CHAPTER 173

COMPLICATIONS OF CHEMOTHERAPY AGENTS

Victoria S. Larson, BSc, DVM, MS, DACVIM (Oncology) • Valerie Madden, DVM

KEY POINTS

- Chemotherapy is one mode of management of cancer in dogs and cats.
- Recent advances in chemotherapy have resulted in increased remission rates and survival times for patients with cancer.
- Complications of chemotherapy occur, and innocent bystanders are also harmed.
- It is imperative that the clinical staff be aware of the toxicities of each chemotherapeutic agent so that complications can be identified.
- Complications should be treated rapidly and thoroughly with supportive measures.

Cancer is a major cause of disease-related death in dogs and cats. Various studies during the last 30 years show that about half of all dogs and one third of all cats will die of cancer. The prevalence of cancer in small animals is increasing, along with an increased awareness of and an expansion of knowledge about diagnosis, treatment options, and prognosis.[1]

As clinicians strive for higher remission rates and longer survival times, treatment protocols are rapidly approaching the cutting edge. The consequence of these advances is that chemotherapy complications have become a reality of practice.

Preparation for, recognition of, and early intervention for such complications are critical for a successful outcome in patients receiving chemotherapy. This chapter focuses on the complications of chemotherapy in dogs and cats.

PRINCIPLES OF CHEMOTHERAPY

Chemotherapy literally means "the management of illness by chemical means."[2]

Simply stated, chemotherapy drugs work by killing cells. Categories of chemotherapy drugs include alkylating agents, antibiotics, antimetabolites, enzymes, hormones, nonsteroidal antiinflammatory drugs (NSAIDs), platinum products, and vinca alkaloids. Each of these effects cell death by various mechanisms of action and all can cause toxicoses because normal cells, as well as cancer cells, are arbitrarily killed in various body systems.

TESTING FOR CHEMOTHERAPY DRUG SENSITIVITY

Many herding dogs have a mutation in the multidrug resistance (MDR1) gene that results in an increased sensitivity to certain drugs, including chemotherapy drugs[3] (Table 173-1). It is currently recognized that dogs such as collies, Shetland Sheepdogs (Shelties), Australian Shepherds, Old English Sheepdogs, English Shepherds, German Shepherds, Long-Haired Whippets, Silken Windhounds, and a variety of mixed breed dogs carry the mutation. Because of this, the authors currently offer testing to all potential chemotherapy patients and recommend that pets of these breeds be tested. The test can be performed in the clinic, with results typically available within 1 week. Dose adjustments or selection of alternative chemotherapy agents may be made pending receipt of results. Further information can be obtained from the Washington State University website (http://www.vetmed.wsu.edu/depts-vcpl).

CHEMOTHERAPY DRUGS

Alkylating agents include cyclophosphamide, chlorambucil, CCNU (1-[2-chloroethyl]-3 cyclohexyl-1-nitrosourea [lomustine]), BCNU (1,3-bis-[2-chloroethyl]-1-nitrosourea [carmustine]), and melphalan. Antibiotic chemotherapy drugs include doxorubicin, actinomycin, epirubicin, bleomycin, and mitoxantrone. Antimetabolites are methotrexate and cytosine arabinoside. L-Asparaginase is an enzyme used in chemotherapy. NSAIDs that commonly are used include piroxicam, meloxicam (Metacam), deracoxib (Deramaxx), etodolac (EtoGesic), and carprofen (Rimadyl). Prednisone is the hormone most commonly used as a chemotherapeutic agent. Platinum products include cisplatin and carboplatin. The vinca alkaloids include vincristine, vinblastine, and vinorelbine.[4-6] Newer chemotherapy drugs include tyrosine kinase inhibitors such as toceranib phosphate and masitinib.[7,8]

Chemotherapy drugs and their potential toxicoses are listed in Table 173-1.

