

MANAGING CHEMOTHERAPY TOXICITY

Barbara E. Kitchell, DVM, Ph.D., DACVIM
Center for Comparative Oncology
Michigan State University College of Veterinary Medicine
D208 Veterinary Medicine Center
East Lansing, Michigan 48824

Medical management of cancer patients involves the use of drugs that are particularly toxic to normal cell populations in the body. These targets of toxicity may be the obligatory rapid division cell populations, or may be selective toxicity targets based on the pharmacology of a particular drug. Some of these toxicities can be avoided by careful dose calculation specific to the individual patient, and also by use of selective agents and protocols designed to limit toxicity. Any significant toxicities seen should be treated appropriately, and patient that will continue therapy should be treated with a 25% dose reduction of the toxic agent on the subsequent treatment.

As in all disciplines in medicine, a dose of common sense in cancer patient management goes a long way in delivering successful therapy. Cancer therapy in animals is a challenging discipline, but it is also a very rewarding one. Prolonging life with dignity and good quality is a gift that we can give our pets, and their owners.

Immune Suppression and Myelotoxicity

Cancer patients are especially susceptible to infectious diseases by virtue of inherent cancer-induced immune suppression (lymphoreticular malignancies, FeLV, FIV), myelosuppressive chemotherapy, and general debilitation. To minimize exposure of these patients to infectious agents such as upper respiratory viruses, chemotherapy patients should be handled before other animals, and by a limited number of people. Patients should be immunized prior to instituting chemotherapy. Dental prophylaxis prior to starting chemotherapy may minimize a potential source of sepsis in leukopenic patients. Extreme care must be taken to ensure sterile catheter placement (especially in animals with neutropenia) and catheter sites should be cleansed and rewrapped with antiseptic ointment daily.

Temperature monitoring should occur twice daily in patients at risk for sepsis (total white blood cell count less than 3,500 cells/microliter or less than 1,500 neutrophils/microliter) Neutropenic animals may generate only a moderate fever while septic. A persistent fever of any magnitude in a neutropenic patient should be taken seriously, with blood and urine cultures obtained and broad-spectrum antibiotics given. Patients that are borderline for severe leukopenia (total white blood cell count around 3,500 cells/microliter) and who are afebrile should be treated with prophylactic antibiotics such as a trimethoprim sulfa type drug or enrofloxacin. These types of antibiotics have been shown to dramatically reduce the occurrence of gut-origin septicemia.

Patients with low white blood cell counts associated with fever should be treated in anticipation of the potential for septic shock. These patients are hospitalized, and a single paired anaerobic and aerobic blood culture is taken, along with a urine culture. An IV catheter should be placed after prepping the area as for surgery, and the

patient started on intravenous fluids and broad-spectrum antibiotics intravenously such as an aminoglycoside plus a cephalosporin, or a cephalosporin plus a floxacillin. This therapy is administered until the fever subsides. In most cases, neutropenic sepsis is controlled within 1-2 days of onset, although appropriate antibiotic therapy, based on culture results when positive, should be continued for 7-10 days.

The advent of hematopoietic growth factors is helpful in combating toxicity of anticancer drugs. Erythropoietin (Epigen[®] 100 IU/kg SQ, adjust dose to maintain PCV at 30-35%) and Granulocyte Colony Stimulating Factor (G-CSF, Neupogen[®], 5 mcg/kg/day SQ to adequate WBC response, typically 7-10 days) may help prevent significant marrow toxicity and allow more dose intense-protocols.

Venipuncture and Extravasation

Because veterinary patients are small, veins are at a premium. Blood from cancer patients should always be drawn from the jugular veins to help maintain peripheral veins. The smallest gauge catheter should be inserted with great care for sterility, and butterfly catheters should be used for short duration injections such as vincristine. As previously stated, sterile catheter placement and maintenance should be followed. For patients with poor veins or difficult temperaments, the use of vascular access ports ("VAPs") may facilitate treatment, increase patient comfort, and minimize technician stress.

In case of extravasation, The catheter should be left in place to facilitate aspiration of as much fluid as possible through the administration catheter. Then the catheter is pulled. The date, time, injection site, chemotherapy drug extravasated and remediation steps taken should be recorded in the patient's medical record. For major volume extravasation of doxorubicin, it is recommended that ice packs be applied for 10-15 minutes every 2 hours for 72 hours, then 3-4 times daily for 10-14 days. For minor extravasation of doxorubicin (ie a drop, or minimal chance of drug being left subcutaneously), icing for the first 24-48 hours may be sufficient. For severe extravasation dexrazoxane may be administered at a dose of 400-600 mg/m² IV over 15 minutes 2-3 hours following extravasation, then again at 24 and 48 hours.

In cases of vinca alkaloid extravasation (vincristine, vinblastine, vinorelbine) the area of concern should be infiltrated with 3-5 ml of 0.9% sterile saline solution and warm compresses should be applied to the area for 15 minutes 3-4 times daily for 24 hours. In severe cases of extravasation, the area may be infused with a solution of hyaluronidase. In this treatment, 150 units/ml concentration hyaluronidase is injected as five 0.2 ml injections around the leading edge of extravasation, with needles changed between each site of injection.

