Pearls of Veterinary Practice

Aftershocks of Cancer Chemotherapy: Managing Adverse Effects

Most cytotoxic chemotherapy protocols used in small animals are designed to have a low risk of adverse effects; however, adverse events can occasionally occur. Timely and appropriate management of adverse events greatly increases client satisfaction and the likelihood of a successful treatment outcome. This article presents guidelines for the management of chemotherapy-associated hematological and gastrointestinal disturbances, extravasation injury, and anaphylaxis.
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Introduction

In general, fewer than one in four animals have adverse effects to chemotherapy, and only 5% have a serious event that requires hospitalization.[1] Several important consequences of a serious reaction are possible, including decreased quality of life, financial consequences (e.g., hospitalization and treatment), delay or alteration of subsequent treatments, and diminished client enthusiasm for continuation of therapy. With appropriate intervention, the risk of a treatment-associated fatality is <1 in 100.[1] Should a serious adverse event occur, doses can be reduced, drugs can be substituted, or additional medications can be dispensed to minimize the likelihood of further events, and these measures are effective most of the time. Studies assessing clients' perceptions of medical treatment for cancer generally report a positive experience.[2,3] Most owners have felt the treatment was worthwhile, that it resulted in improved well-being of their pet, and that quality of life during treatment was good.[2,3]

In practices where chemotherapy is administered, having a protocol in place for the treatment of adverse events dramatically increases the likelihood of a good outcome, as well as increased client satisfaction. It is the veterinarian's responsibility to ensure the client understands the goals of therapy in each case before emotion, time, and money are invested in therapy. The use of client education handouts explaining the potential toxicities, how to manage them, and when to become concerned is encouraged. Even in practices where chemotherapy is not

administered, it may be necessary for the veterinarian to deal with adverse reactions from cancer therapy that may have been administered elsewhere.

For the purposes of standardizing the reporting and analysis of chemotherapy-induced toxicities, the Veterinary Cooperative Oncology Group (VCOG) recently published a consensus document of common terminology criteria for adverse events following chemotherapy or biological antineoplastic therapy in dogs and cats.[4] This consensus document provides descriptive terminology that can be used for reporting events, and a grading (i.e., severity) scale is also provided.

The most commonly encountered adverse reactions (i.e., neutropenia, gastrointestinal [GI] disturbances) generally occur as a result of collateral damage to rapidly dividing cells by the cytotoxic agent.[1] Bone marrow stem cells and GI crypt cells are rapidly dividing cells and are sensitive to the antiproliferative effects of cytotoxic chemotherapy.[1] Additional acute effects that can be encountered and may require intervention include inadvertent drug extravasation and anaphylaxis. The purpose of this paper is to present guidelines for the management of chemotherapy-associated hematological and GI disturbances, extravasation injury, and anaphylaxis.

Neutropenia and Sepsis

Neutropenia is a relatively common side effect of chemotherapy in companion animals. In certain malignancies, bone marrow infiltration or other conditions can exacerbate myelosuppression. The severity of neutropenia and associated sepsis is extremely variable, ranging from clinically silent to life threatening. Compounding the potential seriousness, the onset of chemotherapy-induced neutropenia is usually soon after the worst GI damage occurs from chemotherapy.[1] Gastrointestinal changes can include microscopic ulcerations and loss of the normal protective layer of desquamated cells, saliva, and mucus lining the GI tract. These changes create a favorable environment for overgrowth, translocation, and invasion by aerobic gram-negative and gram-positive bacteria.[5-7]

History and Presenting Complaints

Many animals may be mildly or moderately neutropenic, yet show no outward signs of illness. Most dogs and cats have a low risk of infection if their neutrophil count remains >1000/μL.[1] It is important to remember that the likelihood of infection and subsequent treatment decisions must be made from the absolute neutrophil count and not from the total white blood cell (WBC) count.

Septic animals typically present with vague, nonspecific signs of illness, such as lethargy, weakness, and inappetence. They are often febrile, but a normal or decreased temperature does not rule out the presence of a serious or life-threatening infection. Other physical abnormalities can include tachycardia, injected mucous membranes, slow or prolonged capillary refill time, and weak pulses. An accurate medication history is very important, as the timing of the last chemotherapy treatment helps to determine if

myelosuppression is likely. Neutropenia is likely to occur 7 to 10 days after the administration of most chemotherapeutic drugs. Exceptions to this time interval occur with lomustine and carboplatin, where neutropenia develops as late as 2 to 3 weeks following administration.[1,8-12]

