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What is new in canine and feline lymphoma

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Introduction

Lymphoma is one of the commonest forms of malignancy encountered in small animal practice. It is characterised by the malignant proliferation of lymphoid cells which can arise in any organ containing lymphoid tissue. Lymphoma (*syn*. malignant lymphoma, lymphosarcoma) is one of the more common canine neoplasms. In cats, FeLV remains the commonest cause of lymphoma.

Diagnosis and staging

A number of histopathological classification schemes have been developed, although most veterinary pathologists will only classify canine lymphoma as 'low-grade' or 'intermediate to high-grade'.

The minimum data base

- History and physical examination
- Complete blood count and serum chemistry
- Urinalysis
- Thoracic radiography
- Cytology / Histopathology
- FeLV/FIV (cats)

Once a definitive diagnosis is achieved, clinical staging can be done to allow more accurate prognostication. There are five main stages, designated by uppercase Roman numerals. Dogs that are presented apparently feeling well are designated sub-stage 'a'. Those presented appearing unwell are designated sub-stage 'b'.

New diagnostic tools and prognostic markers

Immunophenotyping

Immunophenotyping of canine lymphoma tissue is straightforward. Laboratories can classify tumours as T-cell (CD3) or B-cell (CD79); the latter being more common and the former associated with a poorer prognosis. In the clinic, the fact that a tumor may be T or B cell does not alter the type of conventional therapy that is offered. However, it may alter an owner's willingness to treat and can be offered as part of the diagnostic work-up. It is possible, however, as we progress to classification systems based upon molecular and immunological markers, that we may adopt different treatment protocol tailored to sub-classifications.

Immunoglobulin rearrangements

The monoclonality of a population of neoplastic lymphoid cells lends itself to providing supporting evidence for a diagnosis of lymphoma. Both B and T cells have cognate receptors which enable them to take part in the immune response. PCR amplification of either the T cell Receptor (TCR) or immunoglobulin chains on B cells will demonstrate either a mixed population (i.e. with a reactive lymphadenopathy) or a clonal population of cells (as with lymphoma)

Other markers

Other diagnostic and prognostic markers have been suggested including serum levels of alpha 1-acid glycoprotein (AGP) and matrix metalloproteinases (MMP 2 and 9) as indicators of relapse. However, currently there are no commercially available tests for these markers. Additionally, validation in large scale clinical trials needs to be performed to give confidence to their clinical use. However, new markers and the use of sophisticated molecular techniques (such as micro and tissue arrays) are being developed to provide information for the clinician. It is possible that their widespread use in clinical practice will become evident over the next 10 years.

Treatment modalities

1. No treatment
2. Single agent therapy
   - ***Prednisone:*** Dogs can be treated with prednisone alone (2mg/kg PO daily for 7 days tapering to 1 mg/kg daily) but this will provide only a short remission (typically 2 to 4 months). Moreover, dogs pre-treated with steroids are less likely to enter into complete remission if the owner subsequently decides to opt for more aggressive chemotherapy.
   - ***Doxorubicin*** is the best agent to use if the client desires the simplicity and convenience of single agent use and is willing to accept a shorter predicted survival. The complete remission (CR) rate is likely to be between 70 and 85% with median survival between 8and 10 months. The drug is given every 21 days as a slow IV infusion (over at least 15 minutes). Typically 5 doses are given over 15 weeks. The dose used is 30mg/m^2 in dogs ≥ 15 kg, 25mg/m^2 in dogs < 15 kg and 1 mg/kg in toy-breed dogs. Dogs with pre-existing heart disease causing decreased cardiac contractility should not be treated with doxorubicin because of its potential cardiotoxicity (see chemotherapy chapter).
   - ***CCNU (Lomustine®):*** May be considered for use as a first-line single agent therapy if the client desires the simplicity and convenience of single agent use and is willing to accept a shorter predicted survival. CCNU is more commonly used for relapse

multicentric lymphoma and for epitheliotropic cutaneous lymphoma (mycosis fungoides). The dose is 60-70mg/m2 every three weeks orally.

3. Multi-drug chemotherapy
   - Many chemotherapeutic protocols are available for the use in the treatment of lymphoma. In general the protocol used will be based upon available drugs and facilities. Protocol are based upon the following drugs: cyclophosphamide (Cytoxan®), vincristine (Oncovin®), prednisone and doxorubicin (hydroxydaunorubicin or Adriamycin®).
   - ***COP protocol for canine lymphoma***
     This is an effective treatment for lymphoma. Complete remission (no evidence of detectable gross disease) occurs in approximately 60-70% of dogs with multicentric lymphoma and median survival times are around 6-7 months. On a practical point, cyclophosphamide tablets are produced in limited doses and should not be divided. This may limit the dose that can be delivered orally.
   - ***CHOP-Based Protocols***
     While COP is a reasonable combination to use in general practice, it has been clearly established that the best combination protocols also include doxorubicin. University and specialist practices dealing with oncology patients should be using protocols containing doxorubicin as 'Standard of Care'. Protocols using doxorubicin (CHOP Protocols) generally result in an 80-90% remission rate and median survival times of 12 months. Although several protocols are in operation world-wide, the author has included the University of Wisconsin-Madison (UW-M) protocol for illustration (see Figure 1).

