



Canine Lymphoma

Lymphoma is a common and biologically diverse cancer in dogs. Diagnosis of lymphoma is most commonly made based on clinical signs (enlargement of peripheral lymph nodes—See photo to the right) and fine needle aspiration (FNA) cytology. While clinical signs and FNA cytology alone are often sufficient to gain a diagnosis of lymphoma and therefore initiate treatment, several ancillary diagnostic tests are used in cases where the diagnosis is less clear cut or if further prognostication is desired by the pet owner and/or clinician. Such ancillary diagnostic tests may include a complete blood count, chemistry profile, bone marrow aspiration, thoracic radiographs, abdominal ultrasound, and biopsy. Advanced diagnostics that may be recommended included immunohistochemistry, PCR for antigen receptor rearrangement, and flow cytometry.

The most common form of lymphoma diagnosed in our canine patients is multicentric lymphoblastic lymphoma. This disease entity is clinically similar to non-Hodgkin's lymphoma in people. Other, more rare forms, include mediastinal, cutaneous (epitheliotropic), gastrointestinal, and indolent lymphoma. Multicentric lymphoma is defined as peripheral lymph node involvement with or without involvement of the liver, spleen and/or bone marrow.

Prognosis for lymphoma varies considerably based on a number of factors. The most consistent and reliable of these factors include clinical stage and phenotype. Clinical stages are defined in table 1. Briefly, the higher clinical stage indicates a greater degree of systemic involvement and thus a more aggressive disease processes. The most common staging system is the WHO five stage scale (Table 1).

Table 1: WHO staging for canine lymphoma

Stage	Definition	Significance
I	One lymph node involved	Progression to higher stage often seen with local therapy (surgery) only.
II	Multiple lymph nodes involved but only on one side of diaphragm.	
III	Generalized lymphadenopathy	Patients with stage I-III disease have similar DFI and ST

IV	Stage III with splenic and/or liver involvement.	Significance of differentiating stage IV from I-III is argued
V	Bone marrow involvement/leukemic, and non-lymphoid tissue involvement (brain, GI tract, etc.)	Patients with stage V disease survive significantly shorter than stage I-IV.

Clinical “substage” is often included into the WHO staging scheme. Substage is based on the patient’s clinical signs at the time of diagnosis/initiation of therapy. Substage “a” is defined as a patient who is showing minimal signs (i.e. overall feeling well) while substage “b” is given to a patient who is clinically ill (i.e. lethargy, weight loss, etc.). The median remission time of substage “a” dogs treated with multi-drug chemotherapy protocols has been shown to be significantly longer than those presenting with a substage “b” status.

In addition to clinical stage and substage, tumor phenotype has been shown to be a prognostic factor. Phenotype describes whether a particular lymphoma is B or T cell in origin. Numerous studies have repeatedly shown that phenotype is a strong predictor of both response to therapy as well as estimated survival. Specifically, the reponse rate and duration of response for dogs with B cell lymphoma is significantly longer than those with T cell lymphoma.

The mainstay of therapy for lymphoma is chemotherapy. It is important to realize when considering chemotherapy for pets, that animals tend to tolerate chemotherapy much better than their human counterparts. Please see “Chemotherapy in Pets” in Client Education A-Z at www.AspenMeadowVet.com.

The following protocols are often discussed with clients regarding various options based on cost, time commitment, and expected outcome:

First Line Chemotherapy Options for Dogs Diagnosed with Multicentric Lymphoma at AMVS:

- 1) **CHOP:** CHOP, also known as UW-Madison protocol, is classically considered the most aggressive protocol offered to lymphoma patients. CHOP based protocols include the use of cyclophosphamide (**C**ytosan), doxorubicin* (doxorubicin **H**ydrochloride), vincristine (**O**ncovin), and **P**rednisone. This protocol has the best response rates in cases of lymphoma (>90% dogs treated with this protocol will go into a complete remission). Dogs that achieve a complete remission typically stay in remission for a median of 10-12 months from the start

of treatment (based on a 19 week "UW Short" protocol). However, after a relapse, the percentage of a second complete response decreases to 50-60%, and duration of remission is often less than half of what is achieved during the first remission. The median life expectancy with CHOP is 12-14 months. Treatment with a CHOP based protocol is more expensive and time intensive relative to other protocols described below.

*Mitoxantrone can be substituted for doxorubicin in cases particularly at risk for cardiotoxicity.

- 2) **Doxorubicin/Prednisone:** Treatment with single agent doxorubicin consists of five treatments spaced three weeks apart. A reported 85% of dogs will respond and median remission times are expected to be 4-6 months. The median life expectancy with Doxorubicin is 6-8 months. Doxorubicin is often administered with prednisone. While the common recommendation is to stop after 5 doses of doxorubicin, additional dose can be delivered safely in most patients. It is important to remember that cardiotoxicity is directly associated with total cumulative dose; therefore owners must be adequately educated of the risks before exceeding recommended cumulative doses of doxorubicin.
- 3) **COP:** COP based protocols are similar to the CHOP protocol, except that doxorubicin is eliminated. This treatment protocol has similar expectations to that seen with doxorubicin alone. This is often a good option for dogs unable to receive doxorubicin either because of predisposing heart disease, or if the patient has previously received doxorubicin as part of another protocol earlier in life. The cost is roughly \$1000 for the first four weeks, then \$250-\$300 per treatment thereafter (q3-4 weeks).
- 4) **L-asparaginase/Lomustine (CCNU):** While this protocol is typically reserved for use as a "rescue" protocol, it can be used as a first line chemotherapy for financial or other reasons. One study reported the use of lomustine without L-asparaginase to result in median remission and survival times of only 60 days and 110 days, respectively. Clinical impression is that dogs do significantly better than this when L-asparaginase is added to the induction phase of the protocol until complete remission is achieved. It is important to note that lomustine has a unique toxicity profile and that it can cause idiosyncratic hepatopathy, and for this reason, liver protectants (i.e. denamarin) are often administered concurrently
- 5) **Prednisone alone:** This consists of an oral medication given once daily. Oral prednisone is relatively inexpensive and has minimal side effects. Side effects associated with prednisone include increased drinking, urination, voracious appetite, panting, and a decrease in

muscle mass. The median life expectancy with treatment with prednisone alone is 6-8 weeks.

Second line or "Rescue" therapy often includes re-introduction of the original chemotherapy protocol if remission is lost >3 months following completion of the original protocol. CCNU/L-asparaginase is the rescue protocol of choice for cases where remission is lost during, or shortly after (<3 months) the completion of CHOP, COP or single agent doxorubicin protocols. The overall response rate in dogs treated with CCNU/L-asparaginase as a rescue protocol is upwards of 75% with a median time to progression of 2-3 months after initiation of the rescue protocol. Again, it is important to note the unique potential for hepatotoxicity with CCNU. MOPP has also been used as a rescue protocol however, response rates using this aggressive protocol were no better than that associated with CCNU/L-asparaginase.