TOXICITIES AND TREATMENT OF CHEMOTHERAPY-RELATED EMERGENCIES

Acute Tumor Lysis Syndrome

Acute tumor lysis syndrome (ATLS) is a rare complication of chemotherapy believed to occur most commonly in patients who have chemotherapy- or radiation-responsive tumors. Risk factors include large tumor burdens, chemotherapy-responsive tumor type, preexisting renal disease, and dehydration.[9,10] This condition results from destruction of tumor cells, which can then lead to release of intracellular electrolytes (potassium, phosphate) as well as the toxic byproducts of cell necrosis into the circulation.[11]

Nucleic acids released from cellular necrosis include purines, which are metabolized to uric acid. Increased levels of uric acid exacerbate metabolic acidosis and renal impairment or failure.[12] Deposition of calcium phosphate salts in the renal tubules in addition to the aforementioned biochemical alterations, intraluminal tubular obstruction, intravascular volume depletion, and release of malignancy-associated nephrotoxins can result in oliguric renal failure.[9]

Biochemical abnormalities include hyperkalemia, hyperphosphatemia, hypocalcemia (as a sequela of elevated phosphate levels), and metabolic acidosis. Azotemia may also be present.[9]

Clinical presentation of ATLS can occur hours to days after therapy has been administered. Characteristically, a patient that has

Table 173-1 **Chemotherapy Drugs and Potential Toxicoses**[4,5,7,8]

Chemotherapeutic Agent	Reported Toxicosis	Specific Toxicities
Alkylating agents	Alopecia Bone marrow suppression Gastrointestinal toxicity Nausea Inappetence Vomiting Diarrhea	CCNU: Cumulative dose–related risk of hepatotoxicity Chlorambucil: neurotoxicity Cyclophosphamide: sterile hemorrhagic cystitis
Antibiotics	Alopecia Bone marrow suppression Gastrointestinal toxicity Nausea Inappetence Vomiting Diarrhea Necrosis, ischemia, and severe soft tissue reaction if given perivascularly	Doxorubicin: Cumulative dose–related risk of dilated cardiomyopathy in dogs, possible renal toxicity in cats, allergic reactions in both species, hemorrhagic colitis
Antimetabolites	Alopecia Bone marrow suppression Gastrointestinal toxicity Nausea Inappetence Vomiting Diarrhea	
Enzymes	Anaphylaxis	L-Asparaginase: Pain on injection, pancreatitis, insulin resistance
Hormones	Iatrogenic excessive hormonal effects	Prednisone/prednisolone: Hypercortisolism, gastrointestinal ulceration, renotoxicity
Nonsteroidal antiinflammatory drugs	Gastrointestinal ulceration Renal toxicity	Carprofen: Liver toxicity
Platinum products	Bone marrow suppression Gastrointestinal toxicity Inappetence Nausea Vomiting Diarrhea	Cisplatin: Pulmonary edema and death in cats, nephrotoxicity in dogs
Protein tyrosine kinase inhibitors (toceranib phosphate, masitinib)	Bone marrow suppression Gastrointestinal toxicity Inappetence Nausea Vomiting Diarrhea	
Vinca alkaloids	Alopecia Bone marrow suppression Gastrointestinal toxicity Ileus Peripheral neuropathies	

CCNU, 1-(2-Chloroethyl)-3 cyclohexyl-1-nitrosourea (lomustine).

ostensibly responded to therapy shows symptoms such as lethargy, vomiting, diarrhea, bradycardia, cardiovascular collapse, and ultimately shock.[10,13]

Workup includes a thorough physical examination, full blood work, and urinalysis. Because the clinical signs of ATLS may mimic other pathologic conditions, additional diagnostic tests such as determination of a coagulation profile, diagnostic imaging, and blood and urine cultures may be indicated.[9,10]

Therapy is directed at cardiovascular support with administration of intravenous fluids and consideration of correction of electrolyte abnormalities and renal parameters. Administration of normal saline is a reasonable choice in patients with hyperkalemia and hyperphosphatemia until such time as the electrolyte abnormalities are corrected, and then a balanced electrolyte solution may be used.[9,10] Please see Chapters 5, 51, and 60 for more detailed recommendations on treatment of shock, fluid therapy, and management of hyperkalemia-associated arrhythmias.