Diagnostic Tests

An initial minimum laboratory database includes a complete blood count (CBC) with manual differential count, a platelet count, serum biochemical profile, and urinalysis. Common changes in animals experiencing chemotherapy-induced sepsis include neutropenia (with or without a left shift or toxic changes), thrombocytopenia, hyper- or hypoglycemia, evidence of dehydration, and metabolic acidosis.[13] Urinalysis may reveal normal sediment; however, urinary tract infections are difficult to rule out if neutropenia causes an absence of WBCs in the urine. Empirical culturing of the urine may be done in neutropenic, septic animals. A coagulation profile is indicated in any animal with signs of septic shock, as disseminated intravascular coagulation can be present and must be treated aggressively. In animals with respiratory signs or a history of vomiting, thoracic radiographs are indicated to search for a nidus of infection. Recent studies in humans suggest there is no benefit in obtaining screening thoracic radiographs in the asymptomatic neutropenic, septic patient.[14,15]

Treatment

Afebrile animals with mild neutropenia (>1000/μL) generally require no treatment. Bright and afebrile animals with <1000 neutrophils/μL can often be managed as outpatients, especially since the risk of nosocomial infection probably outweighs the benefit associated with hospitalization. Prophylactic oral antibiotics decrease the risk of bacteremia and sepsis-associated mortality in afebrile, neutropenic humans with cancer, and they may have similar effects in animals.[16] A broad-spectrum, oral antibiotic that spares normal anaerobic GI flora, such as trimethoprim-sulfa[a] (7.5 mg/kg per os [PO] *q* 12 hours) or enrofloxacin[b] (5 to 10 mg/kg PO *q* 24 hours), may be prescribed for 5 to 7 days. Anaerobe-sparing antibiotics are preferred, as they help prevent overgrowth and invasion of aerobic bacteria in the weakened GI tract.[17] The owner can be instructed to monitor the animal's temperature once or twice daily at home. If the animal becomes clinically ill or the temperature exceeds 103.5˚C, hospitalization may be required.

Febrile or systemically ill animals usually require hospitalization for 24-hour care. Intravenous (IV) crystalloid therapy of these animals is very important. Shock doses of fluids or the addition of colloid solutions are considered in hemodynamically unstable animals. In the stable animal, a fluid rate of 1.5 × maintenance is reasonable after correction of any existing fluid deficits. It is common for fever and clinical status to improve significantly after several hours of fluid therapy.

After IV fluid therapy, the second step is to institute appropriate antibiotic therapy. Although no studies have

evaluated the GI flora in neutropenic, septic animals, both gram-negative and gram-positive bacteria have been isolated from neutropenic, septic humans; fungi and protozoa have been rarely isolated.[5,7] Clinical experience suggests that most bacteria implicated in sepsis in animals with cancer are sensitive to commonly used antibiotics. Intravenous coverage for both gram-positive and gram-negative organisms is employed. Unlike the treatment recommended for afebrile, neutropenic animals, both anaerobic and aerobic bacteria are targeted in sick, febrile, neutropenic animals. Typical drug combinations include a penicillin/aminoglycoside combination, such as ampicillin[c] (22 mg/kg IV *q* 8 hours) and amikacin[d] (10 mg/kg IV, intramuscularly [IM], or subcutaneously [SC] *q* 24 hours) if renal function is adequate, or a first-generation cephalosporin/fluoroquinolone combination, such as cefazolin[e] (20 mg/kg IV *q* 8 hours) and enrofloxacin (5 to 10 mg/kg IV or IM *q* 24 hours). Antipyretic agents are rarely necessary and may make interpretation of response to therapy difficult.

Most animals respond quickly to therapy, and neutrophil counts may rise very rapidly. Many animals are afebrile within 12 to 24 hours, and they can be discharged when their fevers subside and neutrophil counts are >1000/μL. If a clinical response does not occur during the first 24 to 48 hours, further diagnostic tests are performed to identify a potential nidus of infection and to collect samples for bacterial culture and antibiotic sensitivity testing. Additional tests include thoracic radiographs, abdominal ultrasonography, echocardiography, and at least two sets of blood cultures. In animals that do not respond rapidly, antibiotic coverage can be broadened while waiting for culture results. Additional anaerobic coverage is provided with metronidazole[f] (15 mg/kg IV *q* 12 hours) and/or a second- or third-generation cephalosporin. Should protracted (>72 hours) neutropenia occur, a bone marrow aspirate might be useful, especially in animals with hematopoietic neoplasia and possible bone marrow infiltration (i.e., myelophthisis).

