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Emergency Complications Associated with Chemotherapeutics and Cancer

KEY FACTS

- The use of granulocyte colony-stimulating factor in neutropenic, febrile patients is controversial but may improve neutrophil count and function in these patients.
- Ondansetron and dolasetron are newer, selective serotonin antagonist antiemetics that may be beneficial for controlling refractory vomiting.
- Cardiotoxicity generally occurs in dogs with long-term, accumulative use of anthracycline chemotherapeutics and is dose limiting.
- Cyclophosphamide may lead to sterile hemorrhagic cystitis and is a potent myelosuppressive agent that may cause thrombocytopenia, resulting in coagulopathies.

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ABSTRACT: Patients undergoing chemotherapy may present to the emergency clinician with diverse problems. A thorough, systematic approach and an awareness of the unique challenges of cancer-related complications as well as adverse reactions from chemotherapy are essential for proper patient management. This article discusses common historical and physical examination findings and minimum database requirements as part of the management approach. Adverse effects of chemotherapeutics include bone marrow suppression and gastrointestinal (GI), renal, and cardiac toxicity. Specific body systems addressed include the hematologic, GI, cardiac, neurologic, renal and urinary bladder, and dermatologic systems. Acute tumor lysis syndrome and allergic or hypersensitivity reactions are also described.

Cancer is a disease shrouded in emotion. A diagnosis of cancer or the word *chemotherapy* may raise feelings of fear and desperation. The owner may perceive even minor problems as serious emergencies because of increased sensitivity and anxiety. Cancer is one of the most common causes of illness in geriatric pets. Today, pets live longer because of more well-informed and educated caregivers, including owners and veterinarians. Advances in cancer therapy allow veterinarians to treat cancer more aggressively and more effectively, with increased cure and control rates, while maintaining the quality of life and reducing the incidence of adverse reactions. Many owners consider their pets to be integral parts of the family and are willing to seek advanced therapy for cancer.

Various treatments for cancer are not without potential adverse consequences. Oncology cases are often presented to the emergency clinician for diagnosis and

treatment. The emergency clinician must determine whether the complication is associated with the treatment or tumor, decide the appropriate action, and determine how the complication affects overall prognosis.[1] Because many cancer patients are older and debilitated, they require special consideration.

The emergency visit should begin with a thorough and systematic evaluation of the entire patient, including potential complications of chemotherapy along with a careful search for other underlying problems. The most common complications associated with antineoplastic therapy include anorexia, fever, vomiting, neutropenia, respiratory distress, and diarrhea. Other body systems affected by cancer treatment include the cardiac, pancreatic, dermatologic, renal, and neurologic systems.

HISTORY AND PHYSICAL EXAMINATION

A thorough history is invaluable to the emergency clinician. Information about specific chemotherapeutic drugs used and when they were last given should be obtained. The following questions require answers: Were there any previous reactions to the drugs? What is the specific diagnosis, and what was the extent of the tumor burden? What was the health of the patient before beginning chemotherapy?[1,2] Clients should also be asked about previous antibiotic administration because this may influence drug choice during treatment. If owners are not completely familiar with the pet's treatment protocol, they should be encouraged to bring all pertinent documentation with them to the visit with the emergency clinician.[1] The primary clinician responsible for the case should be contacted as soon as possible.

The complete physical examination should focus on the organ systems most commonly affected by chemotherapy, including gastrointestinal (GI), urogenital, and respiratory tracts.[2] It is important to note that common signs of inflammation may be absent, particularly in patients with neutropenia or that have received glucocorticoids.[1–4] In other cases, pyrexia may be the only sign detected on physical examination. Fever can result from bacteremia, neutropenia, occult infection, advanced immunosuppression, or tumor growth.[1,5,6] Systemic inflammatory response syndrome (SIRS) and sepsis are considerations in all patients presenting with fever, tachycardia, and tachypnea.[1,4] SIRS has been defined by the American College of Chest Physicians and the Society of Critical Care Medicine as a systemic, hypermetabolic inflammatory response that does not require evidence of infection (e.g., severe trauma and cancer can initiate SIRS without evidence of infectious agents).[7] A controlled inflammatory response can quickly become uncontrolled because of ongoing injury, the addition of new physiologic insults (e.g., hypoxia, hypoperfusion, infection, surgery), or a compromised immune system (e.g., a result of immunosuppressive therapy, primary immune-mediated disease, and cancer).[8–10]

Examination of the heart and lungs should also be performed. The cardiovascular system is auscultated and palpated to detect arrhythmias, murmurs, pulse synchrony and quality and determine if pulse deficits exist. Auscultation of the lungs should be performed to assess breath sounds for the presence of crackles or wheezes.[1,2] The presence of abdominal pain or fluid accumulation may suggest an intestinal disorder or extracapsular hemorrhage. The presence of petechiae and ecchymoses may indicate underlying thrombocytopenia or underlying coagulopathy.[11] A search for a potential nidus of infection should be performed, including an evaluation of previous injection and catheter sites for evidence of phlebitis or lesions associated with extravasation.[1,2,5] Debilitated and recumbent patients may develop decubital ulcers, which are a source of inflammation and infection.[2,5] Finally, an evaluation of hydration status and level of mentation is highly beneficial in patients with suspected SIRS or sepsis due to changes in electrolyte and serum glucose levels and fluid balance.[1,4]

