APPROACH TO CANINE LYMPHOMA PART TWO: TREATMENT OPTIONS

Author : James Elliott

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James Elliott looks at medication protocols and the prognosis for dogs with lymphoma, and advises on expected survival times following chemotherapy

IN part one of this article (*VT* 40.40), the initial approach to the diagnosis and staging of canine lymphoma was described. In this concluding part, therapeutic options and prognosis will be discussed.

As detailed in part one, the majority of cases are multicentric, and systemic chemotherapy is the only appropriate therapy for these dogs. Several protocols have been studied.

Madison-Wisconsin 25-week discontinuous protocol

The Madison-Wisconsin (MW) protocol consists of using the drugs L-asparaginase, vincristine, cyclophosphamide, doxorubicin and prednisolone (a CHOP-based protocol, see Tables 1a and 1b).

Originally reported by Garrett et al, it led to a 94 per cent complete response rate, with 100 per cent of those patients achieving second remission after re-induction with the same protocol. It has no maintenance phase and, if the animal is in remission at 25 weeks, treatment is withdrawn and re-instituted when relapse occurs[1]. This may lead to greater responsiveness after loss of remission by lack of selection for resistance during the second rapid growth phase. It is well accepted that protocols without extended maintenance phases are as efficacious as those with protracted maintenance phases[1,2].

Median survival using this protocol is around 13 months. It is generally accepted that dogs benefit from doxorubicin added to their chemotherapy treatment. Studies have questioned the value of adding L-asparaginase and some oncologists prefer to “save” this drug for use at relapse[3,4]. If L-asparaginase is used, it should preferably be given intramuscularly[5].

High dose COP protocol

This consists of utilising only vincristine, cyclophosphamide and prednisolone (COP, see Table 2). This is less expensive and less time consuming than CHOP. It understandably results in a lower percentage of patients achieving remission and shorter survival times. Generally, 70 to 75 per cent of patients can be expected to attain remission for around 7.5 months[6], but a percentage of dogs do extremely well on COP, with protracted remission and survival. Some practitioners believe that doxorubicin can be instituted as a “rescue” once COP has ceased to be effective, thus resulting in similar remission/survival characteristics to using MW from the outset[7]. However, oncological principles suggest it would be most effective to use all the drugs together from the outset and, if possible, this should be followed.

Single agent doxorubicin

This consists of five or six treatments with doxorubicin (30mg/m^2 or 1mg/kg if less than 15kg) as a single agent given once every three weeks. The advantages are reduced visits, reduced number of treatments and ease of only having to worry about one drug and its associated side effects. This is effective in around 59 to 79 per cent of patients, with median survivals of around seven to nine months.

Doxorubicin can cause cardiotoxicity. Acutely, this can manifest as arrhythmias, and it is recommended that the drug be provided slowly, rather than as a bolus, over 15 to 20 minutes. ECG monitoring can be used if concern arises during the infusion, and pulse characteristics and auscultation can be intermittently performed during infusion. Chronically poor systolic dysfunction can become apparent, mimicking dilated cardiomyopathy, and this is related to the total cumulative dose. It is generally more common with doses of more than 200mg/m^2, but it can be seen at lower doses. For this reason, it is advisable to obtain a baseline echocardiogram prior to therapy, particularly in at-risk breeds. Interestingly, this toxicity has not been documented in cats, where nephrotoxicity is more of a problem.

This drug is a severe vesicant and a long, well-placed and well-secured IV catheter must always be placed. Someone must monitor the infusion constantly. It can result in tissue sloughing, requiring extensive surgery or amputation if extravasation occurs. In this instance, treatment can be attempted with iron-chelating dexrazoxane. Details can be obtained from a clinical oncologist.

Rescue

It is exceedingly rare for dogs to be “cured” with chemotherapy and never experience tumour relapse. Most relapse eventually. If the dog has finished a discontinuous protocol, this should be re-instituted and continued, if effective. If it is no longer effective, or if the dog relapses while still receiving the protocol for the first time, treatment needs to be changed.

Once the original drugs have ceased to be effective, “rescue” agents can be used to good effect. However, the tumour is usually relatively drug resistant by this point and remission times are substantially shorter than at diagnosis. Depending on the protocol, around 30 to 50 per cent of patients achieve a partial or complete remission for a number of weeks to a few months. Occasionally, a dog will have a really pleasing and durable response to these rescue agents. The author generally finds multi-agent protocols, such as dexamethasone, melphalan, actinomycin D and cytarabine (DMAC), most effective and well-tolerated, but some dogs have very good responses to single-agent lomustine (CCNU)[8,9] and other various drugs[10,11].

Owners need to be aware that once rescue is instituted, the prognosis is guarded, and they need to be prepared to acknowledge the patient’s tumour is becoming difficult to control.

