# Lymphoma: Advances in Treatment

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**Treatment and prognosis – Dogs**

**Chemotherapy**

Is the mainstay of treatment for LSA. A large number of single-agent and multi-agent chemotherapy protocols have been investigated over the last 20 years. However, one optimal chemotherapy protocol has not been identified which can integrate positive outcome, toxicity and cost. In general, combination chemotherapy is considered more efficacious than single-agent chemotherapy.

**Corticosteroids**

Alone have been shown to induce at least partial remission in many dogs with LSA by their direct cytotoxic effect on the tumor cells. In addition, dogs that are systemically ill will often show improvements in appetite, activity and attitude while receiving steroids. Finally, steroids may reduce the magnitude of hypercalcaemia, if present. Oral corticosteroids (most commonly prednisone at 2 mg/kg/day initially, then tapered over time to 0.5-1 mg/kg/day) are an excellent treatment option for some owners if chemotherapy is declined. However, it is important that owners understand the ramifications of utilizing prednisone as a single agent before initiating treatment. I will commonly inform owners that "Prednisone is a one-way street". While most dogs and cats will experience significant short-term improvement, the duration of that improvement is typically on the order of only 1-2 months, and prednisone appears to be a powerful inducer of chemotherapy resistance. In other words, multi-agent chemotherapy is much less likely to be efficacious if a patient has come out of remission after treatment with prednisone alone.

A relatively simple, non-toxic and inexpensive chemotherapy protocol with intermediate efficacy is the COP (CTX/Vincristine/Prednisone) protocol. Prednisone is administered orally as above, cyclophosphamide is administered either orally or injectably at 200 mg/m2 every 3 weeks, and vincristine is injected weekly for 4 weeks, then every 3 weeks thereafter. Response rates of approximately 75% can be achieved, and the median survival times are in the range of 6-8 months in most reports. Another protocol with similar efficacy is single-agent doxorubicin (DOX). This has become more affordable for many clients since DOX has become available in a generic form, and has the advantage of requiring only one injection every three weeks. In addition, if a side effect is encountered the drug responsible is easy to identify. Two unique effects of DOX are its potential for cumulative cardiac toxicity in dogs and cumulative nephrotoxicity in cats, and its potential to cause severe skin necrosis if extravasated.

Generally, the most successful chemotherapy protocols have been multiagent protocols that include doxorubicin. A protocol of this type (one of many published protocols), referred to here as LA-CHOP, is employed at many institutions. (It has also been referred to in publications as the UW-Madison protocol, UW-25, or L-ASP-VCAM.) This treatment utilizes sequential injections of vincristine, CTX, and DOX, combined with daily oral prednisone for the first 4 weeks (See Table 2).

Complete response rates are 85-90% with these protocols, and median survival times are approximately 12 months, with 20-25% of dogs living longer than 2 years. Despite the improvements made in recent years in extending disease-free interval and survival time in dogs with LSA, all but 5% of patients will eventually relapse.

**Table 2: LA-CHOP (UW-Madison) Protocol for Canine Lymphoma**

| | |
|---|---|
| Week 1: Vincristine 0.7 mg/m$^2$ IV | Week 9: Doxorubicin 30 mg/m$^2$ IV |
| Prednisone 2 mg/kg PO QD | |
| | Week 11: Vincristine 0.7 mg/m$^2$ IV |
| Week 2: *Cyclophosphamide 250 mg/m$^2$ IV | |
| Prednisone 1.5 mg/kg PO QD | Week 13: Cyclophosphamide 250 mg/m$^2$ IV |
| Week 3: Vincristine 0.7 mg/m$^2$ IV | Week 15: Vincristine 0.7 mg/m$^2$ IV |
| Prednisone 1 mg/kg PO QD | |
| | Week 17: Doxorubicin 30 mg/m$^2$ IV |
| Week 4: Doxorubicin 30 mg/m$^2$ IV | |
| Prednisone 0.5 mg/kg PO QD | Week 19: Vincristine 0.7 mg/m$^2$ IV |
| Week 6: Vincristine 0.7 mg/m$^2$ IV | |
| Prednisone: *Discontinue* | Week 21: Cyclophosphamide 250 mg/m$^2$ IV |
| Week 7: Cyclophosphamide 250 mg/m$^2$ IV | Week 23: Vincristine 0.7 mg/m$^2$ IV |
| Week 8: Vincristine 0.7 mg/m$^2$ IV | Week 25: Doxorubicin 30 mg/m$^2$ IV |

* 1 mg/kg furosemide is given concurrently with each cyclophosphamide injection to diminish the occurrence of sterile hemorrhagic cystitis

Current versions of this protocol generally suspend all therapy following the 25th week: monthly rechecks are appropriate following completion to assess remission status. This is typically performed simply through a thorough physical examination for those dogs presenting initially with peripheral lymphadenopathy: those dogs whose initial lymphoma presentation was solely internal may require serial imaging in order to assess remission status.

