Standards of Care (How I Treat)
CANINE LYMPHOMA

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It is important that the client be given all the options and that the best option be used first. As a general rule, combination chemotherapy is superior to single-agent therapy. Each time an effective drug is added to the COP protocol, the remission duration increases; however, so do the cost and the potential for toxicity. It is also important that clients realize that a second or third remission is possible with appropriate therapy but that these subsequent remissions are more difficult to attain and that their duration is generally half the duration of the previous remission.

The treatment options below are tiered according to risk of toxicity, cost, and efficacy. First-level protocols provide a low risk of toxicity at low cost but have low efficacy; as the level rises, so do efficacy, cost, and risk of toxicity.

First Level: For clients who cannot afford or will not accept a combination chemotherapy protocol due to the risks of toxicity, a protocol using prednisone alone (40 mg/m2 PO daily for 7 days then every other day) or in combination with chlorambucil (6 to 8 mg/m2 PO every other day) may provide palliation with few risks of side effects. A CBC should be collected every 2 to 3 weeks to make sure that myelosuppression is not occurring.

Second Level: The COP protocol is a relatively inexpensive chemotherapy protocol with a low risk of toxicity. Dogs tolerate the treatments, and veterinarians find the protocol very manageable. CBCs should be taken 1 week after each dose of cyclophosphamide to ensure that myelosuppression (if it occurs) is not severe and that doses do not need to be adjusted.

Doxorubicin administered every 3 weeks for five to eight treatments at a dosage of 30 mg/m^2 (1 mg/kg for small dogs) is the most effective single chemotherapeutic agent. This treatment regimen results in a relatively high remission rate with relatively few serious life-threatening toxicities (<5%). With the advent of generic doxorubicin, the cost is reasonable for most clients. Because the drug is given every 3 weeks, this treatment approach is less time intensive than most chemotherapeutic protocols. A second remission seems more likely if with doxorubicin is used as first-line therapy and COP is used after relapse than if COP is used first.1 Overall remission time for the two-protocol treatment approach is similar to that of the COPA protocol.2

Third Level: The most effective chemotherapy protocols use a five-drug combination of L-asparaginase, vincristine, cyclophosphamide, doxorubicin, and prednisone. Similar remission rates and survival times have been obtained for the protocols that include these drugs.3-7 Although these protocols require more intense client–veterinarian communication and monitoring for toxicity, the overall level of satisfaction for owners, pets, and veterinarians is high. Most oncologists recommend discontinuous protocols such as VELCAP-S or the Wisconsin protocol; however, some clients will not restart chemotherapy when first remission is over.8,9

For dogs with T-cell lymphoma, protocols that rely heavily on alkylating agents, such as Tufts VELCAP-SC, should be used.10

Table 47-10 WISCONSIN PROTOCOL
Vincristine is administered at 0.5 to 0.7 mg/m2 IV. L-asparaginase is given at 400 IU/kg IM. The dose for cyclophosphamide* is 200 mg/m2 IV. Doxorubicin is administered at 30 mg/m^2 IV. The dose for prednisone is 2.0 mg/kg PO, week 1; 1.5 mg/kg PO, week 2; 1.0 mg/kg PO, week 3; and 0.5 mg/kg PO, week 4.

Week	Vincristine	L-asparaginase	Cyclophosphamide*	Doxorubicin	Prednisone
1	•	•			•
2		•	•		•
3	•				•
4				•	•
5					
6	•				
7			•		
8	•				
9				•	
11	•				
13			•		
15	•				
17					
19	•				
21			•		
23	•				
25				•	

From week 25, repeat weeks 11 to 17, but every 3 weeks. After week 49, treatments given every 4 weeks.

Fourth Level: The addition of radiation therapy or, if available, autologous bone marrow support to allow chemotherapy dose intensification represents the best possible treatment option for a dog with lymphoma. The potential for long-term remission and possibly cure is much higher than with other protocols. Dogs with T-cell lymphoma may not benefit to the same extent as those dogs with B-cell lymphoma. Although risks of toxicity are higher, the addition of radiation or chemotherapy dose intensification has not negatively affected the quality of life for treated dogs.

