# BEYOND PREDNISONE: CANINE LYMPHOMA UPDATES 2024

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**WHAT IS IT:**
Lymphoma is a common canine cancer and is a systemic disease that requires chemotherapy in almost all cases. It is a collection of cancers arising from the malignant transformation of lymphocytes. Lymphoma is one of the most common canine cancers, accounting for 7-24% of all canine tumors and 85% of hematopoietic tumors. Dogs of any age, gender, and breed can be affected with lymphoma. Affected dogs are typically middle aged to older dog. Multicentric (peripheral lymph node) is the most common form, accounting for 80% of lymphomas.

**WHAT I SAY TO OWNERS:**
Lymphoma is a cancer of one the white blood cells called the lymphocytes. These cells accumulate on the dog's lymph nodes, also called lymph glands – making the connection with Strep throat and swollen glands. Lymphoma is a treatable disease, and treated dogs live significantly longer, and treatment is very well tolerated.

**CLINICAL APPEARANCE:**
The most common complaint is generalized lymphadenomegaly. Owners commonly report that lymph node size is rapidly increasing – over days to one to 3 weeks. Most dogs are typically asymptomatic and appear healthy in the early stages. Twenty to 40% are clinical (substage b) with anorexia, lethargy, fever, vomiting, diarrhea weight loss, melena.

**DIAGNOSTICS:** Early accurate diagnostics and careful staging are keys to proper clinical decision-making. The minimum tests required for treatment are cytological confirmation (lymph node or affected organ), CBC, chemistry panel and urinalysis. The next diagnostic I encourage owners to submit is phenotyping to determine B vs T-cell subtype. Phenotype is the best independent prognostic factor; prognosis is worse with T-cell than B-cell. Phenotyping is typically determined flow cytometry or PARR from lymph node aspirates, or with immunocytochemistry from aspirates, or immunohistochemistry from biopsy. If there is a peripheral lymphocytosis on CBC (stage V), flow cytometry can be submitted on a whole blood sample to determine phenotype.

**To stage or not to stage?** Complete lymphoma staging includes lymph node cytological confirmation, CBC, chemistry panel, urinalysis, lymph node histology, urinalysis, thoracic radiographs, abdominal ultrasound, bone marrow cytology and phenotyping. These tests are useful and informative, as they provide prognostic factors and a baseline for a patient's response. These tests can also help determine if there is a large tumor burden and risk for acute tumor lysis syndrome with induction chemotherapy. Still, we must consider the owner's financial issues. While it is ideal to perform all the tests, we can also consider each test on a case-by-case basis and help the owner make an educated decision. We can treat without but review pros and cons with the owner and let owner make educated decision and maybe choose more important tests for that dog.

**PROGNOSTIC FACTORS:** There are many prognostic factors, but the more significant predictors include:

- Phenotype: Phenotype is the best independent prognostic factor; prognosis is worse with T-cell than B-cell. 60-80% are B-cell and this is associated with higher rated of CR, longer remission rates, and increased survival time (ST). Most high-grade lymphoma are B-cell.
- Substage: clinically healthy dogs tend to do better than sick dogs
- Histologic grade: high grade has better complete remission (CR) rate than low grade, but low grade often has comparable survival times with less intensive chemotherapy protocols.
- Complete remission: dogs that achieve a complete remission do better than those that achieve a partial remission or stable disease. If a CR is not achieved, a protocol change should be considered.
- Administration of prednisone prior to chemotherapy is a negative predictor and may decrease response rates to other agents
- Higher stage dogs (stage IV and V) tend to do worse than lower stage (I to III)
- Hypercalcemia: negative predictor due to association with T-cell phenotype
- Mediastinal mass: negative predictor due to association with T-cell phenotype

Remember, prognostic factors cannot predict an individual's response, and lymphoma is typically treatable and rewarding to treat for the patient, owner, and veterinarian.

