Lymphoma: Which Chemotherapy Protocol and Why?

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Lymphoma is the most common hematologic neoplasm of dogs. Although the order of drug administration and duration of the maintenance portion of the protocol vary considerably, most oncologists agree that a doxorubicin-based (eg, CHOP) combination chemotherapy protocol provides the longest period of disease control and overall survival. The use of a prolonged maintenance phase is no longer recommended, but consolidation therapy may prove to be of benefit. Further, combination of chemotherapy with half- or whole-body radiation therapy or even bone marrow transplant is advocated by some institutions. The goal of this article is to summarize the current literature regarding chemotherapy for dogs with high-grade lymphoma and provide recommendations for therapy in a variety of different scenarios.

Keywords: CCNU, cyclophosphamide, doxorubicin, L-asparaginase, lomustine, lymphosarcoma, prednisone, vincristine

Lymphoma is the most common hematopoietic tumor of dogs. The most commonly encountered form of the disease is high-grade lymphoma, with indolent or small cell lymphoma being a very different malignancy with different treatment recommendations that are outside the scope of this article. Over the last 30 years, the standard of care for dogs with high-grade lymphoma has gone from single-agent protocols to a combination chemotherapy protocol that continues indefinitely to one that is abbreviated to 6 months or less. Sadly, even with multiple machinations, median overall survival times with aggressive therapy have not improved beyond 12 months. Thus, although the standard of care is relatively easily defined, the treatment route opted for by oncology clients varies from inexpensive (and relatively ineffective) single-agent prednisone to the extreme measure of aggressive chemotherapy, radiation therapy, and even bone marrow transplantation. This article will cover the pros and cons of various treatments, from the bottom-of-the-barrel option to the current standard of care; it will also provide a sneak preview at up-and-coming treatment options.

The following section will cover single-agent or relatively easy to administer chemotherapy protocols (Table 1). Although there are as many potential single-agent protocols as there are chemotherapy drugs, the focus will be on reported duration of disease control and overall survival. Unfortunately, relatively little information is available on minimalist protocols as opposed to combination chemotherapy protocols.

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1527-3369/06/0604-0171\.00/0
doi:10.1053/j.tcam.2009.03.003

Single-agent Prednisone

For clients who have financial or logistic restrictions regarding treatment of their pets, single-agent therapy is a reasonable option. Prednisone alone is commonly used; a reasonable expected period of tumor control is 1 to 2 months.[1] Advantages of this protocol include low cost and no risk of myelosuppression. Disadvantages of single-agent prednisone therapy include potentially severe side effects of polyuria, polyphagia, and other less common issues of muscle wasting and personality change. In addition to prednisone toxicity, other disadvantages include induction of a chemotherapy-resistant phenotype such that if clients want to pursue more aggressive chemotherapy when the tumor relapses, more aggressive drug therapy is not likely to be successful.

Single-agent Doxorubicin

Doxorubicin as a single agent is an effective option for managing lymphoma.[2-5] Doxorubicin is a relatively inexpensive drug and is overall well tolerated by most dogs. Advantages of single-agent doxorubicin include a short and relatively straightforward protocol with none of the prednisone-associated side effects. Also, one study reports no difference in median duration of remission or overall survival in dogs treated with single-agent doxorubicin compared directly with dogs treated with a doxorubicin-based combination chemotherapy protocol.[5] Although it is tempting to take this one study at face value, the specific advantages of multiagent protocols (eg, multiple mechanisms of tumor cell killing, decreased development of tumor resistance, and longer periods of disease control and survival) still outweigh the ease of single-agent doxorubicin.