MINIMUM DATABASE

Blood and urine samples for culture should ideally be collected before the initiation of therapy. Urine culture should be considered in all cases of SIRS or suspected sepsis, even if the urine sediment does not show signs of inflammation. A minimum database can be modified to address the patient's needs, presenting clinical signs, and physical examination findings. In most cases, blood samples are obtained for all anticipated laboratory analyses. In cases of suspected sepsis, more immediate analyses include a stained blood smear to estimate platelet, white blood cell (WBC), and red blood cell (RBC) numbers and to evaluate cell morphology,[12] hematocrit and total protein, blood glucose and blood urea nitrogen analysis, activated clotting time, and urinalysis. As time and laboratory availability permit, a more elaborate analysis can include complete blood cell count, serum biochemical analysis, coagulation profile, thoracic and abdominal radiography, electrocardiography, arterial blood gas analysis, systemic blood pressure, appropriate cultures (i.e., blood, urine, joint, and abdominal or pleural fluid), and abdominal ultrasonography. Ideally, blood for culture should be obtained before administering antibiotics.[5,13,14]

DIAGNOSIS AND TREATMENT

The guidelines for fluid therapy and the pathophysiology and treatment of SIRS and sepsis are well

Table 1. Criteria for Diagnosis of Systemic Inflammatory Response Syndrome[a]

Clinical Parameter	*Dogs*	*Cats*
Heart rate	>120 bpm	<140 or >225 bpm
Respiratory rate	>40 breaths/min or $PaCO_2$ <30 mm Hg	>40 breaths/min
Temperature	<100.4°F or >104.0°F	<100.4°F or >104.0°F
Leukogram	<5,000 WBC/µl or >18,000 WBC/µl	<5,000 WBC/µl or >19,000 WBC/µl

[a]From Brady CA, Otto CM: Systemic inflammatory response syndrome, and multiple organ dysfunction. *Vet Clin North Am Small Anim Pract* 31(6):1147–1162, 2001; with permission.

described in the literature and are beyond the scope of this article.[4,5,7,9,10,15–17] See Table 1 for SIRS diagnostic criteria. Strict adherence to aseptic catheter placement and barrier nursing care measures should be enforced in immunocompromised neutropenic patients to guard against nosocomial infection. Barrier measures include wearing gloves when placing IV catheters, obtaining blood samples, or handling body fluids; aseptic handling of IV catheter ports; and heightened awareness of disease spread among immunocompromised patients.[5] Although antibiotic choice is ideally based on culture results, empirical, broad-spectrum antibiotics should be administered until such results are obtained.[1,11,18,19] The combination of an aminoglycoside plus a first-generation cephalosporin (cefazolin or cephalothin) is a good, reasonably inexpensive first choice provided that renal function and hydration are adequate.[1,14,18,19] Substituting ampicillin for the cephalosporin will improve anaerobic coverage; however, neither combination is appropriate for *Pseudomonas* spp.[1,2,14,18,19] The complexity of these cases requires paying close attention to the patient's status and using sound clinical knowledge to help individualize therapy for the specific problems of each patient[14,18,19] (Table 2).

HEMATOLOGIC COMPLICATIONS

Hematologic abnormalities are common in cancer patients. Problems resulting from hematologic abnormalities can be as nonspecific as lethargy and poor appetite or as serious as sepsis, shock, and disseminated intravascular coagulation (DIC). The most chemosensitive cells in the bone marrow are actively proliferating precursors or those that have committed to a particular lineage but are still immature.[20] Myelosuppression is common because of the high mitotic rate in bone marrow and the short half-life of WBCs.[1,11,20–22] Pancytopenia is common, with the granulocytic line being the most significantly affected clinically.[1,11,20–22] Leukopenia becomes apparent 5 to 10 days after treatment with drugs such as cyclophosphamide, doxorubicin, mitoxantrone, or methotrexate.[1,20]

Myelosuppression is defined as a neutrophil count less than 3,000/µl.[1,21,22] Overwhelming sepsis rarely occurs when neutrophil counts remain above 1,000/µl.[1,20,22] The risk of infection is well correlated with the degree and duration of neutropenia; it rises exponentially as the neutrophil counts fall below 500/µl.[1,22] Counts as low as 200/µl or below are not uncommon.[1,22] In general, neutropenia and thrombocytopenia are short-lived after treatment with cell cycle–active, phase-specific drugs (i.e., paclitaxel, antimetabolites [e.g., cytosine arabinoside]); are of intermediate duration after administration of cell cycle–active, phase-nonspecific drugs (i.e., anthracyclines and most alkylating agents [e.g., cyclophosphamide]); and are prolonged and less predictable after treatment with chloroethylnitrosourea or mitomycin C.[22]

