Proceedings of the
World Small Animal Veterinary Association
Sydney, Australia – 2007

Hosted by:

Australian Small Animal Veterinary Association (ASAVA)

Australian Small Animal Veterinary Association (ASAVA)

Australian Small Animal Veterinary Association (ASAVA)

Next WSAVA Congress

Published in IVIS with the permission of the WSAVA Close window to return to IVIS

WHAT IS THE BEST PROTOCOL FOR CANINE LYMPHOMA?

Antony S. Moore, M.V.Sc., Dipl. A.C.V.I.M. (Oncology)
Veterinary Oncology Consultants
www.vetoncologyconsults.com

Lymphoma is the most common haematopoietic malignancy in dogs, and is the most responsive to chemotherapy. Affected dogs are typically middle-aged. Neither gender nor neutering is a predisposing factor for developing lymphoma. In studies of canine lymphoma epidemiology; boxers, Scottish terriers, German shepherds and poodles were more often affected, and recent evidence suggests a high incidence in golden retrievers. The most common physical finding in dogs with lymphoma is peripheral lymphadenopathy, which is usually generalized but may be localized to a single lymph node or a region of the body. Involvement of other organs, such as spleen, liver, or bone marrow is an indication of advanced disease. Involvement of other (extranodal) sites is rare in dogs.
Untreated lymphoma progresses rapidly (1–2 months) from presentation to terminal stages. With chemotherapy, however, considerable improvement in the duration and quality of the patient's life can be expected.

Staging and Diagnosis

Lymphoma is a systemic disease; therefore, it is important to determine the extent of organ involvement with lymphoma and to identify unrelated or secondary conditions that need to be treated or controlled before instituting appropriate therapy. Staging carries prognostic significance and enables the veterinarian and client to make informed and rational decisions as to the type of therapy best suited for the patient. Each dog is clinically staged based on the results of physical examination, clinical laboratory testing (i.e., CBC, biochemical profile, urinalysis, and bone marrow cytology), and imaging procedures (i.e., radiography and ultrasonography).

Cytologic examination of lymph nodes may be compatible with a diagnosis of lymphoma but rarely provides a definitive diagnosis. A definitive diagnosis is based on histologic examination of a surgically resected lymph node. Examination of nodal architecture enables the pathologist to assign a grade, which is important for prognosis, and immunohistochemistry for T and B lymphocyte markers can be performed. The most accessible, most easily removed lymph node is the popliteal lymph node.

Prognostic Factors

Prognostic factors include stage and substage of disease, histologic type, immunophenotype (B-cell versus T-cell), presence of hypercalcemia, response to therapy, pre-treatment steroid therapy, and possibly gender.

Treatment

Once a definitive diagnosis has been obtained and after the patient has been staged accurately, the veterinarian should schedule a discussion with the owner regarding prognosis and treatment. One of the most important distinctions to make for the client is between remission and cure. When toxicities are discussed, the owner should be given criteria by which to distinguish mild side effects from those that can be life threatening. A copy of the protocol to be administered, with scheduled treatments, rechecks, and blood counts, will assist owners in remembering much of this information.

First-Line Therapy

Single-Agent Chemotherapy: Most veterinary oncologists agree that unless palliation rather than extended remission is the goal of therapy, single agent treatment of lymphoma should be avoided.

Combination Protocols:

COP Protocol: Much of the information regarding efficacy of treatment for canine lymphoma has come from studies using combinations of cyclophosphamide, vincristine, and prednisone. COP is a relatively non-toxic protocol and is relatively inexpensive. Overall, COP chemotherapy causes complete remission in about 70% of dogs with lymphoma for a median of 130 days.

Vincristine, Cyclophosphamide, Prednisone, Doxorubicin, and L-asparaginase (VELCAP) Protocols:

110 dogs were treated with a sequential chemotherapy protocol that used the above drugs (Madison-Wisconsin Protocol or AMC protocol). Complete remission was achieved in 84% of dogs for a median of about 9 months. Approximately 50% of the dogs were still alive one year after starting chemotherapy. Toxicities that required dose reduction occurred in 40% of the dogs.

Ninety-eight dogs with lymphoma were treated using the VELCAP-L (Tufts-1) protocol.[1] The complete remission rate was 69%, with median remission duration of 13 months. Toxicity was frequent but rarely fatal.

Because palliation, rather than cure, is a major goal of chemotherapy in veterinary oncology, there has been recent interest in developing protocols that reduce the number of patient visits as well as cost and toxicity of treatment. The use of short-term chemotherapy given in pulse doses may provide similar remission durations to long-term maintenance chemotherapy. 82 dogs with lymphoma received a single 15-week course of chemotherapy after which treatment was ceased until relapse VELCAP-S (Tufts-2).[2] 68% of dogs achieved complete remission for a median first remission duration of 20 weeks. Forty-eight dogs relapsed, of which 30 repeated the induction cycle. Dogs received maintenance chemotherapy when first remission had been short (< 4 months); the other dogs received 2 or 3 cycles of induction chemotherapy. Second remission rate for these dogs was 87%. Overall disease control for the 38 dogs that remained on protocol was 44 weeks which was not significantly shorter than dogs treated with **VELCAP-L**. Delaying maintenance chemotherapy until after second remission is achieved does not significantly impact overall disease control.