**TREATMENT**
Dogs treated with chemotherapy live significantly longer than untreated dogs, and chemotherapy is generally well-tolerated in most dogs. Only a minority develops significant toxicity. Combination chemotherapy provides improved

remission rates and duration in comparison to single agent protocols. Multi-agent CHOP protocols are the most successful, with complete remission rates of > 80% and remission durations of typically 6-11 months. Median survival times (MST) are 1 year when followed by rescue protocol, and 25% of dogs are long term survivors > 2 years. There are numerous CHOP protocols that vary in drug dosages, scheduling, and dose intensity. The UW-Madison protocol is often recommended for owners choosing a combination protocol for its high complete remission rates, higher remission duration, and lower morbidity and mortality rates. Commonly used UW protocols are the 25 and 19-week protocols. Multi-agent CHOP protocols typically combine vincristine, cyclophosphamide, doxorubicin, and prednisone. Recent studies suggest the inclusion of l-asparaginase at induction does not significantly impact remission duration or survival times and can be omitted and saved for the rescue protocol. Additionally, recent studies suggest there is no survival benefit of maintenance phase. Most current protocols are discontinuous without a chronic maintenance phase and provide comparable remission durations. It is thought the period without chemotherapy may lead to greater responsiveness at relapse by lack of selection of resistant cells.

For some clients, **alternative protocols** are elected over the multi-agent CHOP protocol due to budget, toxicity profile on par with clients' willingness to assume risks of chemotherapy, and schedule and time commitment. In general response rates are lower and survival times are shorter, but they are less expensive and require less visits. In some cases, it is to avoid drugs that target a patient's weakness or concurrent illness. For example, Lomustine is avoided with liver dysfunction and doxorubicin can cause cardiotoxicity so should be used cautiously in dogs with some pre-existing cardiac disease. Alternative chemotherapy protocols include COP (vincristine, cyclophosphamide, and prednisone), single agent doxorubicin or Tanovea for B-cell lymphoma, alternating doxorubicin/Tanovea, and single agent Lomustine for T-cell lymphoma. These protocols generally have lower response rates ranging from 50-80% and shorter remission durations of 6 to 7 months. For B-cell lymphoma, I recommend alternating doxorubicin/Tanovea with an overall response rate of 85% and a remission rate of 6 months. A more cost-effective option would be single agent doxorubicin with a complete remission rate of 60-80% and a MST of 6-8 months (note this is different than remission rate stat for Tanovea/ doxorubicin). For T-cell lymphoma, single agent Lomustine is often recommended but response rate is low (35%) and MST of 4 months, so I will often recommend alternating/adding additional chemotherapy to improve response.

**New Therapies:**

**Tanovea**

Recently in 2021, **Tanovea** was approved by the FDA to treat canine lymphoma. It had been conditionally approved since April 2017, so we have been using it since then. TANOVEA™ (rabacfosadine) is indicated for the treatment of lymphoma in dogs and can be used as a first-line therapy and in dogs that have failed/ relapsed prior treatment. Like all chemotherapeutic agents, Tanovea should be administered under supervision of a veterinarian experienced in use of cancer and use standard measures for the safe handling of cytotoxic drugs. The drug is NOT restricted to only oncologists. It designed to preferentially target and attack cancer cells implicated in lymphoma. The drug is given via the intravenous route at 1mg/kg over 30 minutes every 3 weeks.

The effectiveness and safety of Tanovea was demonstrated in a well-controlled clinical field study involving a total of 158 dogs (120 in the Tanovea group and 38 in the placebo group), that had been diagnosed with multicentric lymphoma with at least one enlarged peripheral lymph node. The study was open to dogs of any breed, except West Highland White Terriers. West Highland White Terriers were not enrolled due to the breed's tendency to develop pulmonary fibrosis, which is a known potential side effect of Tanovea that was identified prior to conditional approval. The study found that Tanovea extended the median survival rate by 61 days and for dogs with a complete response to the drug, the median progression-free survival was extended to 168 days. The best overall response rate (BORR) was 73% (51% CR). For dogs with B-cell lymphoma, the BORR was 80% (59%). The most common side effects seen in dogs treated with Tanovea included diarrhea, decreased appetite, vomiting, lethargy, weight loss and neutropenia. The most serious adverse events included pulmonary fibrosis and dermatopathy, including infection and ulceration in some cases.