Calcium can be administered parenterally in patients displaying clinical symptoms of hypocalcemia. Due to variability in the production and significance of metabolites, therapies such as urinary alkalinization, administration of allopurinol, and administration of urate oxidases are not currently recommended in veterinary patients.[9]

Allergic Reactions

Acute type I hypersensitivity reactions have been reported upon administration of L-asparaginase. Polysorbate 80, the carrier found in etoposide, can also trigger a type I reaction. Doxorubicin administration can directly stimulate mast cell degranulation, causing an anaphylactoid reaction. This is in contrast to true hypersensitivity

reactions, in which mast cell degranulation is activated via immunoglobulin E.

Clinical signs in dogs usually appear within minutes but can occur several hours after administration and can include head shaking, generalized urticaria, erythema, agitation, vomiting, and hypotension leading to collapse. For the most part, dogs tend to manifest allergic reactions in the skin and gastrointestinal (GI) tract. Hypersensitivity reactions are rare in cats and tend to manifest as respiratory signs such as tachypnea, dyspnea, and wheezing.[14]

Hypersensitivity reactions may be prevented by pretreatment with histamine-1 (H_1) and H_2 receptor antagonists. In the emergency setting, therapy should consist of discontinuing the drug, instituting fluid therapy, and administering an H_2 receptor blocker (e.g., diphenhydramine) and glucocorticoids (dexamethasone). Epinephrine can be given in severe and refractory cases.[14]

Bone Marrow Toxicity

Myelosuppression can occur in the oncology patient for a number of reasons, such as secondary to the neoplastic process or as a result of treatment. This chapter addresses bone marrow toxicity resulting from the cytotoxic effects of chemotherapy.

Anemia

Anemia is a common hematologic abnormality in patients with cancer and is most often due to a syndrome of anemia of chronic disease, blood loss, or a paraneoplastic syndrome of immune-mediated hemolytic anemia. Anemia is rarely encountered secondary to chemotherapy because of the longer life span of red blood cells.[14] Although it is uncommon, anemia can occur secondary to bleeding into the GI tract caused by GI ulceration (e.g., from mast cell degranulation and release of vasoactive amines), medications (NSAIDs, glucocorticoids), or chemotherapy. When an animal is bleeding into the GI tract from an ulcer and the underlying cause is a tumor, treatment addresses this underlying cause (resection of the mass, chemotherapy) and supportive care is provided for the gastric ulceration with a proton pump inhibitor (e.g., omeprazole), H_1 receptor antagonist (such as famotidine or ranitidine), and sucralfate. If the ulceration is due to long-term antiinflammatory drug use and this medication is critical to the treatment protocol, the antiinflammatory drugs may be temporarily discontinued, treatment initiated as described earlier, and then antiinflammatory drug therapy reinstituted with the use of a prostaglandin inhibitor. If the bleeding is due to chemotherapy, as in the case of hemorrhagic colitis secondary to doxorubicin chemotherapy, it is usually short term and rarely causes anemia. Supportive care with GI protectants and antidiarrheal medications can be instituted for comfort. The authors prefer the use of sulfasalazine because of its mechanism of action in the large bowel; the diazo bond is cleaved by colonic bacteria to release sulfapyridine and 5-acetylsalicylic acid, which exerts both a local antibiotic and an antiinflammatory action.[15] Anemia secondary to recurrent marrow suppression and exhaustion of the marrow usually is seen after months of therapy and is related to repeated insults to the bone marrow; it is considered irreversible.

Thrombocytopenia

Thrombocytopenia can result from platelet consumption, destruction, decreased production, or loss. For thrombocytopenia resulting from loss into the GI tract, ulcer therapy with antacids and GI protectants, and discontinuation of antiinflammatory drugs is recommended. Thrombocytopenia that results from chemotherapy is rarely of clinical significance and may be treated by delaying the next dose of chemotherapy for 3 to 5 days. Thrombocytosis can be seen in patients after chemotherapy due to bone marrow rebound in response to chemotherapy-induced thrombocytopenia.[14]

Neutropenia

Neutropenia most often is associated with cytotoxic chemotherapy agents. This type of myelosuppression occurs at the nadir, which is defined as the time when the white blood cell count is at its lowest after administration of chemotherapy. The nadir is different for each drug. The nadir for doxorubicin and cyclophosphamide is 7 to 10 days; the nadir for cisplatin is 7 and 16 days; and the nadir for carboplatin is 11 and possibly 21 days after administration. In many instances, treatment is not required for neutropenia because the patient is asymptomatic and the cell counts likely will return to the normal range within a week.

