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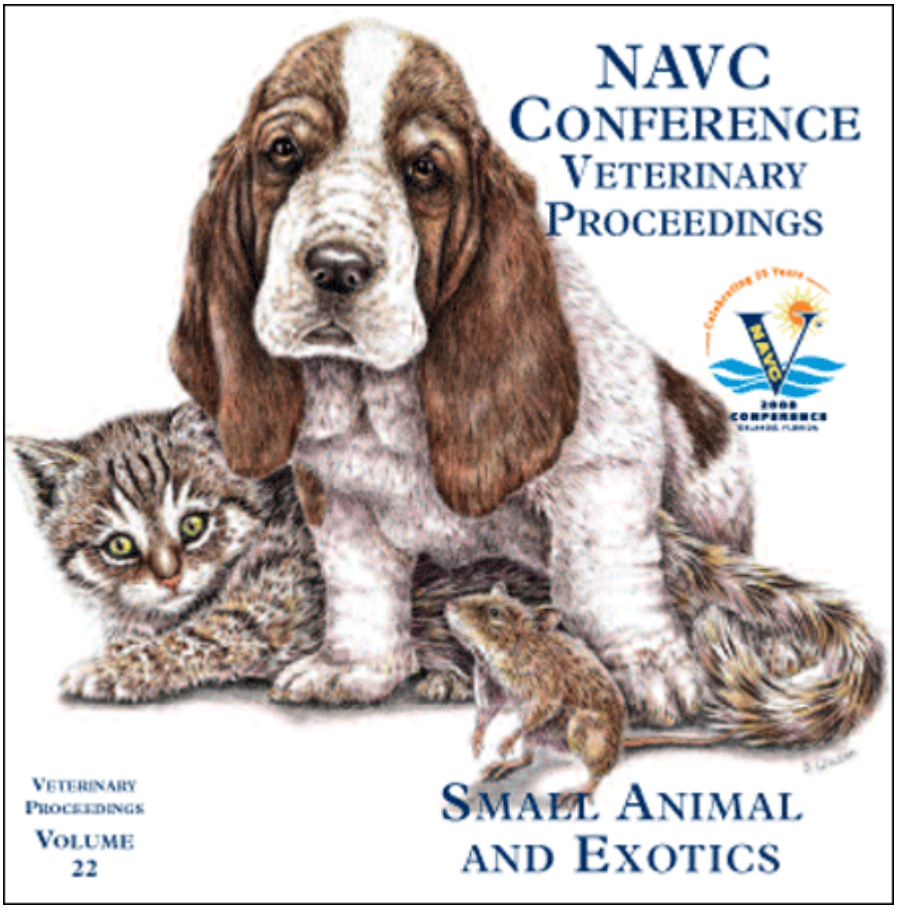

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LYMPHOMA

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CLASSIFICATION OF LYMPHOMA

Lymphoma can be classified according to World Health Organization (WHO) clinical stage, anatomic site, histologic/cytologic phenotype, and immunophenotype.

Canine Classification

The multicentric form, typically WHO stage III or IV, accounts for the majority of cases (80 to 85%) in the dog. Alimentary (~7%), cutaneous (~6%), mediastinal (~3%), and miscellaneous extranodal forms (central nervous system, bone, heart, nasal cavity, primary ocular) are less frequently encountered. The majority (80%) of canine lymphomas are similar to medium- and high-grade non-Hodgkin's lymphoma in people. Approximately 70% to 80% of canine lymphomas are of B-cell immunophenotypic derivation, with the remainder being primarily of T-cell derivation.

Feline Classification

In the last 20 years, the availability of widespread feline leukemia virus (FeLV) testing and vaccination programs has resulted in a shift in the frequency of anatomic type, immunophenotypic derivation, and retroviral association in cats with lymphoma. Prior to this era, the mediastinal and multicentric forms predominated, and lymphoma was associated with younger, FeLV-positive cats. Today, lymphoma primarily affects older FeLV-negative cats and the alimentary form predominates. The majority of affected cats (80–90%) are negative for FeLV antigenemia. As one would predict, along with a shift away from FeLV antigen-associated tumors has come a shift away from traditional signalment and relative frequency of anatomic sites. The median age of 9 to 10 years now reported is considerably higher than the 4 to 6 year medians reported prior to this era. The median age of cats within various anatomic tumor groupings has not changed, and sites traditionally associated with FeLV (ie, mediastinal and multicentric) still usually occur in younger, FeLV-antigenemic cats, while the alimentary form occurs most often in older, FeLV-negative cats. Three distinct classes of lymphoma in cats, small cell lymphoma, large granular lymphoma, and Hodgkin's-like lymphoma, have more recently been described.

