing of patients of childbearing potential and counseling on adequate contraception to both male and female patients of childbearing potential is necessary. Notably, certain anticancer agents have specific contraception requirements and even Risk Evaluation and Mitigation Strategy, or REMS, programs, such as the immunomodulatory agents (eg, thalidomide, lenalidomide) due to known teratogenicity. In men, chemotherapy can produce oligospermia or azoospermia, as well as infertility; however, serum testosterone levels are rarely altered unless the patient is receiving hormonal therapy aimed at lowering testosterone (eg, androgen deprivation therapy). The recovery of spermatogenesis after completing therapy is unpredictable. Age, total dose, duration of therapy, combination chemotherapy, and the chemotherapy mechanisms are other important variables. In women, toxic effects on the ovaries result clinically in amenorrhea, vaginal epithelial atrophy, and menopausal symptoms. These effects are related to dose and age. Younger patients are more resistant to the effects on the ovaries. As with men, the recovery of fertility is unpredictable, but women younger than 25 years of age appear to have the best outcomes. The effects of the alkylating agents on fertility have been extensively studied finding profound and consistently detrimental effects on reproductive function. The risk of infertility with other anticancer agents is largely unknown. The risk of infertility should be discussed with all patients of childbearing potential (ie, informed consent and counseling) before they receive anticancer agents, and they should be informed about options for fertility preservation to allow for referral to fertility specialists if deemed desirable by the patient.[68,69]

Secondary cancers induced by anticancer agents or RT are serious long-term consequences.[70] For curable cancers, the relatively small risk for the occurrence of secondary malignancies is far outweighed by the benefits of survival. The risk of secondary malignancies is of particular concern in patients receiving adjuvant chemotherapy. The risk of secondary malignancies is highest after receiving certain cytotoxic chemotherapy agents, such as alkylating agents, anthracyclines, and epipodophyllotoxins. Most commonly the secondary malignancy is a treatment-related myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), often approximately 5 to 7 years after initial exposure and presenting with a deletion in chromosome 5 or 7. Overall, the prognosis for secondary AML is worse than *de novo* disease. Further, these patients are at risk for secondary solid tumors, such as lung, skin, or breast cancers, typically 10 to 20 years after initial alkylating agent exposure.[70] Cytotoxic chemotherapy is not the only anti-cancer treatment with the risk of subsequent cancer diagnosis. Exposure to radiation can increase the risk of secondary cancers. Additionally, exposure to certain oral anticancer agents, such as poly (ADP-ribose) polymerase, or PARP, inhibitors, which can increase the risk of myelodysplastic syndrome and AML,[71] and BRAF inhibitors which can increase the risk of squamous cell carcinoma.[72]

CONCLUSION

Patients with cancer are at risk for a variety of disease- and treatment-induced complications. Clinicians should consider the type of cancer as well as patient- and treatment-specific risk factors for each complication to provide adequate monitoring, prophylaxis, and evidence-based interventions for management.

ABBREVIATIONS

5-HT3-RA	5-hydroxytryptamine/serotonin receptor antagonist
ACEIs	angiotensin converting enzyme inhibitors
ADR	adverse drug reaction
AF	atrial fibrillation
ALK	anaplastic lymphoma kinase

ANC	absolute neutrophil count
ARBs	angiotensin receptor blockers
ASCO	American Society of Clinical Oncology
BB	beta blocker
BP	blood pressure
BMA	bone-modifying agent
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CAR-T	chimeric antigen receptor T cell
CIA	chemotherapy-induced alopecia
CINV	chemotherapy-induced nausea and vomiting
CIPN	chemotherapy-induced peripheral neuropathy
CNS	central nervous system
CRS	cytokine release syndrome
CSF	colony-stimulating factor
CT	computed tomography
CTCAE	common toxicity criteria for adverse events
CTLA4	cytotoxic T-lymphocyte-associated protein 4
DOAC	direct oral anticoagulant
ECG	electrocardiogram
ECHO	echocardiogram
EEG	electroencephalogram
EGFR	epidermal growth factor receptor
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FN	febrile neutropenia
G6PD	glucose-6-phosphate dehydrogenase

GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
HSCT	hematopoietic stem cell transplantation
HEC	highly emetogenic chemotherapy
HER2	human epidermal growth factor receptor 2
HF	heart failure
HFS	hand-foot syndrome
HFSR	hand-foot skin reaction
HTN	hypertension
HLA	human leukocyte antigen
ICANS	immune effector cell-associated neurotoxicity syndrome
ICI	immune checkpoint inhibitor
IrAE	immune-related adverse event
IV	intravenous
LEC	low emetogenic chemotherapy
LMWH	low-molecular-weight heparin
LVD	left ventricular dysfunction
LVEF	left ventricular ejection fraction
MEC	moderately emetogenic chemotherapy
MEK	mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAIDs	nonsteroidal anti-inflammatory drugs
N/V	nausea/vomiting

PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PI3K	phosphoinositide-3 kinase
PO	oral
PRN	as needed
RT	radiation therapy
SCr	serum creatinine
SQ	subcutaneously
SRE	skeletal-related event
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
TKI	tyrosine kinase inhibitor
UFH	unfractionated heparin
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism
WBC	white blood cell

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SELF-ASSESSMENT QUESTIONS

1. According to NCCN guidelines, which of the following is the most appropriate indication for a granulocyte CSF product, such as filgrastim?

   A. To enhance the recovery of red blood cells after radiation-containing therapy

   B. To enhance the recovery of neutrophils after chemotherapy which has ≥20% risk of febrile neutropenia

   C. To enhance the recovery of platelets after chemotherapy which has >30% risk of thrombocytopenia

   D. To enhance the recovery of platelets and red blood cells after allogeneic hematopoietic cell transplantation

2. Which of the following medications can be used in the prevention of mucositis?

   A. Atropine

   B. Darbepoetin

   C. Filgrastim

   D. Palifermin

3. Which of the following is a risk factor for chemotherapy-induced nausea and vomiting (CINV)?

   A. Age <50 years

   B. Concomitant alcoholism

   C. Concomitant depression or anxiety

   D. Male gender

4. Which of the following is the most appropriate strategy to prevent acute CINV for a patient who is receiving intravenous HEC?

   A. NK1-RA, 5HT3-RA, corticosteroid, and olanzapine

   B. Olanzapine and corticosteroid

   C. 5HT3-RA and corticosteroid

   D. 5HT3-RA alone

5. A warm compress should be applied as part of the initial management following extravasation of which of the following chemotherapy agents?

   A. Daunorubicin

   B. Cisplatin

   C. Paclitaxel

   D. Vinca alkaloid

6. Which of the following is the most appropriate treatment of hyperuricemia for a patient diagnosed with clinical tumor lysis syndrome?

   A. Calcium gluconate plus sevelamer

   B. Hydration plus rasburicase

   C. Insulin plus dextrose

   D. Sodium bicarbonate plus inhaled albuterol

7. Which of the following statements regarding irAEs is true?

   A. Patients commonly require dose reductions to manage irAEs.

   B. irAEs occur due to lack of an immune response.

   C. The most common irAE is myelosuppression.

D. Corticosteroids or other immunosuppressive agents are used to manage irAEs.

8. Which of the following statements is accurate regarding AEs post-CAR-T?

   A. Temperature, oxygen saturation, and blood pressure are necessary monitoring parameters for CRS

   B. CRS is prevented with administration of prophylactic corticosteroids

   C. Neurotoxicity has an onset typically within the first several days of CAR-T infusion

   D. Neurotoxicity is managed with the anti-IL6 agent tocilizumab monotherapy

9. How should a patient with a mild (grade 1) acneiform rash be managed?

   A. Topical corticosteroids

   B. Tetracycline antibiotics

   C. Both topical corticosteroids and tetracycline antibiotics

   D. Benzoyl peroxide

10. Which cancer treatment is associated with the toxicity of hyperglycemia?

   A. BCR-ABL TKIs

   B. c-KIT TKIs

   C. mTOR inhibitors

   D. Radiation therapy

11. Which of the following patients would be considered high risk for development of osteoporosis and may need bone-modifying therapy?

   A. 21-year-old female on GnRH agonists to cause ovarian suppression while on chemotherapy

   B. 42-year-old female with metastatic breast cancer on chemotherapy

   C. 52-year-old male with AML receiving 3 days of dexamethasone for CINV prophylaxis

   D. 63 year-old-male with prostate cancer who just completed radiation therapy

12. Which of the following drug classes is associated with hypertension?

   A. Anthracyclines

   B. ICIs

   C. Proteasome inhibitors

   D. VEGF inhibitors

13. Which of the following statements regarding anticoagulation in cancer patients is correct?

   A. Anticoagulation is generally considered safe as long as the patient has a platelet count of at least 50,000/mm^3 (50×10^9/L).

   B. Ambulatory patients with a Khorana score of 1 or greater are considered high risk for VTE and should be offered prophylaxis.

