



## Monitoring disease remission in canine lymphoma



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Lymphoma is one of the most common malignancies to affect dogs, accounting for around 20 % of all canine tumours and with an estimated annual incidence of 25 per 100,000 dogs. It is a disease that is variable and complex, and the different subtypes show considerable diversity in treatment response and prognosis. Monitoring for disease remission and recurrence is usually performed by palpation of peripheral lymph nodes, a subjective procedure which is only capable of detecting gross changes. Confirmation of lymphoma in cases of recurrent enlarged lymph nodes is often by cytology. However, there are now biochemical methods available that look for circulating markers of the disease and, consequently, offer greater sensitivity, detecting disease recurrence far sooner than physical examination. Veterinary oncologist Sue Ettinger discusses the SENSITEST® canine Lymphoma Blood Test, describing the value of routine testing after chemotherapy and the lessons that can be learnt from further research studies into its practical application.

### Introduction

Lymphoma, a cancer of the lymph nodes and lymphatic system, is one of the most frequently detected malignancies affecting dogs. While the disease generally presents as painless swellings in the peripheral lymph nodes, diagnosis is often complicated by lymphoid proliferation in internal organs such as the liver, spleen and bone marrow. Cytological examination of tissue by fine needle aspiration or histological classification from an excisional biopsy is required to establish a definitive diagnosis. Lymphoma is a disease that is both variable and complex, with the different subtypes showing quite a diverse response to treatment and prognosis; T cell lymphoma generally exhibits poorer prognosis and shows greater resistance to chemotherapy than B cell lymphoma.

Lymphoma is routinely classified as low, intermediate or high grade. Low grade lymphoma typically develops slowly and shows low sensitivity to chemotherapy. Survival times are relatively long. However, intermediate and high grade lymphomas, which account for in the region of 80 % of all cases, develop rapidly. Although these patients tend to respond relatively well to chemotherapy, the disease invariably recurs and the second round treatment is more difficult; the results are usually short lived. Because of this, it is important that dogs undergoing chemotherapy treatment, as well as those that are in remission and no longer being treated, are closely monitored, as re-induction or rescue therapy is more likely to be effective in the early stages of disease recurrence.

At the first relapse, re-induction therapy is recommended.

If the first protocol yielded a durable remission, re-introduction of the same chemotherapy protocol is typically recommended. While some dogs will experience long-term remission, the likelihood of response and duration of a second remission period are about half of that attained during the initial treatment; currently there is no way of predetermining the likely outcome. If re-induction fails, there is the option to treat with rescue agents that were not part of the original protocol. Rescue rates are reported to be in the range of 40 to 50 %, although median survival times are only in the region of two months.

### A biomarker-based test

The usual method of post-treatment monitoring for disease remission and recurrence is palpation of peripheral lymph nodes, which dog owners themselves can be taught to do. Subsequently, the veterinarian may take a tissue sample by fine needle aspiration. The disadvantage of this approach is that physical examination is subjective and only capable of detecting gross changes in peripheral lymph nodes, and aspirates are often non-diagnostic as normal lymph nodes are small and not always easy to access, resulting in fat being sampled in error. An alternative approach is the use of biochemical methods to detect circulating biomarkers of the disease. This has the potential to provide greater objectivity, detecting changes that occur before obvious physical symptoms develop.

Acute phase protein (APP) levels are known to increase in response to inflammatory stimuli and diseases such as lymphoma. In this context, C-reactive protein

(CRP) has proved a valuable prognostic marker for non-Hodgkin's lymphoma in human medicine. Although individual APPs lack specificity for diseases such as lymphoma, dramatic improvements in remission monitoring performance can be achieved by employing a multivariate approach, using specifically designed algorithms to incorporate the levels of several serum acute phase proteins with other parameters. A simple analogy would be the consideration of multiple factors such as age, breed, physical symptoms and biochemistry results when making any diagnosis. This approach forms the basis of a new blood test, the SENSITEST canine Lymphoma Blood Test (cLBT) from Avacta Animal Health, which uses the biomarkers CRP and haptoglobin to monitor dogs undergoing chemotherapy treatment for lymphoma. A database of control and known positive lymphoma samples was used to develop a multivariate algorithm to assess the risk of lymphoma based on the relative levels of CRP and haptoglobin, the age and sex of the animal and the presence of abnormalities in the lymph nodes.