Recent reports have documented the efficacy of lomustine[3] and MOPP[4] (mechlorethamine, vincristine, procarbazine and prednisone) for the treatment of relapsed lymphoma. A protocol that combined VELCAP drugs for induction and consolidation with lomustine and MOPP was investigated to see if it would increase the CR rate and the median duration of first CR of a discontinuous protocol (**VELCAP-SC**)[5]. The population was a group of dogs with advanced disease. 57% were in stage V dogs, 19% stage IV, 21% stage III; 63% were substage b and 30% had T cell lymphomas. The median overall survival of 84 dogs was 302 days (range, 5-1447). The 1 and 2 year survival rates were 44% and 13%, respectively. The only variable that had a significant negative impact on remission rate in this high risk group of patients was inappetance at time of diagnosis, and those negatively affecting survival time were innappetance at the time of diagnosis and not requiring a dose reduction for any drug. This latter finding implies that higher chemotherapy dosages may be associated with a better outcome.

High-dose Chemotherapy with Bone Marrow Support. High-dose chemotherapy with haematopoietic stem cell (HSC) support, or bone marrow transplantation (BMT), is important in the therapy of lymphoma and other malignancies in humans. Since most chemotherapy drugs exhibit a dose-response relationship, increased dose intensity should result in increased efficacy, and strong clinical evidence in cancer patients supports this. However, the clinical utility of dose intensification is limited by the toxicity of the regimen. Most currently used myeloablative BMT protocols offer significantly higher cure rates than those seen with standard therapy, but with significantly increased toxicity. We are studying nonmyeloablative stem cell transplantation by conducting a study with the goal of increasing the tolerable dose of chemotherapy agents in order to allow patients to receive the highest possible chemotherapy dose intensity while still enjoying the best possible quality of life and lowest possible risk of complications. Incremental dose intensification of 500 mg/m^2 cyclophosphamide with autologous bone marrow support at the end of a 12-week 5 drug combination protocol is no more toxic than standard-dose therapy. This protocol provides statistically significant lengthening of remission times in dogs with lymphoma, with a current average remission time of more than 1 year, compared to 5 months for the standard-dose 12 week protocol.

Comparison of different protocols for treatment of canine lymphoma

	VELCAP-L	Madison-Wisconsin	VELCAP-S	VELCAP-SC	VELCAP-HDC
Number of dogs	98	55	82	95	13
Population characteristics	typical	typical	typical	high-risk	typical
% CR	69	84	68	70	100
Protocol duration (weeks)	75	135	15	21	12
Median remission duration (weeks)	55	36	44	24	54
1-year CR %	53	43	36	NR	54
2-year CR %	25	25	12	NR	31

In summary, the best protocol for lymphoma currently available for routine clinical use is a “5-drug protocol” consisting of cyclophosphamide, vincristine, prednisone, doxorubicin and L-asparaginase. As long as these drugs are being used, the exact protocol may not have much of an overall influence on canine patients. However, it does seem that using combinations of drugs wherever possible (rather than single drugs given sequentially) may be more effective. In the future, the use of “dose intensification” such as autologous bone marrow transplant, or radiation therapy may further improve on these data, but those techniques are likely to be limited to specialty practices. In the absence of referral to a veterinary oncologist, the practitioner is encouraged to use a protocol that they feel comfortable with, and make use of expert advice if problems are encountered during treatment.

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 prednisolone alone or in combination with chlorambucil 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 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%). 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 doxorubicin is used as first-line therapy and COP is used after relapse than if COP is used first. Overall remission time for the two-protocol treatment approach is similar to that of the COPA protocol.

Third Level: The most effective chemotherapy protocols use a five-drug combination of L-asparaginase, vincristine, cyclophosphamide, doxorubicin, and prednisolone. Similar remission rates and survival times have been obtained for the protocols that include these drugs. 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 now recommend discontinuous protocols such as VELCAP-S; however, some clients will not restart chemotherapy when first remission is over. For such clients less intensive *maintenance* schedule may be preferred over restarting induction treatment at relapse. For dogs with T-cell lymphoma, protocols that rely heavily on alkylating agents, such as VELCAP-SC, should be used.

Fourth Level: The addition of radiation therapy or, if available, autologous bone marrow support to allow chemotherapy dose intensification represents the most aggressive 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.

References

1. Zemann B, Moore AS, et al. A combination chemotherapy protocol (VELCAP-L) for dogs with lymphoma. *J Vet Internal Med* 12 465-470, 1998.
2. Moore AS, Cotter SM etal.. Evaluation of a discontinuous treatment protocol (VELCAP-S) for canine lymphoma. *J Vet Internal Med* 15 348-354, 2001
3. Moore AS, London CA, et al. Lomustine (CCNU) for the treatment of relapsed lymphoma in dogs. *J Vet Internal Med* 13 395-398, 1999.
4. Rassnick KM, Mauldin GE, Al-Sarraf R, Mauldin GN, Moore AS, and Mooney SC. MOPP chemotherapy for treatment of resistant lymphoma in dogs: a retrospective study of 117 cases (1989-2000) *J Vet Internal Med* 16, 576-580, 2002.
5. Morrison-Collister KE, Rassnick KM, Northrup NC, Kristal O, Chretin JD, Williams LE, Cotter SM, Moore AS. A combination chemotherapy protocol with MOPP and CCNU consolidation (Tufts VELCAP-SC) for the treatment of canine lymphoma. *Veterinary and Comparative Oncology* 1, 180-190, 2004