DIAGNOSIS

Palpation of all assessable lymph nodes, including a rectal examination in the dog, should be undertaken. The mucous membranes should be inspected for pallor or petechia indicative of anemia or thrombocytopenia. Abdominal palpation may reveal organomegaly, intestinal wall thickening, or mesenteric lymph-adenopathy. Thoracic compression in cats and auscultation in both dogs and cats may suggest the presence of a mediastinal mass and/or pleural effusion. Funduscopic and ocular assessment may reveal abnormalities (eg, uveitis, hemorrhage, ocular infiltration).

Hematologic Abnormalities

A complete blood count (CBC) is a necessary part of any evaluation for lymphoma. Anemia, when present, is usually normocytic, normochromic (nonregenerative) reflecting anemia of chronic disease. Cats with FeLV-associated disease often have a macrocytic anemia. The anemia may be accompanied by thrombocytopenia and leukopenia and circulating atypical lymphocytes if significant myelophthises is present. Bone marrow aspiration is required for clinical stagingl; however, if a client wishes to treat irrespective of stage, bone marrow aspiration does not need to be performed.

Serum Biochemical Abnormalities

These may reflect the anatomic site involved (eg, liver-specific enzyme or bilirubin elevations may result from hepatic parenchymal infiltration). Approximately 15% of dogs with lymphoma (40% of those with mediastinal involvement) will have hypercalcemia secondary to a paraneoplastic syndrome.

Retroviral Status

Retroviral screening (ie, FeLV and feline immunodeficiency virus [FIV]) is important in cats from a diagnostic and prognostic standpoint.

Imaging

Imaging by radiography, ultrasonography, or computed tomography (CT) may be of diagnostic importance in those cases lacking peripheral lymphadenopathy or limited to intracavitary or extranodal sites. Imaging is equally important for clinical staging (ie, determining extent of disease), which may have a significant impact on the overall prognosis and alter the caregiver's willingness to pursue therapy. For the more typical cases of multicentric lymphoma in dogs, imaging in the author's practice is limited to thoracic radiographs as there is no prognostic difference between dogs with stage III versus IV disease (absence or presence of hepatic and splenic involvement). However, cranial mediastinal lymphadenopathy is of prognostic significance. Special studies, including contrast imaging of the gastrointestinal tract, CT, or myelographic studies of the central nervous system, and skeletal surveys are reserved for those cases where the appropriate anatomic site is suspected.

Cytologic and Histopathologic Diagnosis

Microscopic confirmation of lymphoma is the cornerstone of diagnosis in both the cat and dog. Cytologic evaluation of fine needle aspirates (FNA) by a skilled clinical pathologist may be adequate to make a diagnosis of lymphoma in dogs; however, conclusive histologic confirmation is recommended. For infrequent situations where the microscopic characteristics are inconclusive—that is, reactivity, early malignancy or low-grade malignancy cannot be differentiated—clonality by

polymerase chain reaction (PCR) is now available at some centers and can be performed on cytology samples (either slide preparations or samples collected in cell media). Histologic and cytologic samples can be analyzed by various histochemical and immunohistochemical techniques to determine immunophenotype (B versus T cell).

In the cat, cytologic evaluation of FNA of lymph node is often not sufficient for diagnosis of lymphoma owing to difficulties encountered in distinguishing lymphoma from benign hyperplastic lymph node syndromes unique to the species.

PROGNOSIS

Prognostic Factors in Dogs

Most studies fail to correlate age, body weight or breed with prognosis. Clinical stage, with the exception of marked stage V disease, does not appear to significantly affect prognosis in dogs. The exception would include those cases where bone marrow is heavily infiltrated, where gross leukemia is present, or if peripheral cytopenias exist secondary to myelophthisis. Two factors that consistently correlate with prognosis in dogs are immunophenotype and WHO substage status. Dogs with CD3 immunoreactive tumors (ie, T-cell derivation) are associated with significantly shorter remission and survival durations. Similarly, dogs with substage 'b' disease (ie, clinically ill) also do poorly when compared with dogs with substage 'a' disease.

Prognostic Factors in Cats

Factors most strongly associated with a more positive outcome in cats are complete response to therapy (unfortunately this cannot be determined prior to therapy), negative FeLV status, early clinical stage, substage 'a,' and the addition of doxorubicin to the treatment protocol. In general, cats that are not FeLV antigenemic and who achieve a complete response on combination-based chemotherapy protocols have a higher likelihood of long-term survival, with approximately one third surviving one and a half years after diagnosis. Cats with nasal lymphoma, overall, have the best prognosis, as local radiotherapy (or chemotherapy if radiotherapy is not available), results in excellent control with median survivals approaching 1.5 years.