The clinical utility of recombinant human granulocyte colony-stimulating factor[g] (G-CSF) is widely debated. Some clinicians routinely utilize G-CSF for febrile, neutropenic animals, while others utilize it only for severe neutropenia (100 to 500/μL) or neutropenia that persists for >72 hours. Although many human studies have suggested no benefit in terms of length of hospitalization or mortality rates if G-CSF is employed after a neutropenic fever has developed, a recent study showed that severely neutropenic (<100/μL) patients given G-CSF had decreased duration of neutropenia and hospital stay when compared to controls, although there was no significant difference in mortality.[18]

Gastrointestinal Effects

History and Presenting Complaints

A careful medical and medication history helps determine if clinical signs are probably associated with chemotherapy administration. Although the majority of small animals undergoing chemotherapy tolerate the treatments well, a small number may experience unpleasant GI side effects, such as nausea, vomiting, or diarrhea. Most side effects are mild and self-limiting; however, severe episodes are occasionally encountered. Certain drugs (e.g., cisplatin) may cause immediate nausea/vomiting because of their activity on the chemoreceptor trigger zone in the brain. Most dogs given cisplatin vomit during or soon after drug administration, unless they are premedicated with an antiemetic, such as butorphanol or dolasetron. More commonly, GI effects are delayed, as damage to the mucosa results in irritation and inflammation, which leads to vomiting and diarrhea about 2 to 5 days after chemotherapy administration. Signs can range from mild inappetence and slightly soft stools to severe, intractable vomiting and profuse, hemorrhagic diarrhea.

Diagnostic Tests

In a severely affected animal, a minimum laboratory database includes a packed cell volume, total solids, blood urea nitrogen, creatinine, electrolytes, and urine specific gravity. A CBC and serum biochemical profile are reasonable tests to perform, and a CBC is indicated in animals with significant hematochezia. If the animal has a history of protracted vomiting, thoracic radiographs are done to rule out aspiration pneumonia. In animals that do not respond to symptomatic therapy, abdominal imaging and other tests are used to rule out other causes for vomiting (such as GI obstruction, pancreatitis, neoplastic involvement of the GI tract, etc.).

Treatment

Many animals with mild signs can be managed at home, because they respond to withdrawal of all oral substances (nothing per os [NPO]) for a brief time, followed by administration of a bland, high-fiber diet. Oral antiemetics (e.g., metoclopramide[h] [0.2 to 0.5 mg/kg PO or SC *q* 8 hours] or prochlorperazine[i] [0.3 mg/kg PO or SC *q* 8 hours]) may be utilized if vomiting is infrequent and the animal is bright and alert. Oral medications for diarrhea, such as loperamide[j] (0.08 mg/kg PO *q* 8 hours), may also be used. Some animals with chemotherapy-associated diarrhea may respond to oral metronidazole (12 to 15 mg/kg PO *q* 12 hours for 5 days).

Animals that are weak, lethargic, dehydrated, or have severe refractory signs are hospitalized in order for fluid, acid-based, and electrolyte disturbances to be addressed. These animals are kept on NPO status until vomiting resolves, and parenteral antiemetics are started [Table 1]. Dehydration is corrected over the first 8 to 12 hours, and then the fluid rate is changed to 1.5 × maintenance. Some animals may be mildly or moderately hypokalemic, which is corrected with potassium supplementation. A bland food diet and oral antiemetics typically can be started after vomiting has subsided for 12 to 24 hours.

For antiemesis, metoclopramide may be started as an IV constant-rate infusion, and prochlorperazine or other drugs are added if the vomiting continues. Ondansetron[k] (a 5-hydroxytryptamine-3 [5-HT3] receptor antagonist) is safe and effective; however, its expense makes it impractical as an initial antiemetic. Recently, another 5-HT3 receptor

Table 1

Commonly Used Antiemetics in Animals on Chemotherapy

Drug	Doses[*]	Comments[†]
Metoclopramide	0.2-0.5 mg/kg PO *q* 8 h 0.2 mg/kg SC *q* 8 h 2 mg/kg per 24 h as constant-rate infusion IV	GI prokinetic; therefore, avoid in animals with potential GI obstruction or ulcers
Prochlorperazine	0.3 mg/kg PO *q* 8 h 0.3 mg/kg SC *q* 8 h	Avoid in animals with a history of seizures May cause sedation or hypotension Chlorpromazine and acepromazine also have antiemetic properties
Ondansetron	0.1-0.5 mg/kg IV, PO *q* 12-24 h	Very expensive
Dolasetron	0.5-0.6 mg/kg IV *q* 12-24 h	
Butorphanol	0.4 mg/kg IM *q* 4-6 h	Excellent for cisplatin-associated emesis