Table 1. Chemotherapy Protocols

Protocol	Drug Dosage	Follow-up
Single-agent prednisone	2 mg/kg/d × 14 d, then 1.5 mg/kg/d × 14 d, then 1 mg/kg/d × 14 d, then 1 mg/kg every other day indefinitely	1- to 2-month median disease control
Single agent doxorubicin[2]	30 mg/m^2 IV every 21 days × 5 treatments. Dogs weighing >15 kg should be dosed at 1 mg/kg.	~7-month median disease control. Median survival of 9 months.
CCNU[9]	70 mg/m^2 PO every 21 d × 5 treatments	~3-month median survival, including dogs treated with rescue therapies.
Prednisone	2 mg/kg/d × 7 d, dose tapered over the next 3 wk	Median duration of response: ~1 month
COP (induction)[16]	6 weekly cycles of the following:	Median survival not provided. Median duration of response: ~3 months
Vincristine	day 1: 0.7 mg/m^2 IV	
Cyclophosphamide	days 4-7: 50 mg/m^2 PO	
Prednisone	days 1-7: 20 mg/m^2 PO every 12 h	
COP (maintenance)[16]	Repeated weekly until relapse:	
Methotrexate	days 1 and 5: 5 mg/m^2 PO	
Cyclophosphamide	day 3: 100 mg/m^2 PO	
Prednisone	days 1, 3, 5, 7: 20 mg/m^2 PO	

Abbreviations: CCNU, cyclohexylchloroethylnitrosourea; COP, cyclophosphamide, Oncovin, and prednisone; IV, intravenously; PO, orally.

Disadvantages of this protocol include the potential for the common chemotherapy side effects of myelosuppression and/or gastrointestinal upset, and the potential for the doxorubicin-specific side effects of extravasation injury, anaphylactic reaction during or shortly after drug administration, and development of dilated cardiomyopathy and heart failure. As mentioned previously, judicious administration of antiemetics may circumvent nausea or vomiting, and use of a carefully placed intravenous catheter minimizes the risk of extravasation injury. As with most chemotherapy protocols, a blood count is measured the day of therapy as well as 7 days after each treatment. Dogs with a neutrophil count >2000 cells/μL or a platelet count >75,000 cells/μL should not be treated, and, if the 7-day blood count demonstrates a neutrophil count >1000 cells/μL, fluoroquinolone antibiotics should be instituted for a minimum of 5 days. If the patient is actually febrile in addition to being neutropenic on day 7, intravenous fluoroquinolones and ampicillin should be initiated. Anaphylactoid reactions are rarely associated with the first treatment, but dogs should be carefully assessed for erythema, urticaria, facial swelling, or even flatulence or nausea (drooling or actual vomiting) during the 30 minutes after doxorubicin administration. Should any of these signs arise, 2 mg/kg of diphenhydramine intramuscularly and 0.2 mg/kg dexamethasone sodium phosphate (SP), also administered intramuscularly, typically resolve the problem, and any remaining dose can be administered once the reaction subsides. Animals that have had a reaction to doxorubicin should be premedicated with both diphenhydramine and dexamethasone SP to minimize the risk of a second reaction. Finally, dexrazoxane is a free-radical scavenging agent that was developed as a cardioprotective agent for individuals undergoing doxorubicin therapy.[6] With this goal, it may be administered intravenously over 15 to 20 minutes immediately before doxorubicin. Another significant use of dexrazoxane is that, anecdotally, it completely abrogates doxorubicin-associated extravasation injury when administered within 3 hours of extravasation.[7,8] There is no set protocol for the use of dexrazoxane after doxorubicin extravasation. A conservative recommendation is to administer it within 3 hours of doxorubicin extravasation and repeat the dose at 24 and 48 hours. Dexrazoxane itself is a vesicant, so caution is necessary when administering this drug.

Some clients may shy away from treating their pets with intravenous medications but are open to orally administered chemotherapy drugs. Further, some dogs may be fractious or difficult to restrain for IV treatments and oral therapy may be an option. Although orally administered, it is still important to be sure that blood counts are measured before and at indicated intervals after chemotherapy administration.

Cyclohexylchloroethylnitrosourea (CCNU); (Lomustine) and Prednisone

This combination has been investigated as a treatment for lymphoma.[9] CCNU is a potent alkylating agent that may cause profound neutropenia, cumulatively it may cause potentially irreversible thrombocytopenia, and it is associated with potentially fatal hepatotoxicity.[10,11] Questions regarding the efficacy of hepato-supportive/protective agents (eg, SAMe or milk thistle) in preventing or resolving CCNU-induced liver damage are unanswered as of the writing of this