

Canine Lymphoma: What's on the Horizon

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Lymphoma is one of the most commonly diagnosed cancers in dogs, cats and people. Canine lymphoma bears similarity to the non-Hodgkin's lymphomas (NHL) in humans and both exhibit similar responses to treatment with chemotherapy. Lymphoma is very difficult to cure and a leading cause of cancer death in dogs and people. Despite many efforts over the last 20-30 years, outcomes in canine patients have not significantly improved over those achieved with CHOP-based chemotherapy protocols (cyclophosphamide, doxorubicin, vincristine, and prednisone). These chemotherapy protocols have extended both the longevity and quality of life in dogs with lymphoma but novel strategies are needed to increase survival times. This presentation will cover a general review of lymphoma and recent advances that hold promise for the future.

Diagnosis and diagnostic advances

Lymphomas are a diverse group of cancers arising from lymphoid cells. There are greater than 30 types of canine lymphoma described that differ in anatomic, histologic and immunophenotypic (T vs. B cell) classification. These different types of lymphoma can vary in their biologic behavior and prognosis; however, further studies are currently needed to correlate the various categories of disease with clinical outcome. The majority of canine lymphomas are intermediate or high grade and are generally characterized as being biologically aggressive and rapidly progressing. Indolent lymphomas may progress more slowly and dogs may experience long-term survival with limited or no therapy; however, indolent lymphomas represent a small percentage of lymphoma in dogs. Diagnosis of lymphoma is achieved via cytology or biopsy. While not performed in every case, the following diagnostics may be helpful to establish a diagnosis of lymphoma or to further characterize the tumor.

Immunophenotyping (cytology, histopathology, or flow cytometry)

Using antibodies against specific cell surface markers (ex. B cell CD 79a/CD20, T cell CD3/CD4/CD8), this test is primarily used to determine if the lymphoma is B or T cell in origin. However, it can also be helpful to support a diagnosis of lymphoma by documenting a homogenous population of the same immunophenotype within a tissue.

Flow cytometry

This test allows immunophenotyping of cells in suspension (blood, effusions, and aspirates of LNs or organs). Flow cytometry can also provide information regarding cell size and expression of other CD molecules that may correlate with prognostic information.

PARR (PCR for antigen receptor rearrangement)

Theoretically, a malignant cell population should be derived from expansion of a single clone. PARR amplifies the variable regions of the T cell receptor or Immunoglobulin (Ig) receptor gene to detect the presence of clonal lymphocyte populations. When it is not possible to differentiate between malignant and benign lymphocytes based on cytology or histopathology alone, PARR may be helpful to confirm a diagnosis (especially useful when the lymphocyte population is heterogeneous). PARR can be used to detect minimal residual disease but investigations are ongoing to determine if this is a useful clinical marker of early recurrence.

Proteomics (ex. PetScreen)

Proteomics analyzes the protein components of a cell, which may be used to identify cancer specific markers. Preliminary studies have been performed in canine lymphoma but clinical application is limited at this time.

Staging

Lymphoma is considered a systemic disease and most dogs are presented in advanced stages (III to IV). Ideally, the extent of disease is determined after diagnosis as a baseline for treatment monitoring. However, the degree of staging necessary is controversial. The completeness of staging in any given case is often dictated by 1) how a diagnostic test affects treatment plan, 2) how it affects client's decision making and 3) how it affects patient prognosis. A thorough physical exam, CBC, serum chemistry profile, and urinalysis are indicated for every patient to obtain vital information regarding organ and bone marrow function before starting treatment with chemotherapy. Additionally, information regarding prognostic factors (hypercalcemia, anemia) may be obtained. Further diagnostics to consider include thoracic radiographs and abdominal radiographs/ultrasound. These imaging studies are non-invasive and may provide information regarding areas of significant disease burden (such as mediastinal or sublumbar lymph nodes). This can be important information when monitoring for lymphoma relapse. In the author's practice, abdominal ultrasound is also highly recommended for any dog with clinical signs attributable to the GI tract in order to rule out involvement, and thoracic radiographs/echocardiogram are recommended for any dog predisposed to heart disease. The value of a bone marrow aspirate in the face of a normal CBC is questionable and rarely pursued in the author's practice.

PET/CT (positron emission tomography/ computed tomography)

PET/CT combines functional and anatomical imaging to allow detection of metabolic or proliferative activity throughout the body. PET/CT is currently the standard of care for monitoring and predicting response to therapy in people with lymphoma. PET/CT has also shown promise for evaluating response to chemotherapy and predicting relapse in dogs with lymphoma.

Standard treatment options

Multiagent chemotherapy is the mainstay of treatment for lymphoma. For intermediate to high grade lymphomas, CHOP-based protocols are typically advised as first line therapy and provide the best response rates (80-95%) and treatment outcomes. At this time, long term maintenance chemotherapy does not appear to improve remission times. Additionally, dogs that do not receive maintenance therapy appear to be more likely to achieve a second remission following relapse. Several studies suggest that inclusion of L-asparaginase in the protocol does not significantly improve outcome (remission rates or duration of remission). In the author's practice, the decision to use L-asparaginase is made on a case-by-case basis and typically reserved for particular situations (ex. sick patient, cytopenic, rescue, etc.). Individual response and remission durations vary depending on prognostic factors. Overall median survival times are 12-14 months with approximately 20-25% of dogs alive at 2 years. Alternative protocols are offered if clients need less costly or more convenient options.

Rescue chemotherapy is associated with lower response rates and shorter remission times. Chemotherapy agents that are commonly used in the rescue setting include lomustine (CCNU), doxorubicin, mitoxantrone, MOPP (mustargen, vincristine, procarbazine and prednisone), actinomycin-D, and dacarbazine (DTIC).

Novel treatment options

Monoclonal Antibodies (Mab): Outcome improvements in people with non-Hodgkin's lymphoma have been due in large part to Mab therapies such as rituximab (anti-CD20 antibody used to treat B-cell lymphomas). However, rituximab is not effective in dogs. Currently, clinical studies are ongoing to evaluate two conditionally approved monoclonal antibodies (Aratana Therapeutics) for use in the treatment of canine lymphoma. These promising canine-specific antibodies are directed against CD20 (AT-004) for B-cell lymphoma and CD52 (AT-005) for T-cell lymphoma.

Bone marrow/ stem cell transplantation

Ablative total body irradiation and/or chemotherapy combined with bone marrow or stem cell transplantation is available for dogs with lymphoma. However, these treatments are not widely accessible, are costly, and are associated with increased morbidity in dogs undergoing treatment. While these treatments present a potential for increased cure rates, results of a large number of treated cases have yet to be reported.

Adoptive T cell therapy

Expanded autologous T cells infused after CHOP chemotherapy has been shown to significantly improve overall and disease free survival in a small number of dogs with B cell lymphoma. While quite promising, this therapy is currently available to client-owned dogs only through clinical trials.

Prognosis

Widely accepted negative prognostic factors include T cell immunophenotype (for multicentric lymphoma), substage b (sick), prior treatment with prednisone, and certain anatomic sites (cranial mediastinal involvement, primary diffuse cutaneous, GI, hepatosplenic, and primary CNS). Recently, it has been shown that B-cell lymphomas expressing low levels of class II MHC or lower than normal levels of B5 antigen also had a poorer prognosis. Presence of anemia is also associated with a worse prognosis. Alternatively, it appears that dogs with indolent lymphoma experience prolonged survival times.