Gastrointestinal Toxicity

Managing the GI system of through a chemotherapy protocol can be especially difficult in animals. Nausea may render them anorexic. Food should be withheld on the morning of chemotherapy treatment to avoid the formation of food aversions. Metaclopramide (Reglan[®] 2.5 mg TID PO or 0.2 mg/kg IM or SQ) may also prove helpful in promoting food intake by decreasing nausea. The anti-emetic ondansetron (Zofran[®]) was developed specifically to counteract vomiting in human chemotherapy

patients. It is available commercially, although the cost is substantial. Suggested doses in veterinary medicine include 500 mg/kg/hour for 6 hours as an IV infusion for dogs, 0.1 mg/kg IV 15 minutes before and 4 hours after chemotherapy, or a 50 mg capsule for a 20 pound dog. Other supportive measures for adverse GI effects include Compazine[®] suppositories, sucralfate (Carafate[®] dogs- 0.5-1.0 gm/25 kg BID -TID PO; cats 0.25 gm BID-TID PO) and H2 antagonists for GI ulceration (cimetidine, Tagamet[®] 10 mg/kg TID IV, IM or PO) , and other standard antiemetic and antidiarrheal measures for treatment of GI signs in animals.

Nutritional support

Nasogastric, esophagostomy, or gastrostomy tubes may be necessary for short- or even long-term use. Water consumption is critical for geriatric animals that may develop renal insufficiency. Support with subcutaneous or intravenous fluids, B vitamins, and electrolytes can be very helpful. Hand feeding food of different consistencies may uncover a type that the patient prefers. Warming the food, cooking special meals such as boiled chicken, or food from home may help animals eat in the hospital setting. Providing hiding boxes for cats may also make them comfortable enough in their surroundings to improve eating. Offering many different foods may be needed to maintain appetite. Hand or forced feedings may be necessary. For feline patients especially, the use of appetite stimulants such as cyproheptidine (Periactin[®] 2 mg/cat TID -1/4 to 1/2 tablet) may be helpful in maintaining these patients. Megasterol acetate (Megace[®], Ovaban[®]) has been used as an appetitive agent in dogs at a dose of 10 mg/kg PO daily for one week, then tapering to a maintenance dose.

Cardioprotectant Therapy For Doxorubicin

An important mechanism to treat chemotherapy side effects is to prevent them from happening in the first place. Dexrazoxane (Zinecard[®]) is an iron chelating agent that is reported to prevent cardiotoxicity induced by doxorubicin. There is some question about the protective agent limiting the cellular efficacy of chemotherapy treatment against the cancer. Thus, we use dexrazoxane for patients with known pre-existant cardiac compromise, such as reduction in shortening fraction on the echocardiogram, or for breeds with known cardiomyopathy predisposition. The protocol from dexrazoxane administration in use at MSU is as follows. Take 10X the mg dose of doxorubicin appropriate for the patient, given as a slow bolus infusion within 5 minutes IV. Doxorubicin is administered no more than 15 minutes after the completion of dexrazoxane administration.

Urothelial Injury

Drugs such as cyclophosphamide and ifosfamide are associated with significant urothelial toxicity, especially when cyclophosphamide is administered IV and in any case of ifosfamide administration. In cases where sterile hemorrhagic cystitis occurs, intravesicular instillation of an anti-inflammatory mixture of drugs can help to limit symptoms and progression to interstitial cystitis with fibrosis. Triamcinolon at a dose of 0.11-0.22 mg/kg is mixed with 8.4% sodium bicarbonate at a volume of 10 ml. Added to this is 5,000 international units of heparin, and the entire

mixture is expanded to a volume of 1-2 ml/lb body weight by the addition of 90% medical grade DMSO liquid. This material is infused into the urinary bladder under patient sedation using a foley catheter, and left in place for 20 minutes. This treatment appears to cause some discomfort to the patient, so treatment with pain medication such as tramadol is recommended. NSAIDS should not be co-administered with intravesicular corticosteroids.

Again, the best treatment for a toxicity is prevention. Cyclophosphamide given IV is associated with urothelial injury at a higher rate than seen in low dose oral administration. Protection for IV dosing can be accomplished by administration of furosemide at a dose of 3 mg/kg IV immediately after the cyclophosphamide dose is given. Ifosfamide is a new generation alkylating agent associated with urothelial toxicity in virtually 100% of treated cases. The urothelial protectant MESNA (2-mercaptoethane sulfonate) essential for treatment safety. MESNA is administered as a fraction of the ifosfamide dose in mgs. The ifosfamide dose is divided by 5. This 1/5th mg ifosfamide dose of MESNA is diluted to a final concentration of 20 mg/ml and is given intravenously over 5-10 minutes prior to the start of the ifosfamide dose, and is repeated at 2 and 5 hours after ifosfamide administration. Thus, the total MESNA dose administered is 3/5th the mg ifosfamide dose.