[*] PO=per os; SC=subcutaneously; IV=intravenously; IM=intramuscularly
[†] GI=gastrointestinal

antagonist, dolasetron,[l] has become available, and it is less expensive than ondansetron.[19] For refractory vomiting, butorphanol[m] (0.4 mg/kg IM) or anti-inflammatory doses of corticosteroids may be added. The addition of a parenteral histamine (H)2 blocker (e.g., famotidine[n] [0.5 to 1 mg/kg IV or SC *q* 12 to 24 hours]) or proton-pump inhibitor (e.g., pantoprazole[o] [1 mg/kg IV *q* 24 hours]) may minimize the risks associated with continued vomiting, such as esophagitis. The histamine H2 blocker, ranitidine,[p] may also promote prokinetic and antiemetic activity from concurrent inhibition of acetylcholinesterase activity.[20]

If hospitalization is necessary, most animals require support for 24 to 72 hours. Over this time, GI mucosal cells usually regenerate, and signs then subside. Vomiting persisting for >72 hours requires further diagnostic testing to rule out other diseases.

Prevention of Serious Adverse Events

Reductions in dosages of antineoplastic drugs are not to be considered lightly, as dose intensity is extremely important for their antitumor effects. A dosage reduction of 20% may be done in dogs with a neutrophil nadir <1000/μL, although some clinicians only reduce the dosage if the neutrophil nadir is 500/μL or is 500 to 1000/μL in animals that are septic or febrile. Generally, a dosage reduction of 20% is recommended at the next scheduled treatment interval if the neutrophil count is <1500/μL. Treatment is also delayed until the neutrophil count rebounds to >1500/μL.

For GI toxicity in the animal, the client's level of comfort with the severity of the adverse event is very important in determining what constitutes a tolerable dose. To some clients, one self-limiting episode of vomiting is too much, while other clients are willing to accept a higher degree of toxicity for real or perceived efficacy. Unless severe (i.e., grade 3 to 4) events are experienced, prophylactic medications are tried first rather than immediate dosage reductions. For example, starting 5 days of antiemetics or antidiarrheal medications the day after chemotherapy is a logical first step. If this approach does not sufficiently alleviate the side effects, then a 20% dosage reduction can be initiated. Occasionally, a particular drug or drug class is not tolerated by an individual animal, and substitutions are indicated.

Perivascular Necrosis

Several chemotherapeutic agents (e.g., doxorubicin, vinca alkaloids, actinomycin D) are vesicants that cause tissue damage if delivered extravascularly. Administration of vesicants must be done through a perfectly placed IV catheter that requires only one penetration of the vein for insertion. Dogs undergoing infusions of vesicants must be constantly observed until completion of the infusion, to ensure the catheter remains patent and the infusion is successful.

Doxorubicin is a very potent vesicant [Figures 1A-1C], and if extravasated, it is extremely damaging.[1] Surgical treatment, including immediate debridement of the extravasated tissues and potential amputation, may be required for doxorubicin extravasations. The free-radical scavenging drug, dexrazoxane,[q] is marketed for the prevention of doxorubicin-associated cardiotoxicity, and it may abrogate extravasation reactions from doxorubicin if given immediately (possibly within 3 hours) in mice and humans.[15,21] Anecdotally, IV administration of dexrazoxane at 10 times the dose of doxorubicin, within 3 hours and again at 24 and 48 hours after extravasation, may significantly reduce local tissue injury in dogs and cats. Additionally, the application of 99% dimethyl sulfoxide (DMSO) topically (q 8 hours for 2 weeks) may abrogate some of the effects.[22] Intralesional administration of hyaluronidase may also help to mitigate local tissue necrosis from vesicant extravasation.[23]

likelihood of these reactions increases with multiple asparaginase injections. For animals demonstrating anaphylaxis from a drug treatment, it is prudent to premedicate with diphenhydramine and dexamethasone 15 to 20 minutes prior to subsequent treatments.

Hypersensitivity reactions occur in all dogs administered paclitaxel, as a result of the emulsifying agent needed to solubilize the drug. Reactions may be severe and include neurological and cardiovascular signs. Even after pretreatment with diphenhydramine (4 mg/kg IM), cimetidine[t] (4 mg/kg IV), and dexamethasone sodium phosphate (2 mg/kg IV) 30 to 60 minutes prior to chemotherapy, most animals exhibit some degree of hypersensitivity reaction.[24] Because of the potential severity of these hypersensitivity reactions, administration of prednisone[u] (1 to 2 mg/kg PO) the night before therapy is recommended, in addition to the above premedications and infusion of the drug slowly over several hours.