Neutropenia in an oncology patient, even one without a fever, should prompt the veterinary staff to recommend careful monitoring of vital signs (temperature, pulse, and respiratory rate), appetite, and attitude. Neutrophil counts below 1000 cells/mcl warrant prophylactic therapy with broad-spectrum antibiotics for a week. If at any time the patient develops a fever or the clinical condition deteriorates (inappetence, lethargy, depression, vomiting, and diarrhea), aggressive intervention is required to prevent a septic crisis. This should begin with a complete physical examination with an emphasis on auscultation of the lungs, basic blood work and urinalysis, and administration of fluid therapy, in addition to four-quadrant protection with antibiotics (gram-negative, gram-positive, aerobic, and anaerobic coverage). Strict aseptic technique should be used at all times. Serial thoracic radiography should be performed in a neutropenic febrile patient to identify pneumonia early in the course of disease. Additional supportive therapies should be administered as indicated (see Chapter 90).

Neutropenia that is profound or persists for longer than 1 week necessitates therapy with granulocyte colony-stimulating factor. This may be instituted in the hospital and continued for up to 5 days.

Sepsis

Sepsis and septic shock are not uncommon in patients with cancer. Sepsis can be a result of the disease itself or a complication of management (see Chapter 91).

Cardiotoxicity

See Chapter 42.

Dermatologic Toxicity

Dermatologic complications can occur secondary to chemotherapy but rarely require emergency or critical care attention and therefore are not discussed in this chapter.

Extravasation

Extravasation of vesicant chemotherapeutic agents can cause severe local tissue reactions leading to necrosis. Doxorubicin is the chemotherapeutic agent most commonly responsible and arguably results in the most severe reactions, but this may be due to the volume that is extravasated. Other chemotherapeutic agents such as the vinca alkaloids and other anthracyclines can also be locally irritating if delivered outside the vein. Clinical signs of pain, pruritus, erythema, moist dermatitis, and necrosis can occur within 7 to 10 days with doxorubicin and within a week if a vinca alkaloid has extravasated.[16]

If doxorubicin is given accidentally outside the vein, the following recommendations apply:

1. Discontinue administration of the drug immediately.
2. Withdraw as much drug as possible from the catheter.
3. Administer dexrazoxane at 10 times the extravasated dose intravenously within 3 hours of the event and then q24h for 3 days.

4. Monitor the site every other day for 10 days for local tissue reaction.
5. Treat any local reaction symptomatically with topical preparations (antibiotics, steroids), bandaging, Elizabethan collar, and surgical debridement if severe.

If a vinca alkaloid is delivered outside the vein, the following recommendations apply:

1. Discontinue administration of the drug immediately.
2. Withdraw as much drug as possible from the catheter.
3. Some oncologists infiltrate the area with sterile saline or with sterile saline and 8.4% sodium bicarbonate and 4 mg dexamethasone sodium phosphate.
4. Apply warm compress.
5. Treat any local reaction symptomatically with topical preparations (antibiotics, steroids), bandaging, Elizabethan collar, and surgical debridement if severe.

Gastrointestinal Toxicity

Some of the common ongoing health complaints of the oncology patient are cancer cachexia, anorexia, vomiting, and diarrhea.

Cachexia and anorexia

Cachexia and anorexia are common conditions in pets with cancer.[17] Cachexia and sarcopenia are considered emerging phenomena in veterinary patients, and new therapies and management strategies can ameliorate symptoms; however, they are not considered common adverse effects of chemotherapy.[18]

Anorexia, on the other hand, is a significant medical condition in pets receiving chemotherapy, secondary either to the underlying primary condition or to chemotherapy. If it is caused by chemotherapy, management strategies such as dose adjustments, prophylactic therapy with antinausea medications, or symptomatic therapy with antinausea medications, appetite stimulants, and, if not contraindicated by the patient's diagnosis, glucocorticoids may be useful. Placement of a feeding tube in patients that are anorexic is indicated early in the course of disease. The authors recommend placement of a feeding tube when more than 10% of body weight is lost due to therapy. A nasoesophageal tube may be used short term, although this method of feeding typically does not allow for administration of a patient's total daily energy requirement unless feeding is by constant rate infusion, which makes this method useful in hospitalized patients only. An esophageal feeding tube is preferable if the esophagus is functional because it uses esophageal function and is generally well tolerated in dogs and cats.

