WHAT EVERY NURSE SHOULD KNOW ABOUT LYMPHOMA IN DOGS AND CATS  
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Lymphoma, also referred to as lymphosarcoma (LSA) or malignant lymphoma is the most common hematopoietic tumor in dogs and cats. Lymphoma originates from lymphoreticular cells that typically arise from lymphoid tissues. Combination chemotherapy protocols are the standard of care for these patients. As the goal of cancer treatment in veterinary oncology is patient quality of life, veterinary technicians plays a key role in these cases.  

Canine Lymphoma  

The median age of dogs with lymphoma is 5 to 9 years old. There is no gender predilection, but Boxers, Basset Hounds, St. Bernards, Scottish Terriers, Golden Retrievers, Airedale Terriers, and Bulldogs are some of the most common breeds reported. The clinical signs associated with canine lymphoma are extremely variable depending on site of disease, extent of organ involvement, and disease progression. Peripheral lymphadenomegaly, gastrointestinal signs (anorexia, weight loss, vomiting, diarrhea and/or melena), respiratory signs (cough, dyspnea, and/or exercise intolerance), and polyuria/polydipsia are some of the most common presenting complaints.  

*Multicentric lymphoma is the most common form of canine lymphoma comprising about 80% of lymphoma patients.* Dogs are typically brought to a veterinarian for evaluation of lethargy and reduced appetite, or the finding of a swelling" under the jaw or behind the back of the pelvic limbs (peripheral lymphadenomegaly). Abdominal palpation may reveal evidence of an enlarged liver or spleen that is associated with stage IV or V multicentric lymphoma. Other forms of LSA include alimentary (gastrointestinal), mediastinal, cutaneous (nonepitheliotropic and epitheliotropic), and hepatosplenic. Lymphoma can involve virtually any organ in the body, including the brain and spinal cord (CNS).  

Feline Lymphoma  

*LYMPHOMA IS THE MOST FREQUENTLY DIAGNOSED FELINE CANCER.* Most cats are domestic shorthair, and a specific feline breed predilection has not been identified. *The most common anatomical location for feline lymphoma is gastrointestinal (alimentary), and clinical signs include weight loss, anorexia, vomiting, diarrhea, and lethargy.* Other anatomical forms of lymphoma include multicentric, mediastinal, nasal, renal, and CNS. The feline leukemia virus (FeLV) is an important predisposing factor for development of mediastinal lymphoma; however, the prevalence of FeLV-associated neoplasia has decreased markedly in the past decade following the widespread use of the FeLV vaccine. Nevertheless, *cats that are FeLV positive are 62 times more likely to develop lymphoma compared to cats that are FeLV negative,* and cats that are infected with feline immunodeficiency virus (FIV) are 6 times more likely to develop lymphoma. Physical exam findings in cats with intestinal lymphoma may include poor body condition, thickened
gastrointestinal loops, and/or a palpable abdominal mass and mesenteric lymphadenomegaly. *It should be emphasized that some cats with small cell lymphoma of the intestinal tract can have an unremarkable physical examination.*

**Diagnosis:**

The diagnosis of lymphoma in dogs and cats is relatively straightforward and is usually obtained via fine needle aspiration cytology of affected lymph nodes, liver, or spleen or via histopathologic evaluation of an intestinal biopsy. A full staging for lymphoma in animals with multicentric lymphoma includes a complete history, physical exam, complete blood count (CBC), serum chemistry, urinalysis, thoracic radiographs, abdominal ultrasound, bone marrow aspiration and lymph node biopsy or cytology. This comprehensive evaluation is expensive, and some veterinarians may forego thoracic radiographs and bone marrow aspirate, unless otherwise specifically warranted based on abnormal respiratory signs (coughing, tachypnea, dyspnea) or evidence of hematological abnormalities such as thrombocytopenia. **About 50% of dogs with lymphoma have bone marrow infiltration with no evidence of cytopenias**. Clinical staging will help in identifying those dogs in need of close monitoring during the post-treatment period.