If the presence of cytopenia cannot be explained by the current therapy or cytopenia goes unresolved, the clinician should evaluate the bone marrow.[1,2,11] Hematopoietic stem cells are often spared from myelosuppressive effects of most agents because they are largely nonproliferating, except when nitrosurea and busulfan have been used.[1,2,11,20,22] In most cases, bone marrow recovery is expected. Serial complete blood cell count evaluation often shows monocytosis followed by an increase in the neutrophil count within 24 to 48 hours as the first indication of bone marrow recovery.[1,11,22] The nadir usually occurs 5 to 7 days after therapy.[1,2,18,20,21] Exceptions to this rule do exist, requiring the clinician to know about the specific drugs. For example, the nadir for paclitaxel is typically on day 3; doxorubicin on day 10; and cisplatin on days 6 and 15 (a double nadir).[1,3]

Signs of illness are unrelated to absolute WBC numbers; rather, they relate to increased susceptibility of a patient to local and systemic infections during a neutropenic crisis.[1,2,20,22] The most common sites of infection are the GI, urogenital, and respiratory tracts.[1,2,20] In the neutropenic patient, however, neutrophil-derived mediators of inflammation are suppressed. Therefore, typical signs of inflammation may not be present.[1–3,20] It thus becomes important to obtain airway samples, urine, and exudates from cutaneous wounds for cytologic evaluation (Romanowsky-type stains and Gram's stain) and for culture for aerobic and anaerobic bacteria; when appropriate, stool cultures are

Table 2. Antibiotics Used to Treat Patients with Septic Cancer

Dosage	*Potential Side Effects*	*Comments*
Gram-Negative Bacteria		
Gentamicin: 6.6 mg/kg/day IV, IM, or SC	Nephrotoxicity (especially when preexisting renal damage is present) Ototoxicity Neuromuscular blockade	Ensure adequate hydration and check frequently for renal damage during use
Amikacin: 15 mg/kg/day IV or IM; daily dose may be divided q8–12h	Nephrotoxicity (especially when preexisting renal damage is present) Ototoxicity Neuromuscular blockade	Ensure adequate hydration and check frequently for renal damage during use
Cefazolin: 20–30 mg/kg IV q6–8h	Phlebitis (muscle pain can occur after IV or IM administration) Nephrotoxicity (rare) Immune-mediated cytopenia	—
Cefoxitin: 22 mg/kg IV q8h	Phlebitis Discomfort with rapid IV injection Nephrotoxicity (rare) Immune-mediated cytopenia	—
Enrofloxacin Dogs: 2.5–20 mg/kg/day IM or IV Cats: 5.0 mg/kg/day IM or IV	Cartilage fails to develop in young, growing puppies (at high doses)	Daily dose may be divided q8–12h
Gram-Positive Bacteria		
Penicillin G sodium or Penicillin G potassium: 25,000 U/kg IV q6h	Allergy to penicillin can cause anaphylaxis, hives, fever, and pain Neurologic signs may occur with rapid infusion Immune-mediated cytopenia	—
Cefazolin: 20–30 mg/kg IV q8h	Phlebitis (muscle pain can occur after IV or IM administration) Nephrotoxicity (rare) Immune-mediated cytopenia	—
Cefoxitin: 22 mg/kg IV q8h	Phlebitis Discomfort with rapid IV injection Nephrotoxicity (rare) Immune-mediated cytopenia	—
Enrofloxacin: 2.5–20 mg/kg/day IM or IV	Cartilage fails to develop in young, growing puppies	Daily dose may be divided q8–12h
Anaerobic Bacteria		
Metronidazole: 10–20 mg/kg/day IV divided tid	Anorexia Vomiting Neurologic signs	—
Cefoxitin: 22 mg/kg IV tid	Phlebitis Discomfort with rapid IV injection Nephrotoxicity (rare) Immune-mediated cytopenia	—
Clindamycin: 5.5–11 mg/kg PO, SC, IM, IV q12h	Vomiting Diarrhea Pain at injection site (IM) Cholestasis	—

also needed, especially with suspected *Salmonella* spp infections.[1,2,5] Common bacterial isolates include gram-negative rods (Enterobacteriaceae) and gram-positive cocci (*Staphylococcus* and *Streptococcus* spp).[1,2,12,13] Early identification of bacteria populations by this method may allow rational antibiotic selection while culture and sensitivity results are pending.[1]

Neutropenic patients exhibiting signs of fever, dehydration, shock, or SIRS require aggressive treatment.[1,2,5–7,9,10] All antineoplastic agents should be discontinued. An IV catheter should be placed aseptically. Parenteral, broad-spectrum, bactericidal antibiotics should be administered.[1,2–6,20] If corticosteroids are part of the patient's treatment protocol, they should be continued at physiologic levels to avoid a hypoadrenal crisis.[1,2] Physiologic dosages of steroids have generally been accepted as 0.1 to 0.2 mg/kg/day. Sepsis may be associated with relative adrenal insufficiency. Recently, in human literature, some benefit of steroid replacement therapy for septic shock has been proposed.[23] These findings have yet to be substantiated in the veterinary literature and are thus not advocated or recommended at this time.[24]