High-dose chemotherapy with hematopoietic stem cell support or bone marrow transplantation (BMT) has become an important component of therapy for lymphoma and other malignancies in humans. Although combination chemotherapy results in a complete remission rate of 75% or greater in dogs, relapses frequently occur after a median of 10 to 12 months. It appears that autologous BMT allows dogs to receive intensified doses of myelosuppressive chemotherapy without increased toxicity and that this intensification improves remission duration and overall survival.

In a reported protocol reported by AS Moore and A Fermberger based on VELCAP-S, dogs in CR at week 8 were treated with filgrastim (G-CSF) followed by bone marrow collection. A high dose of cyclophosphamide was given with mesna followed by prophylactic antibiotics, and bone marrow was administered intravenously. Three dosage levels of cyclophosphamide were used: 300 mg/m^2 (3 dogs), 400 mg/m^2 (12 dogs), and 500 mg/m^2 (13 dogs). Toxicity was acceptable, with only one dog requiring hospitalization after transplant for complications that resolved in 24 hours. Remission duration was not significantly different for dogs receiving 300 mg/m^2 or 400 mg/m^2. For dogs receiving 500 mg/m^2, the median remission was 12.4 months, significantly longer than for dogs receiving 400 mg/m^2, with 6 of 13 dogs still in remission between 6 and 33 months after starting chemotherapy and 1-year survival of 57.1%. Using autologous bone marrow to support chemotherapy dose intensification allows dogs to receive 2.5 times the standard dose of cyclophosphamide without any increase in clinical toxicity. This dose intensification results in significant prolongation of remission.

Supportive and Nutritional Treatment for Canine Lymphoma

The induction death rate decreased markedly for the VELCAP-SC protocol compared with previous protocols, despite an increase in the percentage of dogs needing a dose reduction of at least one chemotherapy drug (toxicity) and despite a higher proportion of substage b dogs undergoing therapy. We attribute the difference in death rate to careful staging that required the owners' commitment to therapy, as well as strict use of hospitalized induction for any animal that was in substage b.

We suggest that any dog that has signs compatible

with substage b (particularly anorexia and other GI signs) be admitted for intravenous fluid therapy (maintenance x 1.5), broad-spectrum antibiotics (cefazolin sodium or enrofloxacin), and GI prophylaxis (metoclopramide and bland diet). This supportive care should be continued for at least 4 days after induction and preferably for a week. Dogs can be discharged to the owner as soon as they are self-supporting. Antibiotics and prophylactic metoclopramide are continued for the first 3 weeks of the protocol.

In addition, in one study, administration of trimethoprim/sulfadiazine (Tribrissen®) to dogs for 14 days, starting on the day of treatment with doxorubicin, markedly reduced the likelihood of GI toxicity (vomiting or diarrhea), hospitalization, and lower quality-of-life (Karnofsky) score. The effect was most marked in dogs with lymphoma and may be due to reduced bacterial translocation in damaged intestinal epithelial layers.[133]

Nutrition is an important part of supportive care for any dog with cancer, particularly for dogs with a systemic disease like lymphoma. Lactate and insulin concentrations in untreated dogs with lymphoma are higher than in dogs without lymphoma and do not improve when dogs enter chemotherapy-induced remission.12-13

Nutrition may also play a role in prolonging remission and survival. Polyunsaturated n-3 fatty acids have been shown to inhibit the growth and metastasis of tumors. In one study, 32 dogs with lymphoma were randomized to receive a diet supplemented with polyunsaturated n-3 fatty acids (menhaden fish oil and arginine) or an otherwise identical diet supplemented with soybean oil.14 Diets were fed from the start of doxorubicin chemotherapy and continued after remission was attained. Dogs fed the diet supplemented with n-3 fatty acids had higher serum levels of n-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid) and lower plasma lactate responses to carbohydrate testing. Increased serum levels of docosahexaenoic acid were associated with longer remission and survival times for dogs with stage III lymphoma.

References: available upon request