Another study looked at the use in **combination with doxorubicin** in naïve lymphoma patients, alternating for a total of 6 doses. The overall response rate was improved to 84% (68% CR, 16% PR) and a progression free interval of 6.5 months. In a new study of 52 dogs with relapsed lymphoma treated with at least one doxorubicin protocol, they evaluated **L-asparaginase given with rabacfosadine** (RAB), Dogs were treated with RAB at 1.0 mg/kg IV every 21 days for up to a total of 5 doses. L-asparaginase was administered at 400 IU/kg SQ concurrently with the first 2 treatments of RAB. The overall response rate (ORR) for all dogs was 67%, with 19 dogs (41%) achieving a complete response (CR). The median progression-free survival time (MPFS) was 63 days (range 5-428 days). Dogs experiencing a CR as their best response had an MPFS of 144 days (range 44-428 days). Adverse events were similar to previous studies evaluating single agent RAB. Failure to achieve a CR and having previously received L-ASP were negative prognostic factors on multivariate analysis. It is exciting that we have new drugs being developed, giving us more options for our patients.

Although most side effects associated with this agent are similar to those of most chemotherapeutics, two unique side effects (and one that is not unusual) occur, that clinicians need to recognize and know how to treat.

- Pulmonary fibrosis: this was recorded in a small percentage of the patients treated and the mechanism is unknown. As this was fatal in some cases, screening with thoracic films and exclusion of patients with pre-existing pulmonary issues, or particular breeds at risk of pulmonary fibrosis, is warranted.
- Dermatopathy occurred in a minority of patients and often appears along the pinna and chest. resolution of the side effects occurs once discontinuing the protocol, increasing the interval (give every 4 weeks), lower the Tanovea dose, and/or low dose steroids.
- Anorexia: The anorexia appears more prolonged than that commonly seen with other agents. I recommend being very proactive with anti-nausea medications and appetite stimulants, using them as preventatives over waiting for anorexia, nausea, and vomiting to occur. To prevent delay chemotherapy induced nausea and vomiting (CINV), I recommend being very proactive with oral nausea/anti-emetic drugs and appetite stimulants given at home in the days following chemotherapy. I always recommend oral Cerenia and Entyce for 7 days following administration, and I have found the drug to be well-tolerated.

**Laverdia-CA1**

On January 11, 2021, the US FDA conditionally approved Laverdia-CA1 (verdinexor) to treat dogs with lymphoma and is licensed to Anivive Lifesciences Inc. Laverdia-CA1 (verdinexor) is a novel orally bioavailable selective inhibitor of nuclear export (SINE) that exhibited anti-tumor activity against non-Hodgkin lymphoma in a prior phase I study. Laverdia-CA1 works to prevent certain proteins from leaving the nucleus of cancer cells, thereby allowing these proteins to control the growth and prevent the spread of cancerous cells in dogs. Laverdia-CA1 is given orally twice per week by the owner, with at least 72 hours between doses.

Verdinexor has demonstrated efficacy as a single-agent treatment for all types of canine lymphoma— B-cell, T-cell, naïve, and first relapse following either a single or multi-agent protocol. In a phase II study of 58 dogs, the clinical benefit rate across both B-cell and T-cell, naïve and relapse cases was 55%, with a median duration of benefit of 71 days (range 21-273 days). T-cell cases, traditionally more refractory to current treatment protocols than B-cell lymphoma, demonstrated clinical benefit in 71% of the dogs, whether naïve or relapse.