**Maintenance *vs.* No maintenance**

One of the debates among veterinary oncologists centers around the utility of "extended maintenance" chemotherapy for dogs with LSA. In human medicine, treatment is rarely continued for longer than 6 to 10 months, and randomized trials have not demonstrated significant survival advantage for patients receiving extended maintenance chemotherapy. However, the dosages of chemotherapeutic agents that dogs with LSA can tolerate are less than half of what a human would receive of the same agents. We previously investigated the effect of discontinuing treatment after 25 weeks of standard-dose chemotherapy. Analysis of a cohort of 50 dogs treated with this protocol showed no statistical difference in survival time or disease-free interval when compared with dogs receiving a similar protocol including extended maintenance chemotherapy.

**Asparaginase *vs.* No asparaginase**

Older publications routinely include a single injection of asparaginase at the beginning of multi-agent treatment. Recently, 2 studies have demonstrated no improvement in any measure of outcome in dogs receiving asparaginase. For this reason, the author chooses to omit asparaginase from initial treatment and save it for use as a potential therapy at relapse.

**Oral *vs.* Intravenous cyclophosphamide**

Although all of the statistics generated regarding the efficacy of multi-agent lymphoma chemotherapy protocols such as the UW-Madison protocol have utilized injectable cyclophosphamide, many clinicians substitute oral cyclophosphamide at the same dose. Until recently it was not clear whether this is as efficacious, owing to cyclophosphamide's unknown oral bioavailability in dogs. Investigators at CSU have recently performed a pharmacokinetic analysis comparing oral versus injectable cyclophosphamide in dogs with lymphoma, and preliminary results indicate that, while there is a significant difference in concentrations of the parent drug, the active metabolite of cyclophosphamide is quite similar between the 2 routes of administration, suggesting probable equal efficacy. One remaining advantage to injectable cyclophosphamide is that the appropriate dose can be administered with greater exactness that can be attained with tablets.

**Is there an all-oral chemotherapy protocol that is effective for canine lymphoma?**

Many owners may be uncomfortable with the idea of injectable chemotherapy but may be more comfortable with the concept of oral chemotherapy pills. While owner education regarding the excellent tolerability of most injectable chemotherapy, and the potential for side effects even with oral medications, may help to change some owners' minds, there remains a subset of owners for whom an oral chemotherapy protocol is the only acceptable choice.

Oral chemotherapy can be efficacious for 1 very specific form of canine lymphoma: cutaneous T cell lymphoma in dogs (lomustine +/- prednisone); approximately 85% of dogs with this form of lymphoma will have at least a partial response to lomustine, although the majority of the responses are incomplete and the median response duration is only approximately 3 months. Anecdotally, dogs diagnosed with low-grade or indolent lymphomas may respond well to a conservative oral protocol such as prednisone and chlorambucil (see below regarding treatment of feline lymphoma). However, for the majority of intermediate- or high-grade multicentric lymphomas in dogs, no efficacious oral protocol as been identified. One recent study evaluated the efficacy of prednisone and lomustine as first-line therapy for canine multicentric lymphoma and found it to be no better than what has been reported with prednisone alone.

**Radiation therapy**

Since LSA is considered a systemic disease in most circumstances, radiation therapy (RT) is not used commonly. One exception is in cases of feline nasal LSA, which is often solitary at presentation. In this disease, RT can be very efficacious. LSA can be very sensitive to RT, and thus is can be useful as a palliative treatment in animals with clinical signs related to lymphoma at a specific site (e.g. pleural effusion from mediastinal disease). Several studies have been published recently evaluating the outcomes of dogs treated with chemotherapy followed by half-body radiation therapy, and some studies have suggested possible improvement over patients treated with chemotherapy alone. Definitive evidence of improvement in outcome is lacking.

**Bone marrow transplant**

One treatment modality which is commonly employed in the treatment of some forms of human lymphoma and leukemia is high-dose chemotherapy and/or whole-body radiation therapy followed by autologous stem-cell or bone marrow transplant to "rescue" the patient from fatal myelosuppression. A combination chemotherapy protocol incorporating high-dose cyclophosphamide and autologous bone marrow rescue has been evaluated in one pilot study in dogs, with encouraging preliminary results.