THERAPY

The management of lymphoma in companion animal species can be quite gratifying initially as response rates approaching 90% in dogs and 60% to 70% in cats result following a variety of chemotherapeutic approaches. Unfortunately, most animals will eventually succumb to disseminated relapse of their disease in a more chemotherapy resistant form. Once a diagnosis is established, untreated dogs and cats will generally live an average of 4 to 6 weeks. Lymphoma, typically a systemic disease, requires a systemic approach to therapy (ie, chemotherapy). Exceptions to this include cases of solitary site or extranodal lymphoma where local therapy involving either surgery or radiotherapy may be indicated.

Systemic Chemotherapy in Dogs with Lymphoma

A variety of chemotherapeutic approaches have been reported in the veterinary literature for the treatment of lymphoma. Prior to initiating therapy, caregivers should be educated as to the advantages and disadvantages of several chemotherapy protocols. Several factors should be considered and discussed, including the cost, time commitment involved, efficacy, toxicity, and the experience of the clinician with the protocols in question.

Combination protocols used in veterinary practice are usually modifications of CHOP protocols initially designed for treating people with lymphoma. CHOP represents combinations of cyclophosphamide (C), doxorubicin (H, hydroxydaunorubicin), vincristine (O, Oncovin®), and prednisone (P). Regardless of which CHOP-based protocol is used, overall median remission and survival times are approximately 8 and 12 months, respectively. Approximately 20% to 25% of treated dogs will be alive 2 years or longer after initiation of therapy. Most modern treatment protocols end chemotherapy after approximately 4 months and after therapy is discontinued, dogs are reevaluated monthly by physical examination with special attention to lymph node size.

Doxorubicin represents the most effective and commonly used single agent chemotherapy protocol available for dogs with lymphoma. Doxorubicin (30 mg/m^2, IV, q 3 weeks) is given every 3 weeks for a total of five treatments. In dogs weighing less than 15 kg and cats, the dose of doxorubicin used is 1 mg/kg. While cardiotoxicity is the dose-limiting toxicity (DLT) in dogs, renal toxicity is the DLT in cats and creatinine and urine specific gravity should be monitored in the cat to ensure safe levels for doxorubicin delivery. Response rates of 75% to 80% result and median remission and survival durations of 5 and 7 months, respectively, are reported for single agent doxorubicin in the dog. Advantages of this single agent protocol include less cost, a shorter time commitment, fewer hospital visits, and side effects that are attributable to one drug.

Alternatives should be offered to caregivers who, for financial or other concerns, decline more aggressive systemic chemotherapy. In these cases prednisone (2 mg/kg, PO, daily) will often result in short remissions of approximately 1 to 2 months. It is important to educate these clients that dogs receiving prior prednisone therapy are more likely to develop multiple drug resistance and experience shorter remission and survival durations with subsequent combination protocols should more aggressive therapy be pursued. This is particularly true if prednisone has been used long-term or if dogs have experienced a recurrence while on prednisone. Therefore, the earlier clients opt for more aggressive therapy, the more likely a durable response will result.

Systemic Chemotherapy in Cats with Lymphoma

In general, cats do not experience as high response rates or remission and survival durations as dogs with

lymphoma; complete response rates are between 50% and 70%, and overall median remission and survival durations are approximately 4 and 6 months, respectively. This is tempered somewhat with the knowledge that a larger proportion of cats (30% to 40%) that achieve a complete response with combination chemotherapy experience more durable (ie, ≥2 years) remission and survival times than do dogs. The response rate and length of response vary according to the presence or absence of prognostic factors discussed previously. CHOP-based protocols are preferred by the author for cats.

For cases of "small cell" lymphoma in cats (eg, GI and hepatic) a protocol combining chlorambucil (20 mg/m^2 PO every 2 weeks) and prednisone (5 mg/day) is usually highly effective and results in long-term remissions.

Reinduction or Rescue Therapy

Unfortunately, most dogs and cats with lymphoma experience a relapse of their disease following initially successful chemotherapy. At the first recurrence, it is recommended that reinduction be attempted by restarting the induction protocol that was initially successful. The likelihood of a response and the length of the response are, in general, half that encountered in the initial therapy; however, a subset of animals will enjoy long-term reinduction.

If reinduction fails, the use of so called "rescue" agents or protocols may be attempted. Rescue agents are drugs or drug combinations that are not found in the standard CHOP protocol and are specifically withheld for use in the drug-resistant setting. The most common protocols include single agent or combination use of CCNU, actinomycin D, mitoxantrone, and MOPP (M, mechlorethamine; O, Oncovin®; P, procarbazine; P, prednisone). Mitoxantrone, doxorubicin, and MOPP have also been advocated in cats with resistant relapse. Overall rescue response rates of 40% to 50% are reported; however, most responses are not durable with median durations of 1.5 to 2 months being the norm. A small subset of animals will enjoy longer rescue durations.