Safe chemotherapy

• Handle all chemotherapy agents with care, wearing appropriate protective clothing, gloves and eyewear.

• Double check all chemotherapy doses.

• Ensure a full haematology and manual confirmatory count (or external laboratory count) is performed before the administration of every chemotherapy drug, and ensure the platelets are greater than 100×10^9/L and the neutrophils are greater than 3×10^9/L before providing a treatment.

• Ensure accurate measurements of all peripheral lymph nodes are taken and recorded prior to every dose of chemotherapy. If the disease has progressed following a particular drug, then it is ineffective and no longer useful.

• A first-stick, intravenous catheter should be placed securely every time a chemotherapy agent is provided intravenously.

• A urine sample should be checked before every cyclophosphamide treatment. If excessive protein or blood is found, further diagnostics should be performed due to the risk of cyclophosphamideinduced cystitis, which is likely to worsen with repeated administration.

• Providing no contraindications are present, 2mg/kg furosemide can be provided twice daily for two days, starting at the time of cyclophosphamide administration, to reduce the risk of cystitis.

• The owner should wear gloves while handling any waste for four days after each treatment. The exact times required are unknown in veterinary medicine, but this should be adequate for most drugs.

• A subcutaneous injection of maropitant can be provided before each doxorubicin injection to prevent nausea and vomiting, and some dogs may require tablets for several days at home.

Breeds predisposed to ivermectin toxicity, such as collietype breeds, can also be very sensitive to certain chemotherapy agents, such as vincristine and the anthracyclines. This is because they have a mutation in the gene ABCB1 that encodes p-glycoprotein, a cellular efflux pump. Defects thus disable the efflux of substances such as chemotherapy agents and result in increased toxicity[12]-[14].

Blood can be tested for the mutation in susceptible breeds and, while results are pending, the protocol can be altered so that therapy is started with a drug class not dependent on p-glycoprotein mechanisms, such as alkylating agents (for example, cyclophosphamide).

Drugs such as vincristine can still be given to these patients; however, they usually require lower doses to prevent myelosuppression and gastrointestinal toxicity. For example, a dose of 0.5mg/m^2 can be tried – as opposed to 0.7mg/m^2 of vincristine. Some dogs need even lower doses that in “normal” dogs would be seen as sub-therapeutic.

Prognosis

Generally, the outlook for a dog with multicentric, highgrade lymphoma is around a year. Some dogs can do significantly better. Alternatively, some do significantly worse and often this can be predicted from the presence of one or more negative prognostic factors (Table 3). Without therapy, most of these dogs will be dead within two months.

Dogs with the rarer, lowgrade disease can have a much better outlook. They often present with mild to moderate, slowly progressive, regional or generalised lymphadenopathy. While their disease is often inherently less chemo-responsive, their tumour is much slower to progress and can often be monitored closely for a long period with no treatment, or treated with much less aggressive chemotherapy protocols, such as chlorambucil and prednisolone alone. Discussion of these cases with a clinical oncologist is recommended prior to therapy.

Palliative care only

Dogs may be treated with prednisolone alone and some dogs will respond for about three months. It is extremely important that the owner realises this therapy will make the tumour drug resistant, and deciding at a later point that they would like to proceed with chemotherapy is likely to seriously

affect treatment outcome.

Other treatments

Rituximab (a CD20 monoclonal antibody) is a standard treatment for humans with certain types of large, diffuse B-cell lymphoma (similar to most canine cases) and has revolutionised therapy. Unfortunately, despite the fact that canine malignant lymphocytes express CD20, rituximab seems to be ineffective in dogs. In several studies, adding half-body radiation to standard chemotherapy has resulted in improved median survival times. However, some have regarded the cost and toxicity to be excessive relative to the gain in survival[15],[16].

To the author's knowledge, this treatment is not offered at any UK centres. Radiation is primarily used for treating the rare cases of localised disease, such as nasal lymphoma and epitheliotropic lymphoma (mycosis fungoides). Some institutions in the USA have used haematopoietic stem cell transplant in addition to chemotherapy with some success, but this is extremely expensive and not available in the UK. The role of bone marrow transplants in canine patients with lymphoma are currently being studied in the USA[17],[18].

Dietary n-3 (omega-3) fatty acid supplementation has been beneficial in canine patients. Metabolic parameters were improved in lymphoma patients eating an n-3-supplemented diet, and survival times and diseasefree interval were improved. Supplementation may benefit these patients, and it is generally cheap and well-tolerated, with minimal side effects[19]-[21].

Conclusion

For most dogs with lymphoma, the presentation is classical and the diagnosis is very straightforward. Most dogs respond to appropriate therapy and live for around a year with a very good quality of life.

Despite a vast amount of research into additional treatments and rescue protocols, the "12-month brick wall" in patient survival is difficult to breach.

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