In patients in which an infectious nidus cannot be identified or preliminary cytologic assay results are negative, blood and urine cultures should be considered.[1,5] Current recommendations for blood culture are to obtain two or three samples at 30-minute intervals.[1,2,25] Blood cultures have been reported as positive in 11% to 50% of human and canine patients.[25] A negative culture result for two or three successive cultures generally rules out bacteremia caused by common pathogens, although less common or more fastidious organisms may take days to weeks to grow.[25] A positive result, in contrast, does not necessarily indicate true bacteremia.[25] Perhaps the greatest challenge in interpretation is that of inadvertent sample contamination with normal skin commensal bacteria.[25] The only way to rule out contamination is to culture multiple blood specimens and isolate the same bacterium from at least two.[25] In addition, recovery of potential pathogens that are not normal commensal organisms of the skin is taken as presumptive evidence of true bacteremia.[25]

Human recombinant granulocyte colony-stimulating factor (rh-G-CSF) has been used to prevent chemotherapy-induced myelosuppression or neutropenia resulting from infectious disease.[26–29] The primary effect of rh-G-CSF is stimulation of proliferation and maturation of neutrophil precursors and, to a lesser extent, monocyte precursors in bone marrow.[26,27,29,30] In addition, rh-G-CSF primes neutrophils for cell killing by enhancing antibody-dependent cellular cytotoxicity, superoxide production, and Fc receptor production, and it promotes neutrophil migration across the endothelium.[26–28,30] Although rh-G-CSF appears to have some usefulness as a prophylactic to modulate chemotherapy-induced myelosuppression as well as a potential immune modulator in cases of bacterial sepsis,[31–33] evidence for its benefit in the afebrile or febrile neutropenic patient is contradictory.[27,30] Further studies of rh-G-CSF are warranted for this population.[19,34,35] Despite the fact that rh-G-CSF is not of canine origin, short-term use (<3 to 5 days) in patients receiving chemotherapy has not been associated with development of antibody to the growth factor. Concerns about administration of rh-G-CSF in hematopoietic malignancies that may use the cytokine as a growth factor have not resulted in any published reports regarding dogs and cats.[a]

After the neutrophil count returns to normal and the fever subsides, the patient can be switched to oral antibiotics on an empirical basis if culture results are not available. Such antibiotics include sulfadiazine–trimethoprim (15 mg/kg q12h), enrofloxacin (5 to 10 mg/kg q12–24h), or cephalexin (30 mg/kg q12h) for an additional 7 to 10 days.[1,2,36] A persistent fever (longer than 3 days) without a nidus of infection being identified may indicate a resistant organism, the emergence of a secondary bacterial infection, inadequate antibiotic dosage, or a nonbacterial infection (e.g., fungal, viral, or rickettsial).[1,5] In such cases, reassessment of the patient is necessary. Catheter sites should be carefully evaluated for evidence of thrombosis and phlebitis at the point of venipuncture.[1,4,5] In addition, reevaluation of current laboratory data, additional radiography, reculture of previous sites of infection and of blood, and reassessment of less common sources of infection should be considered.[1,2,5]

Other hematologic abnormalities occur with much less regularity. After chemotherapy, thrombocytopenia is uncommon but warrants investigation.[1,20,22] Thrombocytopenia can be related to decreased production, such as with myelophthisic disease; increased consumption, such as with DIC; shortened life span; and peripheral destruction.[20–22]

Mild anemia induced by chemotherapeutic agents is relatively uncommon and rarely a problem in cats and dogs undergoing chemotherapy.[1,20–22] Hydroxyurea, used to treat polycythemia vera and chronic myelogenous leukemia in dogs and cats, can cause severe anemia.[20] Polycythemia has been uncommonly reported; it has usually been noted with paraneoplastic syndromes associated with renal cell carcinomas, lymphosarcomas, transmissible venereal tumors, and hepatic tumors.[1,22]

[a]Ogilvie G: Personal communication, Colorado State University, January 18, 2002.

GASTROINTESTINAL COMPLICATIONS

Three basic chemotherapy-induced GI complications include anorexia and vomiting, enterocolitis, and pancreatitis.[1–3,20] Vomiting can occur within hours of chemotherapy and may persist for days.[1,2] Chemotherapeutic agents induce vomiting through centrally mediated actions on the vomiting center in the medulla and chemoreceptor trigger zone or peripherally by direct actions on the gastric mucosa or via local GI tract irritation to stimulate the gut neurotransmitter receptors and subsequently activate the vomiting center through the vagus and sympathetic nerves.[1–3,20] Neurotransmitters that mediate the vomiting response include dopamine, histamine, acetylcholine, opiates, and serotonin.[1,2] Serotonin release from enterochromaffin cells in the GI tract is an important pathophysiologic mechanism of acute vomiting; the other neurotransmitters may be more responsible for delayed vomiting. The hydrated, stable patient can benefit from symptomatic treatment with metoclopramide (0.5 mg/kg PO or SC q6–8h or 1 to 2 mg/kg/day IV constant-rate infusion), chlorpromazine (0.2 to 0.4 mg/kg SC q8h), or prochlorperazine (0.5 mg/kg IM or SC q8h or 1 mg/kg PO q12h).[1,2,36,37] Newer and more potent antiemetics used in patients with chemotherapy-induced vomiting include ondansetron (0.1 mg/kg PO or IV q8–12h) and dolasetron (0.6 to 3.0 mg/kg PO or IV q24h).[1,2,9,20,36,38] Combinations of metoclopramide and ondansetron or dolasetron can be used in refractory cases of vomiting.[1] For additional GI support, the selective histamine-2 (H_2) blocking agents ranitidine (dogs: 2 mg/kg IV q12h; cats: 2.5 mg/kg IV or PO q12h) and cimetidine (dogs: 5 to 10 mg/kg PO, IM, SC, or IV q8–12h; cats: 10 mg/kg IV q6h) aid in treating gastric hyperacidity associated with nausea and vomiting.[36] For IV administration, it is best to dilute the drugs and give them over a period of 20 to 30 minutes to help minimize vomiting, especially if the patient is already nauseated.