North Carolina State University currently has an active stem cell transplant program for dogs with lymphoma. This involves the use of leukapheresis, which harvests hematopoietic stem cells from the peripheral blood. Leukapheresis is used in conjunction with granulocyte-macrophage colony-stimulating factor to mobilize stem cells from the bone marrow into the peripheral circulation. The harvested stem cells are then reintroduced after total body irradiation is used to kill residual cancer cells remaining following induction of remission with traditional chemotherapy. Data regarding the efficacy of this form of therapy are currently unavailable.

**Treatment and prognosis – Cats**

The basic tenets of treatment for feline LSA are very similar to canine. One important difference, however, is that single-agent doxorubicin appears to have less activity in feline LSA. Even with injectable multiagent chemotherapy, response and survival rates are lower in cats than in dogs, with approximately 70% of cats achieving a complete response, and median survival times in the 6-8 month range, even with aggressive therapy. However, approximately 30% of cats may do well for a very long time, with survival times exceeding 2 years.

Recent reports suggest that cats with low-grade gastrointestinal LSA may respond favorably and enjoy median survival times in the 18-month range when a protocol employing oral chlorambucil (15 mg/m2 PO daily for four days, repeated every 3 weeks, or 20 mg/m2 PO every 2 weeks) and prednisone is employed. Importantly, this designation can only be made histologically – if a cytologic diagnosis of feline lymphoma is made, we feel it is obligatory to assume that the disease is intermediate or high-grade and treat accordingly.

The most important prognostic factors for feline LSA are early clinical stage, clinical substage (the vast majority of cats, unlike dogs, are substage "b"), incorporation of doxorubicin into the chemotherapy protocol, and FeLV status.

There are no studies in the literature investigating the necessity for maintenance chemotherapy in feline LSA. In the Author's practice, this knowledge gap is discussed with owners and a choice is provided between discontinuation after 6 months of treatment and continued maintenance chemotherapy. Similarly, the necessity/utility of asparaginase when utilized within a CHOP-type protocol has not been assessed in cats. For this reason, it is typically still administered at the first treatment in the Author's practice.

**Rescue**

When remission is lost (either after an interval with no chemotherapy or after treatment at 2 or 3 week intervals), a large number of patients may experience a second remission simply by returning to the "top of the protocol", i.e. switching back to weekly treatments and re-initiating prednisone therapy. However, a rule of thumb is that the second remission is likely to be about half as long as the first. After a period of time, the tumor cells will acquire resistance to the initial drugs utilized, and "rescue" or "salvage" chemotherapy drugs or protocols can be considered. A summary of rescue agents/protocols that have been systematically evaluated in dogs is shown in Table 3.

**Table 3: Published Rescue Protocols for Canine Lymphoma**

| | %CR | %PR | ORR | MRD | N | Reference |
|---|---|---|---|---|---|---|
| GS-9219/VDC-1101 | 48 | 14 | 62 | 99 | 17 | Vail 2009 |
| Mitoxantrone | 26-47 | 0-21 | 21-47 | 84-126 | 68 | Moore 1994, Lucroy 1998, Ogilvie 1991 |
| Actinomycin D | 0-44 | 0-33 | 0-77 | 0-42 | 34 | Moore 1994, Hammer 1994 |
| Etoposide | 8 | 8 | 16 | NR | 13 | Hohenhaus 1990 |
| CCNU | 7 | 20 | 27 | 86 | 82 | Moore 1999 |
| PEG-Asparaginase | 12 | 38 | 50 | 30 | 8 | MacEwen 1994 |
| Ifosfamide | 0 | 2.6 | 2.6 | 112 | 39 | Rassnick 2000 |
| DTIC | 2.3 | 30 | 35 | 43 | 40 | Greissmayr 2009 |
| MOPP | 31 | 34 | 65 | 63/47 | 117 | Rassnick 2002 |
| DOX/DTIC | 47 | 27 | 74 | NR | 15 | Van Vechten 1990 |
| DMAC | 44 | 28 | 72 | 61 | 54 | Alvarez 2006 |
| BOPP | 28 | 21 | 50 | 130/140 | 14 | LeBlanc 2006 |
| LOPP | 27-36 | 24-25 | 52-61 | 98-112 | 44 | LeBlanc 2006, Fahey 2011 |
| ASP/CCNU | 52-65 | 23-35 | 87-88 | 63-70 | 79 | Saba 2007, Saba 2009 |
| TMZ-Anthracycline | 50 | 22 | 72 | 40 | 18 | Dervisis 2007 |
| DTIC - Anthracycline | 62 | 9 | 71 | 50 | 35 | Dervisis 2007 |
| CCNU-DTIC | 23 | 12 | 35 | 83/25 | 57 | Flory 2008 |