Vomiting

Vomiting is a common consequence of chemotherapy. Although it is usually self-limiting and stops within 2 to 3 days after it starts, routine supportive care can improve the patient's comfort and shorten the duration of this adverse effect. The authors typically send the patient home with a 5-day course of maropitant citrate (Cerenia) to be administered at the first sign of inappetence or nausea. If the patient does not respond to therapy or continues to vomit for longer than 24 hours, or is vomiting unrelentingly, more aggressive treatment is recommended. This could include admission to the hospital for intravenous fluid therapy, injectable antiemetics (maropitant citrate, ondansetron, or dolasetron, and/or metoclopramide), and GI protectants such as a slurry of sucralfate and an injectable H_2 receptor antagonist (e.g., ranitidine). When a patient has experienced significant vomiting after treatment with a chemotherapy drug, subsequent treatments with the same medication may be reduced in dose by 10% to 25% and ancillary prophylactic medication administered for several days after therapy.

Diarrhea

In oncology patients that are stressed by their treatment or hospitalization, clostridial colitis can result. This condition is characterized by passage of a small volume of loose stool that may or may not have frank blood and mucus in it. Historically, it has been diagnosed by identification of clostridial endospores on a fecal smear in conjunction with clinical signs. An enzyme-linked immunosorbent assay kit is available for detection of *Clostridium perfringens* endospores in fecal specimens. The recommended antimicrobial therapy for clostridial diarrhea is based on sulfasalazine, metronidazole, ampicillin, or tylosin. Dietary management by increasing fiber content in the food through the addition of canned pumpkin or psyllium hydrophilic mucilloid fiber (Metamucil) may also be useful. In mild cases of diarrhea, treatment with bismuth subsalicylate (Pepto-Bismol) often results in resolution of signs within a day or so.

Hemorrhagic colitis is a unique toxicity of doxorubicin (Adriamycin). This form of large bowel diarrhea usually responds to sulfasalazine or metronidazole. If the diarrhea is moderate to severe, persists for longer than 2 to 3 days, or if the patient is exhibiting signs of lethargy, depression, fever, vomiting, or general malaise, more aggressive intervention with hospitalization, resting of the GI tract, fluid therapy, and antibiotics is recommended.

Neurologic Toxicity

Peripheral neuropathies have been reported after administration of the vinca alkaloids, particularly vincristine. Hind limb weakness, partial paralysis, and ileus leading to abdominal pain and constipation have been reported in dogs and cats.[14] Therapy includes supportive care and alleviation of the discomfort of ileus with metoclopramide. Discontinuation of the drug, administering it at a reduced dosage, or substituting vincristine with vinblastine or vinorelbine may be effective.

Cisplatin has resulted in cortical blindness according to a case report of two dogs.[14] 5-Fluorouracil is extremely neurotoxic in cats and should never be administered; it results in a fatal reaction that may include excitability, blindness, tremors, dysmetria, and death. In dogs, it can also result in excitation, seizures, and ataxia.[14]

Urologic Toxicity

Cyclophosphamide has been associated with sterile hemorrhagic cystitis characterized by clinical signs including pollakiuria, hematuria, and dysuria. Diagnosis is made by demonstration of plentiful red blood cells, white blood cells, and the absence of bacteria in urine. Ultrasonography of the bladder reveals a diffusely thickened bladder wall. Therapy consists of discontinuation of the drug, prevention of infection with antibiotics, diuresis, and administration of antiinflammatory medications. Most cases resolve within days to a week after discontinuance of the medication and institution of the supportive measures indicated. Additional therapies reported to be effective in refractory cases are intravesicular administration of a 1% formalin solution and dimethyl sulfoxide (DMSO).[14] It is important to note that cyclophosphamide therapy will likely continue to cause cystitis if it is reinstituted, so substituting chlorambucil for cyclophosphamide may be reasonable. Some cases of sterile hemorrhagic cystitis are reported to be refractory to treatment; however, this has not been the authors' experience. Administration of cyclophosphamide has been associated with the development of transitional cell carcinoma in the bladder later in life.