Diarrhea occurs in response to direct GI mucosal injury 3 to 7 days after chemotherapy.[1,3,20] Chemotherapy-induced crypt cell death, related to rapidly dividing mucosal cells, may allow bacteria to migrate across the mucosal barrier, resulting in sepsis.[1,2,39] It is believed that bacteria that translocate to intestinal lymphatic tissue are killed by host defenses, stimulating a proinflammatory state characterized by release of cytokines, vasoactive substances, complement, and other inflammatory mediators.[39] Gut-derived endotoxemia may be the signal that triggers and perpetuates a hypermetabolic SIRS state.[39] Endotoxemia is a known stimulus for cytokine release and has been implicated in causing impaired function of the immune system, coagulation system, and GI mucosal barrier.[39] Diarrhea may or may not be accompanied by vomiting. Mild diarrhea without concurrent vomiting may respond to supportive treatment with bland diet and antidiarrheal agents.[1,19] Clinical signs generally resolve within 3 to 5 days.[1–3,20] Patients with more severe diarrhea or those that have received myelosuppressive agents with concurrent dehydration require more aggressive treatment.[1,20] Parenteral antibiotics, IV fluids, and supportive care are indicated for all patients with hemorrhagic diarrhea or in the presence of pyrexia, leukocytosis, neutropenia, or shock.[1,20]

Pancreatitis is another possible complication reported to occur in some species when L-asparaginase, cisplatin, doxorubicin, methotrexate, azathioprine, or corticosteroids are used.[1,2,20,40] Patients presenting with severe, intractable vomiting, diarrhea, abdominal pain, and other hallmarks of pancreatitis may require extended treatment and are at a higher risk for SIRS, septic shock, and multiorgan failure syndrome caused by release of endogenous cytokines.[1,20,40]

CARDIOTOXICITY

Cardiotoxicity is associated with the use of the anthracycline agents doxorubicin, epirubicin, and daunorubicin in dogs.[1,2,20,41,42] Cardiotoxicity tends to occur during long-term administration and is dose limiting. Dogs receiving doxorubicin may develop electrocardiographic (ECG) and echocardiographic abnormalities and signs of overt heart failure.[1,2,20,42] Multiple types of cardiotoxicity have been identified. Acute toxicity is mild, uncommon, and transient and is characterized by acute dysrhythmias and hypotension that occurs at the time of doxorubicin administration.[2,20,41] Acute pericarditis is reported as an idiosyncratic, potentially fatal form of congestive heart failure (CHF) that appears to be related to histamine and catecholamine release.[2,42] Doxorubicin-induced cardiomyopathy occurs in dogs receiving more than 240 mg/m^2.[20,42] In contrast, cats are rarely reported to experience doxorubicin-induced cardiotoxicity.[20,43]

Chronic cardiotoxicity resulting in dilated cardiomyopathy is seen with cumulative doxorubicin doses of 150 to 240 mg/m^2.[2,20,42] Lower dosages have also resulted in toxicity.[20] The precise mechanism of doxorubicin-induced cardiotoxicity is unclear.[1,2,20,42] Experimental evidence suggests that the drug induces an iron-dependent free radical cascade that overwhelms the myocardial antioxidant defense mechanisms, which leads to oxidation of cardiac proteins and membrane components.[20,41–45] This cardiotoxicity prompted development of an experimental drug, dexrazoxane (Zinecard, Pharmacia & Upjohn), which has proved effective in preventing doxorubicin-induced cardiotoxicity.[20,45,46] Dexrazoxane is an iron chelator, similar to EDTA, and can reduce the free radical formation that

occurs with doxorubicin use.[20,45,46] Dexrazoxane has no clinical benefit once cardiac damage is present.[20]

The most common ECG abnormalities reported with doxorubicin-induced cardiotoxicity include multiform ventricular premature excitations or complexes, supraventricular arrhythmias (sinus tachycardia), and changes in R wave amplitude.[1,2,20,42] These ECG abnormalities can occur within hours to days of drug administration and may persist without signs of CHF.[1,2,20,42] Regardless of the presentation, any ECG abnormalities detected in the emergency setting should be recorded and followed up by serial ECG and echocardiographic evaluations.[2,42]