The serum chemistry panel is usually unremarkable, but lymphoma is the most common cause of hypercalcemia in dogs, particularly in cases of mediastinal lymphoma or those with bone marrow involvement. A urinalysis should be routinely performed in animals with lymphoma to rule out subclinical urinary tract infections, especially if chemotherapy may be instituted. Additional studies are occasionally required on neoplastic tissue to confirm a diagnosis of lymphoma, and differentiate it from other infiltrative or inflammatory disorders. Routine histopathology is occasionally needed to confirm the diagnosis and determine the grade of the lymphoma (high grade and low grade), and special stains can be used (immunohistochemistry) to delineate whether the lymphoma subtype is of B-cell or T-cell origin. A separate PCR-based technique called clonality can be used for difficult-to-diagnose cases by determining whether the tissue is of a single clone (cancer) or multiple clones (inflammation or non-neoplastic process).

**Management and Prognosis:**

*Dogs with multicentric lymphoma that are not treated for lymphoma have a median survival time of only about 30 days after diagnosis. Dogs treated with prednisolone therapy alone can live 30 to 60 days. Complete response rates using multiagent chemotherapy protocols range from 68% to 92.3%; however median remission duration remains 8-16 months, and the majority of dogs die of their disease within 2 years.* A recent study evaluating autologous peripheral blood stem cell transplantation in dogs with B-cell lymphoma showed a prolonged overall survival of 463 days, and 33% of the dogs that underwent the transplant are still alive with a median overall survival of 524 days. The survival times for dogs with lymphoma are variable and depend on the type of lymphoma and prognostic factors such as patient status, T-cell vs B-cell origin, the presence of hypercalcemia, pulmonary involvement, or pre-treatment of steroids. **Patients that are treated with steroids before beginning chemotherapy usually do not respond as well as those that begin chemotherapy and prednisolone concurrently.**
Combination chemotherapy using multiple chemotherapeutic agents with different mechanisms of action affords the best response, and is far superior to single agent chemotherapy. Chemotherapy administration is separated into different stages, including **induction**, the stage of intensive chemotherapy administration typically characterized by weekly administration of chemotherapy in order to attain a complete remission (CR). **CR means no detectable disease, and lymph nodes should be normal or subnormal in size, and of normal texture. Extranodal disease should be undetectable. Many tumor cells remain even in CR. Partial remission (PR) refers to a reduction in tumor volume of more than 50%; however, there is a large tumor burden of resistant cells. Dogs and cats that are not able to attain a CR following the induction phase of chemotherapy (PR or no response) have a much poorer prognosis than those in CR.** The 2nd phase of chemotherapy administration is **maintenance** and involves treatments every 2 to 3 weeks. When the lymphoma relapses a "**rescue**" protocol is initiated in an attempt to achieve a second remission. The duration of each remission period becomes progressively shorter in duration, until the lymphoma is no longer responsive to the chemotherapy and the animal is euthanized because of recurrence of clinical signs and a poor quality of life.

The best single agent for lymphoma is doxorubicin. Most canine lymphoma protocols include tapering doses of prednisone and a combination of L-asparaginase, vincristine, cyclophosphamide, and doxorubicin. In general, the more drugs added into the protocol, the longer the patient will survive. The two drugs of choice for the management of cats with intestinal low grade (small cell) lymphoma are prednisolone and chlorambucil, and both drugs can be given orally by the owner. The median survival for cats with small cell lymphoma given these chemotherapeutic agents is approximately 20-24 months. Cats with intestinal lymphoma frequency have a deficiency of vitamin B12 (cyanocobalamin) due to malabsorption of this vitamin in the ileum of the bowel. It is important to supplement this vitamin parenterally, and owners can give cyanocobalamin to their cats at a dose of 250 µg per dose SQ, once weekly for 6 consecutive weeks, and repeat the injections approximately every 2-3 weeks indefinitely.

The most commonly used chemotherapy drugs used in management of dogs and cats with multicentric lymphoma include vincristine, cyclophosphamide, doxorubicin, L-asparaginase, and prednisone (dogs) or prednisolone (cats) (modified Madison Wisconsin protocol).

**Vincristine is a severe perivascular irritant and must be given strictly intravenously with a catheter (butterfly catheters work well).** In the event of suspected extravasation, a hot compress should be applied immediately. Hyaluronidase (300 units diluted in 6ml of 0.9% saline, administered circumferentially to site, immediately then weekly) may limit tissue necrosis and promote recovery. Topical DMSO may be applied by the owner at home.