%CR: Percent complete response. %PR: Percent partial response. ORR: Overall response rate. MRD: Median response duration.
CCNU: Lomustine. DTIC: Dacarbazine.
MOPP: Mechlorethamine / Vincristine / Procarbazine / Prednisone
DOX: Doxorubicin
DMAC: Dexamethasone / Melphalan / Actinomycin D / Cytosine arabinoside
BOPP: BCNU / Vincristine / Procarbazine / Prednisone
LOPP: Lomustine / Vincristine / Procarbazine / Prednisone
TMZ: Temozolomide

The take-home message is that while there are many different drugs that can be utilized in this setting, no one agent or protocol is uniformly superior over the others in terms of response rate and duration. As a group, response rates tend to be higher for multi-agent protocols than for single-agent protocols, although the average response duration remains in the 2-3 month range for both types of protocol. Sometimes, attaining a second or third remission can be a matter of trial and error, until an efficacious drug or protocol is found.

Unfortunately, virtually no information is available regarding the efficacy of rescue therapy for feline lymphoma. Generally, similar drugs and protocols are attempted in cats.

In summary, although LSA is a disease that can rarely be cured, it can be managed effectively in the majority of cases. Therapy is typically very well tolerated, and patients experience an excellent quality of life. Significant improvements have been made in recent years with regard to the treatment of this common disease, and we are hopeful that the coming years will bring equally great improvements.

**References**

Cotter SM (1983). Treatment of lymphoma and leukemia with cyclophosphamide, vincristine and prednisone: 1. Treatment of dogs. JAAHA Vol. 19: 159-165.

Frimberger AE, Moore AS, Rassnick KM, et al (2006). A combination chemotherapy protocol with dose intensification and autologous bone marrow transplant (VELCAP-HDC) for canine lymphoma. JVIM 20: 355-364.

Garrett LD, Thamm DH, Chun R, et al (2002). Evaluation of a six-month chemotherapy protocol with no maintenance therapy for dogs with lymphoma. JVIM Vol. 16: 704-709.

Kristal O, Lana SE, Ogilvie GK, et al (2001). Single-agent chemotherapy with doxorubicin for feline lymphoma: a retrospective study of 19 cases (1994-1997). JVIM Vol. 15: 125-130.

Lingard AE, Briscoe K, Beatty JA, et al (2009). Low-grade alimentary lymphoma: clinicopathological findings and response to treatment in 17 cases. J Feline Med Surg Vol. 11: 692-700.

Lurie DM, Gordon IK, Théon AP, et al (2009). Sequential low-dose rate half-body irradiation and chemotherapy for the treatment of canine multicentric lymphoma. JVIM 23: 1064-1070.

MacDonald VS, Thamm DH, et al. Does L-asparaginase influence efficacy or toxicity when added to a standard CHOP protocol for dogs with lymphoma? JVIM 2005; 19(5): 732-736.

Postorino NC, Susaneck SJ, Withrow SJ, Macy DW (1989). Single agent therapy with adriamycin for canine lymphosarcoma. JAAHA Vol. 25: 221-225.

Risbon RE, de Lorimier LP, Skorupski K, et al (2006). Response of canine cutaneous epitheliotropic lymphoma to lomustine (CCNU): a retrospective study of 46 cases (1999-2004). JVIM 20: 1389-1397.

Sauerbrey ML, Mullins MN, Bannink EO, et al (2007). Lomustine and prednisone as a first-line treatment for dogs with multicentric lymphoma: 17 cases (2004-2005). JAVMA 230: 1866-1869.

Teske E, van Straten G, van Noort R, Rutteman GR (2002). Chemotherapy with cyclophosphamide, vincristine, and prednisolone (COP) in cats with malignant lymphoma: new results with an old protocol. J Vet Intern Med Vol. 16: 179-186.

Vail DM, Thamm DH. Hematopoietic tumors. In: Ettinger S, Feldman E (eds), Textbook of Veterinary Internal Medicine, 6th Ed. Philadelphia: Saunders, 2005. pp. 732-746.

Vail DM, Young KM. Canine lymphoma and lymphoid leukemia. In: Withrow SJ and Vail DM, eds. Small Animal Clinical Oncology (4th Ed). Philadelphia: Saunders, 2007. pp. 699-733.

Vail DM. Feline lymphoma and leukemia. In: Withrow SJ and Vail DM, eds. Small Animal Clinical Oncology (4th Ed). Philadelphia: Saunders, 2007. pp. 733-756.