Figures 1A, 1B, 1C—A 6-year-old, spayed female, mixed-breed dog developed a severe reaction after extravasation of doxorubicin that was not noted at the time of infusion. Lateral images of the left thoracic limb demonstrate the appearance of the lesions **(A)** 3 days, **(B)** 7 days, and **(C)** 21 days postinfusion. An amputation of the affected limb was performed at 21 days postinfusion.

Anaphylaxis

Several antineoplastic agents may cause immediate anaphylaxis or anaphylactoid reactions in animals. These include asparaginase, doxorubicin, and especially the taxanes.[1,24] The shock organs of the dog are the GI tract and skin, and they are the most severely affected during and immediately after administration of these chemotherapeutic agents. The lung is the shock organ in the cat. Should acute drug reactions occur during infusion of doxorubicin (e.g., pruritus, facial edema [Figure 2], wheals, erythema of skin and mucous membranes, head shaking, vomiting, restlessness, dyspnea), stop the administration and give diphenhydramine[r] (3 to 4 mg/kg IM) and dexamethasone sodium phosphate[s] (0.5 to 1.0 mg/kg IV). When the reaction subsides, administration of doxorubicin can be resumed at a slower rate.

Asparaginase can result in anaphylaxis (usually within 60 minutes); therefore, monitor for hypersensitivity reactions for 60 minutes following drug administration. The

Breed Predispositions to Adverse Effects

Certain breeds, particularly the collie-type breeds, have a higher risk of toxicity reactions from cancer drugs that are actively transported by the p-glycoprotein (P-GP) pump. These drugs include vinca alkaloids, doxorubicin, dactinomycin, and the taxanes.[25-29] These breeds have a high frequency of a mutation of the multidrug resistance 1 (MDR1) allele. This mutation diminishes the excretion of P-GP substrate chemotherapeutic drugs, leading to increased drug exposure. If a dog is homozygous for the mutant allele, it is affected and at risk. If it is a heterozygote, it is a carrier. The frequency of these mutations has been characterized in several breeds in different geographic locations [Table 2].[25,27,29] A genotyping assay (performed on cheek swabs) for mutation status is available through the College of Veterinary Medicine, Washington State University.[v] The P-GP substrate drugs are either avoided entirely (preferred) in dogs that are homozygous for the MDR1 mutation, or they are administered cautiously at significantly reduced dosages.
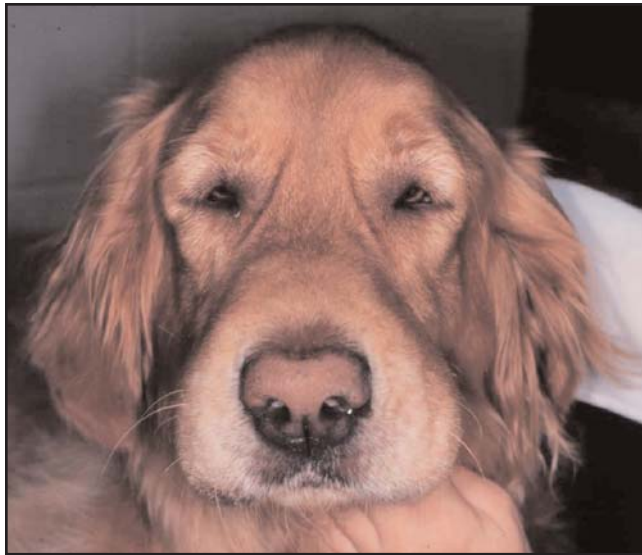
Figure 2—In an 11-year-old, castrated male golden retriever, angioedema of the face (lips, periocular tissues) developed secondary to an asparaginase injection.

Conclusion

With proper adherence to published protocols, the risk of serious adverse effects from cytotoxic chemotherapy is low, but it does still exist. Appropriate owner education and preparation of a basic plan for the treatment of these adverse effects is an important part of cancer treatment, and it will result in greater treatment success and enhanced client satisfaction.

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Table 2

Frequency of Mutant Multidrug Resistance 1 (MDR1) Allele

Dog Breed[18,20,22]	United States (%)		France (%)		Australia (%)	
	H_T*	H_O†	H_T*	H_O†	H_T*	H_O†
Australian shepherd	29.8	1.7	NA‡	NA	42.8	21.4
Miniature Australian shepherd	44.6	3.6	NA	NA		
Collie	46.8	31.2	32	48	64	24
Long-haired whippet	51.7	15.7	NA	NA	NA	NA
Shetland sheepdog	14.7	1.1	NA	NA	42.8	0

* H_T=heterozygote
† H_O=homozygote
‡ NA=not available

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