**Cyclophosphamide** can cause **myelosuppression** (5-7 days following IV administration) and **GI toxicity** (vomiting and diarrhea) 1-3 days following administration. The drug can also cause **hemorrhagic cystitis**, and a urinalysis should be routinely performed every 2-3 weeks to look for increased red blood cells in the urine sediment (free catch urine sample is superior to cystocentesis), and the drug should be discontinued if blood is detected in the urine.
**L-asparaginase** is an enzyme, and is a foreign protein. To reduce the risk of an anaphylactic reaction, the drug is given intramuscularly or subcutaneously, and some institutions pretreat the animal with antihistamines to reduce the likelihood of an anaphylactic reaction.

**Doxorubicin or epirubicin** are used interchangeably in treatment of lymphoma; however, epirubicin is a structural analogue of doxorubicin, but is much less cardiotoxic in dogs. Both are severe perivascular irritants, and the complications of extravasation can be catastrophic. An indwelling intravenous catheter should always be carefully placed to facilitate administration of these drugs. In the event of suspected extravasation, a cold compress should be applied immediately. Hyaluronidase may reduce the risk of severe tissue injury as above, and topical DMSO may then be applied by the owner at home. Doxorubicin and epirubicin may cause an irreversible dose dependent cumulative cardiotoxicity in dogs. The maximum cumulative dose of doxorubicin for dogs is 240 mg/m² (8 standard doses) but many dogs will show changes in myocardial function at lower doses. Echocardiographic evaluation prior to the first treatment and then at the third and each alternate treatment is recommended as a minimum.

Veterinary chemotherapy protocols use lower drug dosages and fewer drug combinations than in human oncology, and pets undergoing chemotherapy experience fewer and less severe side effects than human cancer patients. Chemotherapeutic agents generally affect rapidly dividing cells; hence the most common adverse effects involve the bone marrow (myelosuppression) and the gastrointestinal tract (anorexia, nausea, vomiting, and diarrhea). The hair follicle cells in dogs such as terriers, poodles, and the Bichon Frise, Lhasa Apso, and Shih Tzu may be particularly susceptible to chemotherapy induced alopecia. Cats usually do not lose their hair, although many will lose their whiskers, and long-haired cats may lose their outer coat. The hair will regrow once chemotherapy is stopped or once treatments are being administered less frequently, but it may initially have a modest change in color or texture.

Gastrointestinal toxicity, if present, usually manifests about 3 to 5 days after drug administration. Some patients may just be slightly inappetent, while others may develop severe vomiting and/or diarrhea requiring hospitalization. Prophylactic administration of antiemetics at the time of chemotherapy administration is often useful in minimizing adverse GI effects. Metoclopramide, ondansetron, and maropitant (Cerenia®) are commonly used in oncology patients to decrease nauseous and prevent vomiting. Bone marrow suppression typically causes a decrease in the neutrophil count, potentially leading to increased susceptibility to infection. A complete blood count (CBC) should be performed 7-10 days following administration of a chemotherapeutic drug that is known to have a high potential for myelosuppression. The presence of fever, severe lethargy or anorexia, neutrophil count < 3,000 cells/μL usually results in delayed administration of the next dose of chemotherapy, prophylactic antibiotic administration for 5 days (trimethoprim sulphonamide, enrofloxacin), or hospitalization for more intensive fluid support and intravenous antibiotic administration if the patient is febrile and neutropenic. Owners should be instructed in the use of a rectal thermometer and take the pet’s temperature twice a day around the neutrophil nadir. Nutritional support plays a pivotal role in the management of dogs and cats with lymphoma, and enteral feeding devices are a viable option for animals with prolonged anorexia.
Role of the Veterinary Nurse in Patient Care

Chemotherapy Drug Handling

An appropriate understanding of safe handling and administration of chemotherapy is imperative for those offering oncology services in their practice. Workers in the area where chemotherapy drugs are used can be exposed through inhalation, dermal contact and ingestion of the drug. Precautions must also be taken to protect owners of pets undergoing chemotherapy from inadvertent exposure to drugs or excreta.