Dogs with overt heart failure induced by doxorubicin may present clinically with tachypnea, weakness, cough, pale mucous membranes, and evidence of pulmonary edema.[1,2,42] Radiography, ECG, and echocardiography may show signs consistent with CHF, although ECG and echocardiographic alterations can be relatively insensitive measures of doxorubicin-induced cardiotoxicity.[2,42] Dogs presenting with signs consistent with CHF and pulmonary edema should receive immediate oxygen therapy via face mask, flow-by oxygen, nasal cannula, or oxygen cage.[1,2,46–48] Intravenous furosemide (2 to 4 mg/kg q2h) can induce rapid diuresis and reduction of preload.[1,2,47,48] Dosage and frequency of furosemide administration can be adjusted on the basis of the patient's clinical response. Nitroglycerin 2% paste (0.25 to 1 inch topically q6–8h for cats and dogs), with a primary action as a venous smooth muscle dilator, can be used as adjunctive therapy to reduce preload and decrease venous pooling.[1,2,47,48] Morphine (0.05 to 0.1 mg/kg IM q4–6h) reduces pulmonary edema (by causing dilation of splanchnic vessels), decreases anxiety, and reduces myocardial oxygen demand.[1,2,47,48] Angiotensin-converting enzyme inhibitors, such as enalapril, captopril, and hydralazine, help reduce afterload and may be considered for adjunctive treatment.[48]

Dogs that respond poorly to these initial treatments may benefit from the use of sodium nitroprusside (0.5 to 10 µg/kg/min via constant-rate infusion titrated to effect).[1,2,47,48] Nitroprusside is a potent vasodilator that can induce profound hypotension, especially at higher dosages.[48] Therefore, it is imperative that serial arterial blood pressure (direct or indirect) be monitored, along with central venous pressure or pulmonary artery wedge pressures, heart rate, and rhythm.[1,2,48] Dogs that present with signs of CHF after receiving doxorubicin are often refractory to treatment and have a poor prognosis.[2,20,42]

NEUROTOXICITY

Chemotherapy-induced neurotoxicity is rare, with only isolated reports to a few agents published. In a patient exhibiting neurologic signs, the primary differential diagnosis includes metastasis of the primary tumor to the central nervous system (CNS), direct tumor invasion of the CNS, and indirect effects, such as thrombosis, hemorrhage or vascular accidents, or hepatoencephalopathy.[1,2] 5-Fluorouracil has been reported to cause refractory seizures; tremors; hyperexcitability; ataxia; mucositis; diarrhea; potentially profound, although transient, leukopenia and thrombocytopenia; and death in cats and (occasionally) dogs.[20,49,50] Vincristine has caused direct axonal injury to the spinal cord, peripheral nerves, and CNS.[2,51] There is one report of fatal cerebral thrombosis, hemorrhage, and progressive seizures with respiratory arrest in a dog with preexisting glomerulonephritis associated with L-asparaginase administration.[3]

NEPHROTOXICITY

Acute renal failure (ARF) has been reported in dogs treated with cisplatin and rarely with methotrexate and doxorubicin in cats.[1,2,52] Cisplatin-induced ARF is associated with decreased renal blood flow, acute tubular necrosis, reduced glomerular filtration rate, transient hypomagnesemia, and polyuria followed by an irreversible decrease in glomerular filtration rate.[2,52] These

changes precede increases in serum urea nitrogen and creatinine concentrations.[2,52] In dogs, 80% to 90% of the drug is eliminated in the urine within 48 hours.[2,52] Cisplatin is less toxic in a high-chloride environment, and the use of short-term saline diuresis has greatly reduced the incidence of cisplatin-induced nephrotoxicity.[2,52] Renal failure has been reported to occur rarely in cats receiving doxorubicin at total cumulative doses of 130 to 320 mg/m^2.[43]

HEMORRHAGIC CYSTITIS

Sterile hemorrhagic cystitis is a potential complication of cyclophosphamide and ifosfamide therapy in dogs and occasionally cats.[53–55] Although this effect can occur acutely, it is more commonly associated with long-term use of the inciting agent.[2] In one study, 14 of 203 dogs (7%) and 1 of 32 cats (3%) treated with oral cyclophosphamide had hemorrhagic cystitis.[53] Sterile hemorrhagic cystitis occurs because of one metabolite of cyclophosphamide, acrolein, that affects the bladder mucosa.[53–55] Urinalysis in cases of sterile hemorrhagic cystitis reveals an abundance of RBCs with few to no WBCs. Although chronic hemorrhagic inflammation is initially a sterile process, it may predispose to secondary bacterial infection, proliferative mucosal lesions, and fibrosis.[1]

Diagnosis of sterile hemorrhagic cystitis is made via history and physical examination, along with typical urinalysis and negative urine culture results.[53–55] Cyclophosphamide is also a known myelosuppressive agent that can cause thrombocytopenia; this and other potential coagulopathies should be ruled out.[2] Treatment of cystitis involves permanent discontinuation of the drug and induction of diuresis.[2,56] More aggressive diagnostic tests and treatment protocols, including abdominal radiography, ultrasonography, contrast cystography, parenteral antibiotics, IV fluids, and piroxicam (0.3 mg/kg q24–48h if renal function is normal), may be required in complicated cases in which bacterial infection is noted.[2]

