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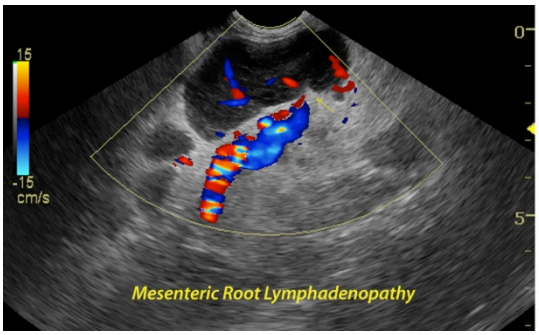
CANINE LYMPHOMA – 2 PAGES



Multicentric lymphoma is a common form of neoplasia in dogs and is typically treated with chemotherapy with reasonable remission rates. **Chemotherapy** is the mainstay of treatment after surgical cytoreduction, if indicated, has been performed. The most critical key to successful cancer cell eradication is stimulating apoptosis; the cell's own programmed death.[14] Given that remission and survival times in cases of single agent therapy are much shorter than those of multi-agent protocols, utilization of different mechanisms by multi-modal chemotherapy agents is the preferred course of action and are, therefore, more effective in this type of cell killing efficiency.[15,16] Typical response rates vary between 65-96% with first remission times of 6-9 months depending on the protocol and tumor location.[15] To date, the most effective multi-drug chemotherapy induction protocol for canine lymphoma appears to be ***L-CHOP*** (L-asparginase, cyclophosphamide, vincristine, prednisone and adriamycin). For multicentric lymphoma, this protocol has a 90% remission rate, and 12 month survival is generally achieved, with 25% of patients living past 2 years. The University of ***Wisconsin*** protocol utilizing vincristine, l-asparginase, prednisone, cyclophosphamide, and doxorubicin[14] displays an 84% complete remission rate, 91% partial remission rate, and 12 plus month average survival time is universally achieved with this protocol in cases of systemic lymphoma. The major difference is that induction time in the Wisconsin protocol is 6 months.[14,15] Inclusion of doxorubicin in the protocol dramatically increases first remission and survival times.[16] The ***ACOPA*** (L-asparginase, cyclophosphamide, vincristine, prednisone, doxorubicin) protocols developed by Tufts University alters the Wisconsin scheduling of doxorubicin and asparginase yielding slightly inferior results.[14] The ***CHOP*** (cyclophosphamide, doxorubicin, vincristine, prednisone, sulfa-trimethoprim) protocol is known for its low risk of relapse in dogs with 74% complete remission and 15% partial remission rates.[17] The ***COPLA*** protocol, an independent variation of ACOPA developed by the University of Illinois, also yields survival times in the 11-12 month range but has a lower adverse rate of side effects (15%).[14] Hahn et al. reports a median survival time of 123 days with remission in 69% of dogs using the traditional **COP** (cyclophosphamide, oncovin (vincistine),prednisone) protocol. However, the U. of Wisconsin studied 55 dogs utilizing vincristine, L-asparaginase, chlorambucil, methotrexate and doxorubicin continued for 3 years or until relapse. The overall response rate was 91%, median remission of 252 days, and median survival time (mst) of 357 days with minimal side effects due to toxicity; 43% were still in remission at 1 year, 25% at 2 years. A similar protocol with PEG-L-asparaginase revealed mst of 319-356d with 10% total cure rate. Doxorubicin presents the best single agent chemotherapeutic selection with 60-96% achieving positive response. Prednisone as a single agent has a fairly abbreviated remission rate but may palliate clinical signs for a short period of signs. Overall, first remission average ranges from 6-9 months. Second remissions are usually shorter and overall average survival ranges between 10-12 months.

Once the patient is out of remission, **rescue therapy** has historically entailed the use of asparginase, doxorubicin, combination of doxorubicin and dacarbazine, or ifosfamide. All of these rescue protocols carry significant side effects but are usually capable of inducing short-lived remissions.[14] Most rescue protocols result in 30-50% response rates with second remission durations of only 1-5 months.[8] As a single agent, ***L-Asparginase*** can yield good remission results, however dogs are at risk of developing hypersensitivity to this agent after multiple exposures, and should always be pre-treated with injectable diphenhydramine (2 mg/kg IM). ***CCNU*** (70 mg/m^2) given orally once every 4 weeks can also display good remission results in some patients, however this drug is extremely myelosuppressive, and CBC needs to be evaluated at 7 and 28 days post treatment. In addition, prophylactic use of antibiotics while on CCNU is recommended should the severe leukopenia develop. CCNU is also hepatotoxic, and ALT needs to be monitored closely. Patients that display elevations in ALT of 3 fold (when

starting from a normal baseline) or 2 fold (when starting from an elevated baseline) should NOT receive treatment. The ***MOPP*** (mechlorethamine, vincristine, procarbazine, and prednisone) protocol from human lymphoma trials has been investigated and was applied in a retrospective study.[8] This protocol gave 65% of rescue patients partial or complete remission for 60 or more days (range 0-763 days).[8]

Novel treatments for lymphoma

Promising immunotherapy protocols are being developed targeting CD20 and IL-2R on B cells in human trials but have yet to be developed for canine lymphoma.[14] University of Pennsylvania is currently investigating an immunotherapy trial (autologous vaccine trial) in dogs diagnosed with multicentric lymphoma. Dogs with prior treatment of steroids or chemotherapy are not eligible.

Radiation therapy has been used in some protocols for lymphoma – using half body radiation in the maintenance phase after induction with chemotherapy. Williams et al (Williams LE et al. J Vet Intern Med 2004; 18:703) reported on a group of 52 dogs with 11 weeks of chemotherapy (prednisone, L-asparaginase, vincristine, cyclophosphamide and doxorubicin) with half body radiation (cranial and caudal half body done 3 weeks apart). Median remission was 486 days and the protocol was tolerated well.

Bone marrow transplantation is now available at North Carolina State University as the country's first bone marrow transplant unit for dogs. Eligible dogs are those in remission following a combination chemotherapy protocol. Dogs are treated with high dose chemotherapy to kill remaining neoplastic cells, followed by G-CSF administration to stimulate bone marrow stem cells. Leukapheresis is used to harvest peripheral stem cells/ mononuclear cells. The dog is then treated with almost lethal doses of whole body radiation followed by transplantation with harvested stem cells to allow for bone marrow recovery. The role pf bone marrow transplantation is still to be determined with the hope of increasing the chance of possible cure as can occur in human medicine (Williams L. What's new in the treatment of Cancer in Small Animals ACVIM Proceedings 2010).

Flow cytometry can be informative as part of the work up to determine the cell type (B cell vs T cell and receptor subtype) which may allow us to improve prognostication. Consultation and referral to your local oncologist is advised to determine which protocol is best for the individual patient.

This information has been obtained from ACVIM 2001-2011.

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