Nephrotoxicity secondary to cisplatin use has been reported in dogs, and renal failure has been reported in cats after administration of doxorubicin.[14]

Drugs used to treat reactions to chemotherapy are listed in Table 173-2.

Table 173-2 Drugs Commonly Used to Treat Adverse Effects or Complications of Chemotherapy[12,14]

Medication	Drug Class	Dose	Frequency	Route	Indications
Amoxicillin or ampicillin	Extended-spectrum penicillin antibiotic	11-22 mg/kg	q8-12h	PO (amoxicillin) or IV, IM (ampicillin)	Infection
Dexrazoxane	Antidote	10 times extravasated dose	Once within 3 hr of event, then q24h for 3 days	IV	Doxorubicin extravasation
Diphenhydramine	H_1 receptor antagonist Antihistamine	1 mg/kg 2-4 mg/kg (not to exceed 40 mg)	q8-12h q8-12h	IV PO	Allergic reaction
Enrofloxacin	Fluoroquinolone antibiotic	5-20 mg/kg (not to exceed 5 mg/kg in cats)	q24h (or divided q12h)	PO or IV	Infection
Famotidine	H_2 receptor antagonist	0.1-0.2 mg/kg	q12h	PO, IV, IM	GI ulcer management *Note:* Anecdotal reports of intravascular hemolysis in cats
Granulocyte colony-stimulating factor	Cytokine hematopoietic agent	5 mcg/kg	q24h until neutrophil count exceeds 3000/mcl for 2 days	SC	Neutropenia
Omeprazole	Proton pump inhibitor	0.5-1.5 mg/kg (0.7 mg/kg for adjunctive therapy)	q24h	PO	GI ulcer management, prevention
Ondansetron	5-HT_3 receptor antagonist	0.5-1 mg/kg	Can be given 0.1-0.5 mg/kg IV over 15 min q8h or 30 min before chemotherapy)	PO	Chemotherapy-related vomiting
Oxybutynin	Genitourinary smooth muscle relaxant	1.25-5 mg total dose (dogs) 0.5-1 mg total dose (cats)	q8-12h	PO	Sterile hemorrhagic cystitis
Maropitant citrate	Antiemetic Neurokinin-1 receptor antagonist	1-2 mg/kg (can give 0.5-1 mg/kg in cats)	1 hr before emetogenic event and then q24h for up to 5 days	PO (2 mg/kg) or SC (1 mg/kg)	Inappetence, nausea or vomiting
Metoclopramide	Central dopaminergic antagonist, peripheral 5-HT_3 receptor antagonist and 5-HT_4 receptor agonist	0.2-0.4 mg/kg	q6h or may be given at 1-2 mg/kg/24 h IV CRI	PO, SC, IM	Vomiting
Metronidazole	Antibiotic	15-25 mg/kg	q12-24h	PO	Diarrhea
Misoprostol	Prostaglandin E_1 analog	2-5 mcg/kg	q6-12h or may be given at 3 mcg/kg q8-24h for prevention of ulcers in pets receiving NSAIDs	PO	Treatment or prevention of GI ulcers
Pantoprazole	Proton pump inhibitor	0.7-1 mg/kg	q24h	IV	GI ulcer management, prevention
Ranitidine	H_2 receptor antagonist	0.5-2 mg/kg (dogs) 1-2 mg/kg (cats)	q12h	PO, IV, IM	GI ulcer treatment, prophylaxis
Sucralfate	Aluminum salt, binds proteinaceous exudate	0.5-1 g (dogs) 0.25-0.5 g (cats)	q8h	PO	GI ulcer management
Sulfasalazine	Sulfonamide, salicylate antibacterial, immunosuppressive	20-40 mg/kg (dogs) 10-20 mg/kg (cats) *Note:* Use caution in cats due to salicylate	q8h q24h	PO PO	Hemorrhagic colitis

5-HT_3, 5-HT_4, 5-Hydroxytriptamine 3 and 4; *CRI,* constant rate infusion; *GI,* gastrointestinal; *H_1, H_2,* histamine 1 and 2; *IM,* intramuscularly; *IV,* intravenously; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PO,* per os; *SC,* subcutaneously.

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