Therapy for Extranodal Lymphoma

If extranodal involvement is part of a multicentric disease process then systemic therapies previously discussed should be instituted. However, if the extranodal site is solitary and not part of a multicentric presentation, local therapy may be performed without institution of systemic chemotherapy. In these cases strict adherence to staging diagnostics, including bone marrow evaluation and radiographic/ultrasonographic imaging of the thorax and abdomen, are warranted to ensure the process is localized.

ALLEVIATING ADVERSE EVENTS FROM CHEMOTHERAPY

Breed Predisposition to Adverse Effects of Chemotherapy

Certain breeds, in particular collies, are known to be at risk for toxicity from chemotherapeutics that are actively transported by the p-glycoprotein pump (eg, vinca alkaloids, epipodophyllotoxins, anthracyclines, dactinomycin, and the taxanes). These breeds have a high frequency of a pharmacogenetic mutation of the MDR1allele. If a dog is homozygous for the mutant allele, they will be affected and at risk; if they are heterozygous for the mutant allele, they are a carrier. A clinically relevant PCR assay (performed on cheek swabs) for the mutant status is available through Dr. Katrina Mealey's group at the Washington State University Veterinary School. It is recommended that if you are contemplating treating a breed at risk, non-p-glycoprotein substrate chemotherapeutics (eg, alkylators) be substituted in protocols until the results of the analysis are available (turnaround time of approximately 1 week).

Gastrointestinal (GI) Toxicity

Gastrointestinal (GI) toxicity may be secondary to direct damage to intestinal epithelial cells or via efferent nervous stimulation of the chemoreceptor trigger zone (CRTZ). It typically manifests as inappetence, nausea, vomiting, and/or diarrhea beginning 3 to 5 days after therapy. When direct stimulation of the CRTZ is responsible, vomiting is maximal on the day of therapy (eg, when using cisplatin). The consequences of significant gastrointestinal adverse events are several-fold and include dehydration, nutritional deficiency, delay of subsequent therapy, dose reduction, financial burden (ie, hospitalization), and diminished client enthusiasm for continuation. The judicious use of antiemetics and antidiarrheals is recommended. If an animal has had significant gastrointestinal events following a particular chemotherapy, sending the client home with 3–5 days of prophylactic therapy is indicated. The most effective class of antiemetics in people undergoing chemotherapy are the NK-1 receptor antagonists; Cerenia® (maropitant; Pfizer Animal Health), which recently received FDA approval for use in dogs is a superior antiemetic in dogs receiving chemotherapy and has several advantages over off-label antiemetics used in the past. It is important to keep in mind that most side effects of chemotherapy are self-limiting and will resolve with minimal veterinary intervention. Most clients are able to perform the nursing care required to support animals through GI side effects. Typically, dose reductions of 20% are recommended for severe gastrointestinal toxicity at the time of the next scheduled treatment. Dose reductions should not be contemplated lightly as dose intensity is extremely important for antitumor response; therefore, if adverse effects can be abrogated by symptomatic treatments (antiemetics, antidiarrheals) rather than dose reduction, this should be attempted first.

Myelosuppression

Myelosuppression is secondary to damage to the rapidly dividing bone marrow stem cells. Cells with the shortest circulating life span are most susceptible; therefore, myelosuppression is most commonly manifested as a decrease in neutrophil and/or platelet counts. Specifically, chemotherapy treatment should be delayed with a neutrophil count of ≤1500 to 2000/μL or a platelet count of ≤50,000/μL. The exception to this rule is if the cytopenia is believed to be secondary to the tumor, either a paraneoplastic syndrome or from myelophthisis. In either case, treatment of the neoplasia is needed to resolve the low cell count. Moderate (≤1000 neutrophils/μL) myelosuppression in an otherwise clinically normal animal can usually be managed with prophylactic oral antibiotic administration and body temperature monitoring. Repeating the neutrophil count in 5–7 days generally will reveal marrow recovery. The use of human hematopoietic growth factors is controversial and rarely necessary in veterinary-based protocols. If the myelosuppressed animal is ill, or pyrexic, hospitalization with broad-spectrum parenteral antibiotics, fluid support, and careful observation are indicated. Hunting for a source of infection (eg, occult pneumonia, urinary tract infection, or sepsis) may be indicated if clinical signs do not rapidly normalize with broad-spectrum antimicrobials and fluid support. Typically, dose reductions of 20% are recommended if the neutrophil count falls below 500/μL at nadir, or below 1500/μL at the time of the next scheduled treatment. Dose reductions should not be contemplated lightly as dose intensity is extremely important for antitumor response.

References are available from the author upon request.