   C. DOACs are preferred in patients with gastrointestinal cancers.

D. Warfarin is the preferred first-line agent for VTE treatment.

14. Which of the following agents would be appropriate to recommend and supported by the ASCO guidelines to manage chemotherapy-induced peripheral neuropathy?

    A. Duloxetine

    B. Methadone

    C. Oxycodone

    D. Sertraline

15. When counseling a patient about long-term complications from cancer treatment, which of the following statements is most accurate regarding secondary malignancies to tell the patient?

    A. Agents with the highest risk of leading to diagnosis of secondary cancers are the ICIs

    B. Most commonly diagnosed secondary malignancies are myelodysplastic syndrome and AML

    C. Patients diagnosed with a secondary leukemia have improved prognosis compared to those with a de novo diagnosis

    D. Secondary malignancies with solid tumors are most likely to be diagnosed in the first 5 to 7 years after initial cancer treatment

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** GCSF is utilized for prophylaxis of chemotherapy-induced neutropenia for regimens with ≥20% risk of febrile neutropenia as per NCCN Hematopoietic Growth Factors Guideline. See section "Hematologic Toxicities: Anemia, Neutropenia, and Thrombocytopenia."

2. **D.** Palifermin is indicated to prevent chemotherapy-induced mucositis in specific patient populations. See section "GI Toxicities: Diarrhea, Mucositis, and Nausea/Vomiting."

3. **C.** Concomitant depression/anxiety, age >50 years, and female gender are risk factors. See section "GI Toxicities: Diarrhea, Mucositis, and Nausea/Vomiting."

4. **A.** Guidelines recommend quadruplet therapy for acute prophylaxis for IV HEC regimens with an NK1-RA, 5HT3-RA, dexamethasone and olanzapine. While triplet prophylaxis is an option for HEC, the appropriate triplet regimen would be an NK1-RA or olanzapine plus dexamethasone and a 5HT3-RA. See section "GI Toxicities: Diarrhea, Mucositis, and Nausea/Vomiting" and Table 150-1.

5. **D.** Only vinca alkaloid agents are managed with warm compress after extravasation. See section "ONCOLOGIC EMERGENCIES: TLS AND EXTRAVASATION, PATIENT CARE PROCESS" and Table 150-3.

6. **B.** Hydration and rasburicase are indicated to manage hyperuricemia. See section "Oncologic Emergencies: TLS and Extravasation" and Table 150-2.

7. **D.** irAEs typically require treatment with corticosteroids or other immunosuppressive agents. Therapy is held or discontinued, not dose-reduced. irAEs are a result of immune system activation and do not include myelosuppression. See section "Immune-Related Adverse Events".

8. **A.** CRS monitoring includes fever, oxygen saturation, and blood pressure. Corticosteroids are not indicated to prevent CRS or ICANS. ICANS typically has an onset after at least a week of CAR-T infusion and is managed primarily with corticosteroid. CRS, not ICANs, can be managed with tocilizumab. See section "Cellular Immunotherapy ADRs: CRS and Neurotoxicity."

9. **C.** Both topical and oral agents should be used to manage acneiform rash. Traditional acne medications like benzoyl peroxide should be avoided. See section "Dermatologic Toxicities" and Table 150-4.

10. **C.** mTOR inhibitors are linked with the development of hyperglycemia. The other agents are not. See section "Endocrine Toxicities."

11. **A.** Premenopausal women receiving GnRH therapies causing ovarian suppression are at risk for rapid bone loss and should be considered to bone-modifying treatment. See section "Bone Health."

12. **D.** VEGF inhibitors are associated with the cardiovascular toxicity of hypertension. The other answer choices are associated with other cardiac toxicities. See section "Cardiovascular Toxicities."

13. **A.** Thrombocytopenia is a common complication of cancer treatment and the use of anticoagulation must be balanced with the increased risk for bleeding. However, anticoagulation is generally considered safe to use as long as the patient has a platelet count of at least 50,000/mm^3 (50×10^9/L). See section "Special Considerations – VTE Prevention and Management".

14. **A.** Duloxetine is the only agent recommended by the ASCO guidelines for the management of CIPN. While opioids may have benefit in cancer pain management, they are not beneficial in CIPN and not recommended by the ASCO guidelines. See section "Special Considerations – Pain Management."

15. **B.** ICIs are not affiliated with secondary malignancies. Most common secondary malignancies are myelodysplastic syndrome/AML which are most likely in first 5 to 7 years after initial cancer treatment and have a poorer prognosis than de novo disease. Secondary solid tumor diagnosis typically occurs 10 to 20 years after initial treatment. See section "Long-Term Effects/Survivorship."