This data supports the use of verdinexor as a monotherapy: whether as a targeted option in lieu of palliative care, when referral and chemotherapy are not an option, or when a dog has relapse following a chemotherapy treatment protocol. For those dogs for whom referral and chemotherapy is not an option, verdinexor in combination with prednisone may provide an option that has the potential to provide clinical benefit for a period beyond that typically seen when prednisone is used alone for palliative care. Laverdia was well tolerated in all dose groups with grade 1-2 anorexia being the most common adverse event. Anorexia was responsive to symptomatic and supportive medications, including prednisone. The other most common adverse reactions were vomiting, diarrhea, weight loss, lethargy, polyuria, polydipsia, elevated liver enzymes, and thrombocytopenia.

The package insert for prescribing veterinarians includes detailed user safety information and special instructions for handling and administering the drug. Gloves tested for use with chemotherapy drugs should always be worn when handling Laverdia-CA1 and cleaning up after a dog undergoing treatment and for three days following the last treatment. This includes handling the dog's food and water bowls, as well as feces, urine, vomit, or saliva from the dog. Laverdia-CA1 also comes with a client information sheet for prescribing veterinarians to give to their clients. This sheet is written specifically for dog owners and explains how to safely handle Laverdia-CA1, how to safely clean up after a dog undergoing treatment and other important safety information. Laverdia-CA1 should be given to dogs immediately after eating, as this increases the amount of drug absorbed into the bloodstream.

Nuclear factor kappa B (NFκB) plays a role in both canine lymphoma cell proliferation and the development of resistance of those cells to glucocorticoids. Inhibition of NFκB activation has been shown to restore glucocorticoid sensitivity and synergistically suppress proliferation of canine lymphoma cell lines resistant to glucocorticoids. SINE class drugs have demonstrated the ability to suppress NFκB activity as one means of inducing tumor cell death. These factors may provide a mechanistic reason for integrating verdinexor in combination with prednisone as therapy for canine lymphoma, whether naïve or relapse. For those dogs that relapse, verdinexor provides a novel mechanism of action targeting the malignant cells and should not be subject to MDR, the mechanism by which many lymphoma cases become refractory to chemotherapy treatment.

**If chemotherapy is declined** If chemotherapy is declined, another option is single agent steroids. Typical response rates are 50% with duration of 2 to 3 months. I recommend 30mg/m2 SID for 2 weeks, then 20 mg/m2 SID if clinical response is seen. Prednisone should not be started prior to chemotherapy since it may decrease efficacy of chemotherapy started after the steroids. Pre- chemotherapy steroids use is associated with shorter remission and survival times due to induction of multi-drug resistance. If staging tests are done after prednisone is started, higher stage patients may appear to be lower stage (down-stage). Without chemotherapy the prognosis for lymphoma is poor, with MST of 1 month.

**Prednisone vs. No Prednisone**
Recent studies suggest there is no survival benefit of prednisone in a multi-agent protocol. We have certain patients when prednisone therapy maybe contraindicated, such as a dog with diabetes mellitus or nonregulated hyperadrenocorticism. Two recent randomized trials looked at dogs that received a vincristine-cyclophosphamide-doxorubicin based protocol with and without prednisone and found no difference in any measure of outcome. In my opinion, I still include prednisone in the multi-agent protocol, but I will eliminate it if there's a medical reason, or I will taper it more quickly (and discontinue if needed) if the patient is having moderate to severe side effects.

**Should Dogs with T-Cell Lymphoma be Treated Differently than Dogs with B-Cell Lymphoma?**
Phenotype is the best independent prognostic factor; prognosis is worse with T-cell than B-cell, except for low-grade/indolent subtypes. While it is known that dogs with T-cell lymphoma generally do worse when treated with CHOP based chemotherapy compared to B-cell dogs, the question remains how and if to change the protocol for dogs with high grade T-cell lymphoma. We will discuss some of the alternative protocols that are "alkylator rich", as it is possible, they may result in improved outcomes for dogs with non-indolent T-cell lymphoma.