DERMATOLOGIC TOXICITY

Dermatologic complications may result from accidental extravasation of materials at the injection site.[1,2] The prevalence of this complication in veterinary medicine is unknown. Tissue necrosis can result even if treatment is initiated immediately after the accident, and wounds can worsen over a period of weeks.[1,2,57] Not all agents are alike in their ability to cause injury. Drugs can be classified as vesicants, irritants, or nonvesicants.[58] Vesicants induce a blister with or without necrosis. Irritants cause signs of pain when injected with or without inflammation. Nonvesicants rarely cause acute reactions or necrosis.[58] Agents most likely to cause necrosis are also potential irritants, including doxorubicin, vincristine, vinblastine, actinomycin D, DTIC, and streptozocin.[1,2] Clinical signs of perivascular reactions include erythema, edema, pain, moist dermatitis, necrosis, and evidence of sloughing and pruritus.[2,57] Signs are usually evident within 1 to 10 days after the incident at the site of injection, although late reactions also occur.[2] Perivascular doxorubicin causes the most severe tissue damage, with the damage directly related to the amount injected.[2,58]

Single-use, indwelling catheters that are placed carefully and checked throughout the chemotherapy infusion should prevent extravasation.[2] If extravasation does occur, various treatments have been advocated. Diluting the drug locally with saline or use of 8.4% sodium bicarbonate or dexamethasone sodium phosphate at the site of perivascular reaction has been recommended.[1,2] The use of hyaluronidase to treat accidental extravasation of chemotherapeutic agents has been advocated in both human and veterinary medicine.[58,59] The use of dexrazoxane at the site of extravasation with anthracyclines has been suggested for humans.[60] The use of this therapy in veterinary medicine has not been evaluated.

Some authors believe that these strategies may not be beneficial and may only distribute the drug over a wider area.[1] In some cases, surgical debridement and plastic reconstructive surgery may be necessary. Daily bandage changes, reassessment of wounds, and appropriate use of analgesics are warranted.[1] Certain chemotherapeutic agents (e.g., prednisone, cyclophosphamide, doxorubicin) may delay healing.[1] Infected wounds or wounds associated with severe necrosis or ulceration should encourage aerobic and anaerobic cultures of the affected area.

ACUTE TUMOR LYSIS SYNDROME

Acute tumor lysis syndrome (ATLS) results from rapid, massive cell death of primarily malignant cells. The death of these malignant cells causes the release of cellular contents in amounts in excess of what the body can eliminate. ATLS has been reported in humans with chemosensitive tumors, such as lymphoma and leukemia[61]; although it occurs most often in patients receiving chemotherapeutic agents, it may occur spontaneously.[61,62] In veterinary medicine, ATLS has been reported during treatment of lymphoma with chemotherapeutic agents and/or radiation.[2,61] Dehydrated patients with stage IV or V lymphoma that undergo rapid remission after chemotherapy are at the highest risk of developing ATLS.[2,61] ATLS is characterized by hyperphosphatemia, hyperkalemia, hypocalcemia, metabolic acidosis, and azotemia.[2,61] Clinical signs include mental depression, vomiting, hemorrhagic diarrhea,

Table 3. Complications from Chemotherapeutic Agents

Body System/Reaction	*Clinical Signs*	*Findings*	*Species*	*Agents Associated*
Hematologic	Lethargy Poor appetite Sepsis Shock DIC	Myelosuppression Pancytopenia Granulocytic lines most affected	Cats and dogs	Paclitaxel Cyclophosphamide (and most other alkylating agents) Anthracyclines Mitoxantrone Methotrexate Cytosine Arabinoside Mitomycin C Cisplatin Chlorethylnitrosourea
GI	Diarrhea/vomiting Anorexia Pancreatitis Vomiting Diarrhea Abdominal pain	—	Cats and dogs	All L-Asparaginase Cisplatin Doxorubicin Methotrexate Azathioprine Corticosteroids
Cardiovascular	Dysrhythmia Hypotension Congestive heart failure	Mild toxicity Acute pericarditis (tachypnea, weakness, cough, pale mucous membranes)	Dogs	Anthracyclines
Neurologic	Refractory seizures Tremors Hyperexcitability Ataxia Peripheral nerves and CNS	Uncommon toxicity Progressive seizures Cerebral thrombosis	Cats > dogs	5-Fluorouracil Vincristine
	Cerebral thrombosis		1 Dog	L-Asparaginase
Renal	Polyuria/polydipsia/ anuria	Acute renal failure	Dogs Cats (rare)	Cisplatin Doxorubicin Methotrexate
	Hematuria	Hemorrhagic cystitis	Dogs > cats	Cyclophosphamide/ Ifosfamide
Dermatologic	Tissue necrosis	Extravasation	Dogs and cats	Doxorubicin Vincristine Vinblastine Actinomycin D Dacarbazine Streptozotocin
Allergic	Hypersensitivity Restlessness Cutaneous erythema Head shaking Vomiting Urticaria Facial edema Pruritus	—	Dogs and cats	L-Asparaginase Doxorubicin Etoposide Taxanes

bradycardia related to hyperkalemia, cardiovascular collapse, and shock.[2,61] Rapid diagnosis is essential.[2,61] The clinical course of ATLS is acute; therefore, successful treatment requires rapid institution of definitive treatment protocols for this shock-like syndrome.[1,2,61]