The role of maintenance therapy

The role of sustained maintenance therapy in management of canine lymphoma has recently come under scrutiny. It has been reported that a 25-week CHOP protocol (i.e the. UW-M short protocol) followed by routine re-examination and re-initiation of chemotherapy at time of relapse provides results similar to a CHOP protocol with sustained maintenance treatments. Similar clinical results are achieved when the UW-M protocol is delivered in 19 weeks rather than 25 weeks. The 19-week protocol uses the same number of treatments but they are delivered in a shorter period of time. (See figure 1).

Protocols for therapy

It is important to educate clients on the expectations and side effects of therapy for lymphoma. Chemotherapy is not a cure for canine lymphoma and 90% of dogs will eventually relapse even with gold standard therapy such as multi-agent (CHOP based) chemotherapy. It is important that clients understand that if non-maintenance protocols are used, reported median survival times reflect multiple courses of chemotherapy (i.e. re-initiation of chemotherapy at the time of relapse if relapse occurs after chemotherapy has been discontinued).

Quality of life for dogs on chemotherapy is largely good, hence the treatment is generally well tolerated.

Alimentary tract lymphoma

If solitary lesions are to be treated then surgical resection of the affected bowel should first be performed (including mesenteric lymphnode). Chemotherapy can be instituted following resection (ensuring an adequate time for healing) but response are poor. Treatment of diffuse alimentary tract lymphoma in the dog is often unrewarding. If treatment is to be attempted then the individual drugs should be introduced in a staggered fashion. Introduction of all drugs on the same day can lead to perforation of the bowel.

Feline Lymphoma

The various anatomical forms of feline lymphoma (mediastinal, alimentary, renal, multicentric and extranodal) have been well described.

Alimentary

This is characterised by gastric, intestinal, or mesenteric lymph node involvement; it is one of the more common forms of feline lymphoma. Gastrointestinal lymphoma may present as a solitary mass lesion or as a diffuse infiltration of extensive areas of bowel. Clinical signs are non-specific, including anorexia, vomiting, and diarrhoea. Animals previously diagnosed with lymphoplasmacytic gastroenteritis have been reported subsequently to develop gastrointestinal lymphoma. Most cats with alimentary lymphoma are FeLV ELISA negative.

For those cats with solitary intestinal lesions (+/- mesenteric node involvement) surgery + chemotherapy is the treatment of choice. For cats with the diffuse form of small cell lymphoma then a protocol consisting of daily prednisolone and chlorambucil (pulsed at 20 mg/m^2 every 2 weeks) offers a good treatment modality.

Renal

Renomegaly and renal failure are typical features of feline renal lymphoma. Some cats become anaemic, a few polycythaemic. Most affected cats are middle-aged and FeLV ELISA negative.

Mediastinal

Most cats with mediastinal lymphoma are relatively young and FeLV ELISA positive. The incidence of this form of the disease has been shown to have decreased in Holland, in parallel with a decrease in the prevalence of FeLV infection. Typical clinical signs include dyspnoea and exercise intolerance due to the presence of the

space-occupying lesion and pleural effusion. Coughing may occur secondary to compression of the trachea by the large mediastinal mass. The heart sounds may be muffled and caudally displaced. It is often abnormally difficult to 'spring the ribs' of the cranial thorax of affected young cats.

Multicentric

Unlike the situation in dogs, this is a relatively uncommon form of feline lymphoma. It must be distinguished from various forms of generalised reactive lymphadenopathy, including some forms that occur in retrovirally-infected cats. Fine needle aspiration can sometimes provide a definitive diagnosis, but cutting needle biopsy or excisional biopsy may be necessary.

The role of radiation in the management of lymphoma in dogs

Lymphoma is exquisitely sensitive to the effects of radiation. For stage negative solitary lesions (e.g. single cutaneous lesions that do not lend themselves to wide surgical resection) then radiotherapy is an excellent modality.

Despite the sensitivity of lymphoma to the effects of radiation, the use of total body irradiation to treat multicentric disease has been limited by the lack of haematological support and autologous bone marrow transplantation that would be required to treat complications. However, the use of half body irradiation is being investigated as a possible alternative strategy to reap the benefits of radiation but limit the side effects. In this regime, half of the body is irradiated at a time point and then the other half is irradiated 4 weeks later. Although this has been studied as a modality to treat dogs in the maintenance stage of lymphoma, the commonest application will probably be in dogs which fail therapy during the chemotherapy induction period.

Week	V	P1	P2	P3	P4	C	D
1	X	X					
2			X			X	
3	X			X			
4					X		X
5							
6	X						
7						X	
8	X						
9							X
10							
11	X						
12						X	
13	X						
14							X
15							
16	X						
17						X	
18	X						
19							X

Figure 1: 19 week protocol for dogs

V (vincristine) = 0.5-0.7mg/m² IV
P (prednisone)1=2 mg/kg PO sid
P2 = 1.5 mg/kg sid
P3 =1 mg/kg sid
P4 = 0.5 mg/kg sid
C = cyclophosphamide (Cytoxan) at 250 mg/m² IV, or PO over 2-4 days
D = doxorubicin at 30mg/m² (25 mg/m² for dogs below 15kg and 1 mg/kg for toy-breeds) IV

Treatments no. 8 -16 may be delivered on a q 2 week schedule if this is more tolerable for the dog or convenient for the client. The duration of the protocol is 25 weeks in this case.