

Lymphoma: Anything New?
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General Information

Lymphoma (LSA) is the most common tumor of the cat and represents approximately 80-90% of hematopoietic tumors in cats. LSA is the third most common tumor in the dog with an estimated annual incidence of 13-24/100,000 dogs at risk. The mean age of cats diagnosed with LSA over 10-15 years ago was 2-5 years of age, however, recent reports suggest the mean age of cats diagnosed with LSA is now 8-12 years. The mean age of dogs afflicted with LSA remains stable at 6-9 years of age, however, the range of age in dogs can be as short as weeks to months. The most common site of LSA diagnosis in cats from over 10-15 years ago was mediastinal and/or multicentric, whereas recent reports suggest the most common site presently is alimentary. Why has there been such a significant change over the years??

Much of this sea-change in age of onset and location for cats with LSA can be attributed to changes in feline leukemia virus (FeLV). FeLV was the most common cause of hematopoietic tumors in cats, and these cats generally had T-cell mediastinal LSA. B cell alimentary LSA in cats is usually seen in older FeLV negative cats, and this is by far the most common presentation for cats presently. Some oncologists believe that all cats with LSA are FeLV positive. This author disagrees with this statement, as specific viruses have never been found to be responsible for all types of LSA in other species, and evidence for strong associations with certain herbicides (e.g. 2,4-D) continues to accumulate in people. Some oncologists believe that the rise in alimentary LSA seen recently is due to a decreased incidence of FeLV with a concomitant increase in food-related carcinogens, though no scientific evidence for the latter is available.

Lymphoma Categorization & Classification

Dogs & cats with LSA are generally categorized based on anatomic and histologic classifications. The five major anatomical sites are alimentary, mediastinal, multicentric, leukemia and extra-nodal (CNS, cutaneous, other). Though there are a number of histologic classification systems available, the NIH Working Formulation has been the system most widely adopted by histopathologists. This system generally suggests that approximately 10%, 30% and 60% of dogs and cats with LSA have low, intermediate and high-grade tumors, respectively.

History & Clinical Signs

The history and clinical signs of dogs & cats with LSA are extremely variable and dependent on the extent of disease and anatomic location. For example, cats with alimentary LSA usually present for anorexia/weight loss, vomiting, diarrhea and an abdominal mass, whereas cats with mediastinal LSA usually present for tachypnea, dyspnea and vomiting/regurgitation. Many dogs with multicentric LSA present for abnormal lumps being found by the owner or groomer, or on routine physical examination by a veterinarian

Diagnosis

The diagnostic evaluation of dogs & cats with a suspicious diagnosis of LSA should include a full physical examination, bloodwork (CBC/platelet/biochemistry profile), retroviral testing in cats (FeLV/FIV) and urinalysis. Additional staging diagnostics may include abdominal radiography and/or ultrasonography, chest radiography and bone marrow aspiration/cytology. Additional tests may be necessary depending on the anatomic location of the LSA (e.g. mediastinal aspirate for mediastinal mass). Caution is noted for NOT making the diagnosis of multicentric LSA off of fine needle aspiration and cytology specifically in cats due to the common syndrome of non-neoplastic retroviral-associated lymphadenopathy. Similarly, the diagnosis of LSA should not be made cytologically with fine needle aspirates of the mandibular lymph nodes in dogs as these lymph nodes are responsible for drainage of the oral cavity, and may have focal areas of hyperplasia that could cytologically mimic LSA. Additional information will be presented in the lecture on the utility of more recently available molecular diagnostics such as IHC, ICC, PARR, Flow Cytometry, etc.

Treatment

The last 20 years have shown significant advancements in the treatment of canine LSA, however, such advances have not been made in the treatment of feline LSA. The chemotherapeutic agents and protocols used in dogs are the same ones used in cats. These agents include cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate and L-asparaginase. The same approximate dosages for the above drugs can be used in dogs as well as cats except for doxorubicin. When cats are given doxorubicin at the originally described 30 mg/m² dose, they may experience significant toxicity including myelosuppression, vomiting, diarrhea, and hepato-/nephrotoxicity. When cats are given doxorubicin at 1 mg/kg, the toxicity is quite manageable and typically self-limiting. In addition, the induction of adriamycin-associated cardiomyopathy that can be seen in dogs and humans is rarely if ever seen in cats.

Combination chemotherapy protocols generally induce a complete remission in 70-85% of dogs and 50-60% of cats with LSA. Similarly, the median remission time for dogs is generally 6-11 months, whereas in cats it is 4-5 months. The median survival time of dogs on multi-agent chemotherapy protocols is 12-26 months, whereas in cats it is only 5-7 months. That said, the range of remission times and survival times in cats can be extremely wide, ranging from weeks to years. It is also important to note that it is extremely difficult to recommend precise treatments for the wide variety of clinical types of LSA seen in dogs and cats. Though studies have not specifically addressed this, this author believes that cats generally tolerate chemotherapy much better than dogs do. Other treatment modalities such as radiation therapy can be utilized in dogs and cats with mediastinal, nasal and CNS LSA, whereas surgery may be useful for dogs and cats with truly extra-nodal non-metastatic LSA (e.g. single small mycosis fungoides or epitheliotropic LSA lesion). A significant amount of time during the presentation will be allotted to discuss options and case scenarios for rescue chemotherapy with lymphoma as well as the recently approved agent Tanovea from VetDec/Elanco and recently conditionally approved Laverdia-CA1 from Anivive/Dechra.

Prognosis

The prognosis for dogs and cats with LSA is extremely variable. A large number of prognostic factors have been identified in the dog and these will be presented and ranked as much as possible at the oral discussion. The duration and response to therapy will depend on stage, location and FeLV status. Recent studies suggest that the most important negative

prognostic factors are lack of response to therapy, FeLV +, whether the cat is sick or not, advanced stage and lack of doxorubicin in the chemotherapy protocol. This author and others have noted extremely variable remission and survival times for cats with alimentary LSA treated with a wide variety of chemotherapy protocols, ranging from leukeran and prednisone (a la Fondacaro) to typical aggressive multi-agent chemotherapy protocols. This author is presently investigating: 1) the potential for multiple sub-classifications of alimentary LSA in cats with hopeful prognostic and therapeutic significance, and 2) the use of immunohistochemical-based prognostic panels utilizing known prognostic factors (AgNOR, immunophenotype, proliferation markers, drug resistance proteins, etc.).

Canine LSA Prognostic Factors:

STRONG	MEDIUM	NEW
Substage	Stage	Proliferation Markers
Grade	Hypercalcemia	P-Glycoprotein
Immunophenotype	Gender	Pulmonary
Location	Weight	Steroid Use
Response to Rx	Hypoalbuminemia	Apoptotic Markers

Canine Lymphoma Chemotherapy & Response:

Therapy	Remission %	Median Rem. (Mos.)	Mortality from Therapy	Median Surv (Mos.)
None	0%	0	None	1-2
Pred only	33%	1	Very Low	2
COP or Adria	60-77%	4-6	Low	6-8
CVT-X or CHOP	80-82%	5-8	Low	8-11
ACOPA I & II	75-88%	8-9	Medium	N/A
VELCAP-S	68-87%	9	Medium	N/A
VELCAP-L	69%	13	Medium	N/A
UW-Madison (2 yr.)	82-85%	8.5	Low	11-12
UW-Madison (6 mo.)	91-94%	9	Low	13

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