ALLERGIC AND HYPERSENSITIVITY REACTIONS

Allergic reactions to cancer chemotherapeutics can occur as with any drug. Several agents have been shown to induce hypersensitivity reactions, including L-asparaginase, doxorubicin, etoposide, and taxanes (paclitaxel, docetaxel).[20] L-Asparaginase has been associated with type I hypersensitivity, IgE-mediated reactions.[2,20] In other cases, the carrier or solvent that is added to improve the solubility of the agent (e.g., Cremophor EL [BASF] with etoposide or polysorbate 80 with Taxol [Bristol-Myers Squibb]) may lead to allergic reactions.[2,20] Doxorubicin can cause acute mast cell degranulation, without IgE mediation, when infused rapidly and has been associated with hypersensitivity reactions in approximately 10% of cases.[1,2,20]

Clinical signs of hypersensitivity reactions are most commonly associated with the skin or GI tract.[1,2,20] Pretreatment with histamine-1 (H_1) blockers (diphenhydramine, 0.2 to 0.5 mg/kg slow IV) or corticosteroids (dexamethasone sodium phosphate, 1 mg/kg IV) has been recommended by some practitioners; however, pretreatment is not used in many veterinary cancer treatment centers.[1,2,20] Treatment for the more severe anaphylactic or anaphylactoid reactions is the same as it would be for any other drug-related anaphylaxis.[2,20] If the reaction occurs during the administration of the agent, administration should be halted immediately, and the use of antihistamine, corticosteroids, aggressive use of IV fluids, and epinephrine (0.1 to 0.3 ml of a 1:1000 solution IV) may be necessary.[2,20]

SUMMARY

The most common urgent care situations involve chemotherapy- or cancer-related vomiting, enterocolitis, anorexia, neutropenia, SIRS, sepsis, DIC, heart failure, neurotoxicity, nephrotoxicity, hemorrhagic cystitis, tissue necrosis or cellulitis, and conditions such as ATLS and allergic or hypersensitivity reactions (Table 3). Clinicians should be prepared to treat oncologic emergencies at any hour of the day. Knowledge of common emergencies will provide clinicians with the skills to manage these problems while maintaining or improving the patient's quality of life.

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ARTICLE #3 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. *Choose the best answer* to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium.*

1. Which question does not need to be asked of a client concerning a patient presenting with an emergency after antineoplastic therapy?
   a. Which chemotherapeutic agent was used?
   b. Was a high-protein diet fed?
   c. What was the patient's health status when cancer treatment was begun?
   d. Have antibiotics recently been used; if so, what type?

2. Which of the following is not a reported benefit of granulocyte colony-stimulating factor?
   a. stimulation of WBC mitogenesis
   b. decreased WBC function (e.g., chemotaxis, phagocytosis)
   c. stimulation of stem cell differentiation
   d. mobilization of mature WBCs

3. The nadir in the WBC count occurs in most cases _____ after therapy.
   a. 21 to 30 days
   b. 5 to 7 days
   c. 6 months
   d. 1 year

4. The cardiotoxicity induced by doxorubicin is proposed to occur by
   a. heat-shock enzymatic injury.
   b. iron-independent free radical cascade.
   c. direct cytotoxic injury.
   d. iron-dependent free radical cascade.

5. Under which category can drugs that cause dermatologic injury with extravasation be classified?
   a. irritants
   b. desiccants
   c. nonvesicants
   d. a and c

6. The hallmarks of inflammation are most likely absent in the myelosuppressed patient because of
   a. suppressed neutrophil-derived inflammatory mediators related to neutropenia.
   b. endotoxemia, which results from bacterial translocation.
   c. crypt cell death within the GI tract.
   d. a hypoadrenal state, which occurs in most cancer patients.

7. Common neurotransmitters that mediate vomiting include all the following agents except
   a. dopamine.
   b. histamine.
   c. γ-aminobutyric acid.
   d. opiates.

8. Which statement regarding blood cultures is correct?
   a. All positive results are 100% accurate.
   b. A negative result on two or more successive cultures generally rules out bacteremia for most common bacteria.
   c. A positive result always indicates bacteremia.
   d. Recovery of commensal organisms on blood culture is generally considered a presumptive positive result.

9. Doxorubicin-induced hypersensitivity reactions are due to
   a. IgE-mediated, type I hypersensitivity.
   b. liquefactive necrosis.
   c. nicotinic receptor antagonism.
   d. direct mast cell degranulation.

10. Which of the following has reduced the incidence of cisplatin-induced ARF?
    a. short-term diuresis with solutions containing high chloride concentrations
    b. short-term diuresis with fluids containing high potassium concentrations
    c. use of alkalinizing solutions to reduce serum chloride concentration
    d. use of systemic corticosteroids at immunosuppressive dosages