SENSITEST cLBT is a simple test requiring just 2 ml of whole blood, which can reliably detect the recurrence of lymphoma up to two months prior to the appearance of any physical signs such as changes in the size and appearance of the lymph nodes. By regularly monitoring a dog's remission status with the SENSITEST cLBT, any relapse can be detected earlier, enabling re-induction or rescue strategies to begin much sooner than might otherwise be possible. Equally, pre-treatment testing has the potential to provide a good prognostic indicator for the disease.

### Early warning of probable relapse

The Animal Specialty Center in Yonkers, New York, USA, is a busy multi-veterinarian specialty clinic offering 24-hour emergency care for dogs and cats. Animals with a diagnosis, or suspicion, of cancer are referred to the oncology department either through the Center's Internal Medicine or Surgery departments, or from the patient's primary veterinarian. In most cases, a diagnosis has already been made, and care involves discussing the type of cancer, staging tests to establish how advanced the disease is, and outlining the available treatment options with the pet owner, as well as monitoring disease status and progression.

The presentation of preliminary cLBT data at the Veterinary Cancer Society 2013 Annual Conference in Minneapolis, USA, highlighted the potential benefits of using a biomarker-based test for ongoing monitoring of remission status. Whereas previously there had not seemed to be an effective means of accurately monitoring the remission status of dogs with lymphoma, the development of the cLBT offered oncologists a viable alternative to physical examination and fine needle aspiration.

Lymphoma is a cancer that progresses very rapidly; a patient seemingly in remission can appear to relapse just a couple of days later when, in reality, the disease has actually been progressing unnoticed. To determine the effectiveness of the cLBT, the Animal Specialty Center monitored 'healthy' patients thought to be in remission to establish whether a relapse could be detected earlier using the blood test than by physical examination or aspiration. The results were impressive. Some tests recorded elevated results,



indicating that the patients could be coming out of remission and, when these patients were recalled early, after two weeks rather than the usual four to six weeks, they were found to have enlarged lymph nodes; they had indeed relapsed.

The oncology department at the Animal Specialty Center now routinely uses the test for monitoring purposes once chemotherapy is complete – a pre-treatment baseline measurement, where possible, can also be helpful – usually starting when the dog returns for its 1-month recheck. An elevated score at this stage is an indication that the dog may not be in remission and may relapse in the upcoming weeks. For some visits, the cLBT is now the only

test performed in addition to the physical examination. It is an easy test to carry out, simply requiring a blood sample to be taken and submitted to the Avacta-approved laboratory for analysis. Initially, this entailed sending samples to the UK with a turnaround time of about a week, but there is now a laboratory in the US, which means that results arrive even more rapidly. Further work is underway to elucidate whether restarting therapy earlier positively impacts on the length of the patient's second response.

#### A potential predictor

There are many different types of lymphoma which can be

phenotyped, looking at different cell markers; this approach has been shown to be prognostic. Ultrasound and radiographs can also help to establish how advanced a cancer is. In this respect, the cLBT may have the potential for predictive as well as monitoring purposes, which is an exciting prospect. A pre-treatment, baseline measurement could provide a useful starting point for future monitoring of a patient's remission status. Further studies are required, but it will be interesting to see whether a baseline test result above or below a certain level can provide an indication of the likelihood of a patient having a better response or a longer remission. It would also be valuable to determine whether or not the cLBT can be used to distinguish between the B and T cell lymphoma subgroups; lymphoma is treated using a multi-drug – CHOP (cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin® (vincristine), and prednisone or prednisolone) – protocol, which works well with B cell lymphomas, while T cell lymphomas tend not to respond as well. There is just a wealth of information that oncologists can potentially learn from the canine Lymphoma Blood Test.

#### Conclusion

"Is there a blood test for cancer?" is a question that is frequently asked. Although for most cancers the answer is no, the cLBT seems set to change this situation. From a clinical perspective, the cLBT is proving a very valuable – and economical – test that achieves good results. It is minimally invasive with no sedation required, the cost is comparable to performing a lymph node aspirate, and the results are more consistent, which is good news for both pet and owner.

**In press:** Utility of a multiple serum biomarker test to monitor remission status and relapse in dogs with lymphoma undergoing treatment with chemotherapy. *Journal of Veterinary and Comparative Oncology*

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