A retrospective study was published evaluating a mechlorethamine-vincristine-procarbazine-prednisone (MOPP) based protocol in dogs with T-cell lymphoma. An overall response rate (ORR) of 98% (78% complete remission), a median progression free survival (PFS) of 189 days, and a MST of 270 days was reported. (Note a study documented a similar overall response rate, MST, and PFS with CHOP in dogs with T-cell lymphoma.
More recently, additional reports have described outcomes including LOPP (Lomustine-vincristine-procarbazine-prednisone) or VELCAP-TSC (asparaginase-vincristine-CYC-DOX-actinomycin D-procarbazine-lomustine).
In these reports, overall response rates ranged from 73% to 97% (64–90% CR), median PFS was 175 – 431 days and MST was 237 to 507 days. I have personally also modified the CHOP protocol as well to replace Lomustine for doxorubicin (unpublished), aka "CLOP".

**RELAPSE**
Relapse is the return of lymphoma in a patient that previously attained and maintained a complete remission for at least 30 days after completing treatment. At this point, a rescue therapy is recommended. When a dog relapses, I recommend reintroducing the initial CHOP protocol if it was successful, meaning the expected remission duration was achieved. For example, if a dog relapses one month after completing a CHOP protocol I will not recommend restarting front-line chemotherapy. However, if the dog was off chemotherapy for 4-5 months with a 1$^{st}$ remission of 9-10 months, I will recommend restarting the induction protocol as re-induction rates of 90% can be expected. It is important to consider there is a cumulative dose of doxorubicin, so doxorubicin is typically replaced after a total of 6 doses. When a dog no longer responds front-line chemotherapy, rescue protocols are recommended. There is decreased likelihood of response (30-50%) and shorter remission durations, typically half the length of the initial remission. Still some patients experience long-term re-inductions. Some commonly used protocols include Tanovea, single agent Lomustine, MOPP, LOPP, doxorubicin or mitoxantrone with DTIC, and Lomustine/l-asparaginase/prednisone (LAP).

**JUST IN CASE MEDICATIONS AND INFORMATION SHEET**
I recommend all patients go home on the first day of chemotherapy with Cerenia, Entyce, metronidazole or Canalevia, a probiotic, and a client information sheet. My client information sheet that walks owners through managing side effects at home can be found at on my website in the Resources section. (https://drsuecancervet.com/pet-owner-resources/). I also have videos and resources on my YouTube channel to help owners as well.

**PROGNOSIS:**
**With treatment:** Multi-agent CHOP protocols are the most successful, with complete remission rates of > 80% and remission durations of typically 6-11 months. Median survival times (MST) are 1 year when followed by rescue protocol, and 25% of dogs are long term survivors > 2 years. Alternative protocols generally have lower response rates ranging from 50-80% and shorter remission durations of 6 to 7 months. With prednisone only, typical response rates are 50% with duration of 2 to 3 months.
**Without Treatment:** 1 month

**REFERENCES:**

1. Vail DM, et al. Hematopoietic Tumors, Canine Lymphoma & Lymphoid Leukemia. In: Small Animal Clinical Oncology. 6$^{th}$ ed. St. Louis Missouri: Elsevier Saunders; 2020: 688-715.
2. Williams LE. Lymphoma, Dog (Multicentric) in Clinical Veterinary Advisor Dogs and Cats. 4$^{th}$ edition. St. Louis Missouri: Elsevier Mosby; 2020: 609-611
3. Bryan JN. Lymphoma. In Cancer Management in Small Animal Practice. Saunders 2010. 343-350

4. Thamm DH, et al. Alternating Rabacfosadine/Doxorubicin: Efficacy and Tolerability in Naïve Canine Multicentric Lymphoma. J Vet Intern Med. 2017 May;31(3):872-878.
5. Cawley JR, et al. J Vet Intern Med. 2020 Mar;34(2):882-889. doi: 10.1111/jvim.15723.
6. Weishaar KM, et al. Multicenter, randomized, double-blinded, placebo-controlled study of rabacfosadine in dogs with lymphoma. J Vet Intern Med. 2022 Jan;36(1):215-226.