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Lymphoma in dogs

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Abstract

Lymphoma is the most common haematopoietic malignancy in dogs, and is the most responsive to chemotherapy. With combination chemotherapy using VELCAP protocols (vincristine, cyclophosphamide, prednisone, doxorubicin, and L-asparaginase) more than 80% of dogs will achieve a complete clinical remission for a median of more than 1 year. The important prognostic factors include substage of disease (specifically anorexia), immunophenotype (B-cell versus T-cell) and response to therapy. Dogs that are sick, those that have a T-cell lymphoma have a lower chance of entering remission, and if remission is achieved, that remission is usually shorter than for a dog with B-cell lymphoma and/or a dog that is physically well. The use of autologous bone marrow transplantation may allow increases in dose intensity that translates into longer remission times.

Introduction

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 inappetence at the time of diagnosis and those negatively affecting survival time were inappetence 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 hematopoietic 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/m² 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.

References

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