Environmental Control

All chemotherapy drugs should be clearly identified as hazardous and the area in which the drugs are stored should have controlled access and be a low traffic area. Chemotherapy drugs should ideally be stored safely in cabinets, and drugs requiring refrigeration should be stored in a refrigerator where no food is stored and the refrigerator should be clearly labeled as containing hazardous materials. A Class II vertical (laminar flow) biological safety cabinet (BSC) protects against aerosols created during drug preparation using a HEPA filter and maintains drug sterility as well. The work surface of the BSC should be covered with an absorbent, plastic backed pad to collect any drugs dripped during transfer. Chemotherapy drugs should be reconstituted in the BSC and chemotherapy tablets should be counted and bottled in the BSC. If this is not available, protective eyewear, a gown, and a respirator-mask should be used in addition. Some materials should always be kept in the hood. These include a disposable plastic-backed absorbent pad to line the work surface and wipe up any leaks and spills (which should be changed when the cabinet is cleaned or when it is contaminated with any drug), a stack of gauze squares, and alcohol-soaked cotton balls or swabs. A large, plastic style-style bag should be available for chemotherapy waste, and a puncture-proof container is needed for all contaminated sharps.

Recently, closed drug transfer systems (CDTS) have become available to prevent escape of chemotherapy agents into the environment. The BD PhaSeal CDTS builds on two unique features: its Double Membrane technology, which creates a dry, leak-proof connection, and its airtight Expansion Chamber, which contains all aerosols, particles and vapors as well as equalizes the pressure in the vial. Daily cleaning of the surfaces in the chemotherapy area should be performed with 70% alcohol. Weekly, all surfaces should be cleaned with a high pH agent followed by rinsing.

Spill kits should be in the chemotherapy area to clean up any chemotherapy spills that occur. They are commercially available and contain the necessary equipment and protective devices required for clean up. All persons in the chemotherapy area should be familiar with the information contained in the Material Safety Data Sheets (which are provided with each drug).

Waste Disposal

All waste must be disposed of within the guidelines of the Environmental Protection Agency, Federal, State and Local agencies for handling of cytotoxic waste. In addition, your
local regulated medical waste company should be consulted for their requirements. Bags should be 4 mil thick polyethylene or 2 mil thick polypropylene and have labels clearly indicating they contain cytotoxic waste. Needles used with chemotherapy agents should not be recapped or clipped. All IV apparatus components should be disposed of in puncture proof containers clearly labeled as cytotoxic waste. Puncture proof clearly labeled containers should be used for "sharps". A small "sharps" container should be placed in the BSC to facilitate disposal of needles, syringes and bottles used for drug reconstitution. While waiting pickup and disposal, cytotoxic waste should be maintained in a secure cabinet in a closed, plastic lined container.

All excreta from chemotherapy patients should be handled as if they were contaminated with chemotherapy drugs. Staff cleaning cages should wear chemotherapy gloves to handle fecal material and urine should be mopped up rather than hosed down a floor drain.

Pet Owner Protection

Pet owners should handle excreta as described above for 1 week after treatment. In addition, they should double launder any soiled bedding. Chemotherapy tablets dispensed for owner administration at home should be compounded to the correct size and not split to create the correct size for the patient since that increases the risk of drug expose during administration. Owners administering chemotherapy agents at home should have chemotherapy gloves dispensed and the vials of drugs labeled with a "Wear Gloves" and "Chemotherapy" sticker. Gloves and vials should be returned to the veterinary hospital for disposal as cytotoxic waste. Pregnant owners should not handle chemotherapy drugs or chemotherapy patient waste. For drugs that are excreted in the urine (such as cyclophosphamide metabolites), the pet should be encouraged to urinate on soil where urine will drain quickly, and any urine in other areas should be handled and disposed of as chemotherapy. These precautions should be followed for approximately 48-72 hours following administration.

When oral use is indicated, gloves should be worn while handling the drug, and hands washed following administration. The tablets or capsules can be given normally, but it is important to be sure that the patient has swallowed the mediation. In order to dose small animals appropriately, it may be necessary to have drugs compounded by pharmacies specially equipped to handle cytotoxic medications. This should never be attempted in the veterinary clinic setting.

Veterinary hospitals offering oncological services should develop specific policies and procedures for handling and administration of chemotherapy as well as safety training for personnel, including spill management procedures. Continued monitoring of compliance is imperative for the consistent safety of staff, patients, and clients.

Recommended reading:

7. Oncology Nursing Society (ONS) and American Society of Clinical Oncology (ASCO), chemotherapy safety standards: [www.ons.org/CNECentral/Chemo/Standards](http://www.ons.org/CNECentral/Chemo/Standards)