Virginia-Maryland College of Veterinary Medicine

VIRGINIA-MARYLAND COLLEGE OF VETERINARY MEDICINE
ANIMAL CANCER CARE AND RESEARCH CENTER
VIRGINIA TECH

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Clinical Research Project
Client Consent Form

Study Title: AIM: Ablative Immune Modification with Nanopulse Stimulation prior to treatment with doxorubicin in dogs with diffuse large B-cell lymphoma

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One of the missions of the Virginia-Maryland College of Veterinary Medicine is to create, disseminate and apply medical knowledge through discovery, learning, and engagement. You are invited to participate in this mission by enrolling your animal in a clinical research study. Your participation is voluntary, and you may withdraw your animal from the study at any time by notifying the Principal Investigator. There is no penalty if you choose not to participate.

Study Purpose:
Large cell lymphoma affecting the peripheral lymph nodes (multicentric) is one of the most common cancers diagnosed in dogs, of which, diffuse large B-cell lymphoma (DLBCL) is the most common subtype. DLBCL in dogs is clinically and genetically similar to DLBCL in people; clinical trials in dogs are helping to identify new treatments to benefit both dogs and people diagnosed with this cancer. One of cancer's strategies is to evade the immune system by suppressing immune cell recognition and the ability of these immune cells to kill cancer cells. Treatments that address this by using drugs, antibodies, or directly training a patient's immune system, are becoming common in people, but we are far from curing lymphoma in dogs or people. The use of local ablative strategies to modify the immune system (AIM, or ablative immune modification) and shift it from a suppressed to an active environment has been shown to be effective in mouse models and people with other cancer types. **The purposes of this study are 1.) to evaluate the impact on the number and types of immune cells and their gene expression following a single treatment to a lymph node in dogs with DLBCL, and 2.) whether NPS pre-treatment prolongs the remission time when treated with standard chemotherapy with doxorubicin.**

Study Design/Procedures:
This is a prospective, single-blind, randomized, proof-of-principle clinical trial. Dogs will be randomized to either AIM (NPS), or placebo. Only the investigation team will know whether your dog has received AIM(NPS). Blood and lymph node needle biopsies will be obtained periodically throughout the study to monitor the immune response. All dogs will undergo standard chemotherapy treatment with doxorubicin following AIM(NPS) or placebo. Chemotherapy will be given under the direct supervision of a board-certified veterinary medical oncologist at the ACCRC. If you agree to participate in the study, we will perform the following procedures:

(a) Pretreatment evaluation (screening, prior to enrollment)
Before beginning treatment your dog must undergo the following tests to determine if s/he is a good candidate to enroll in the study. These tests are for your pet's safety and to ensure that the data generated by this trial is the most meaningful as possible. Items 1 and 4 must be done at ACCRC:

1. **Complete physical exam**
2. **Lab work:** We will obtain blood samples from your pet for a complete blood count and chemistry profile. Six milliliters (about 1 teaspoon) of blood will be collected from a vein in your pet's neck, which is the easiest access point. We will also collect 5 milliliters of urine. This is to ensure that your dog is healthy enough to receive treatment with chemotherapy.
3. **Biopsy or fine needle aspirate of a lymph node:** A needle or wedge sample of a lymph node will be obtained for diagnostic purposes. This must be evaluated by a board-certified veterinary clinical or anatomic pathologist and include special testing identifying the immunophenotype (B- vs. T-cell) of lymphoma. The pathology report provided to the research team.
4. **Thoracic and abdominal imaging:** Chest x-rays and abdominal ultrasound must be performed by the Oncology

service at the ACCRC. This is to determine if your dog has stage 5 lymphoma.

Eligibility criteria / Screening visit

To be eligible for enrollment:

1. Your dog must have an official diagnosis of multi-centric diffuse large B-cell lymphoma.
2. S/he must be at least 1 year of age and weigh at least 10 kg (22 lb).
3. Your dog cannot have received any treatment for lymphoma, including prednisone.
4. The stage of your dog's lymphoma cannot be stage 5 (bone marrow, lung, kidney, eye, gastrointestinal tract, skin, or other non-lymphoid organ involvement).
5. His or her lab work must show adequate organ and bone marrow function to safely receive treatment with chemotherapy; be expected to live for at least 4 weeks even if s/he were to receive no treatment or only supportive, palliative care; and have no significant heart dysfunction (arrhythmia or weak pumping). *A consultation with a cardiologist may be required at the time of screening to determine whether your dog can safely receive doxorubicin, which can be toxic to the heart, especially in breeds predisposed to heart issues*.
6. You must agree to return to the ACCRC for all required appointments within 2 days of the scheduled visits. You must agree to the required diagnostic and monitoring tests. You must agree to sedation for chemotherapy treatments if this is required for safety reasons by the attending oncologist. You must agree to only administer medications approved by the researchers.

(b) Treatment

Once your dog is enrolled in the study, there are (13) protocol clinic visits which include (1) NPS or placebo treatment under general anesthesia or heavy sedation, (5) chemotherapy treatments, (2) imaging visits, (13) blood draws, and (8) fine needle aspirates (needle biopsy) of a lymph node. Please see the study visit summary below. Upon completion of the chemotherapy protocol, monthly exams are required to monitor for remaining in complete remission: the number of these visits will vary.

- If your dog meets the eligibility criteria and is enrolled, s/he will be scheduled to receive NPS treatment or placebo as soon as possible, but within 1 week of signing this consent form.

- NPS/placebo treatment: While sedated or anesthetized, the overlying fur will be clipped over a single lymph node. A small needle will be inserted through the skin into the lymph node. Treatment does not involve heat and is considered painless. In the treatment group, approximately 1 cubic cm of lymph node will receive several rapid (nanoseconds) pulses of electrical stimulation. Dogs in the placebo group will have the electrode needle inserted, but no pulses delivered. S/he must return 3 days after NPS/placebo treatment for an exam, blood draw, and lymph node sampling.

- One week after NPS/placebo, your dog will begin chemotherapy treatment with doxorubicin. Five treatments given 3 weeks apart will be planned. One week after each chemotherapy treatment, a CBC, temperature, and weight measurement must occur. These can be performed with your regular veterinarian.

- An exam and lab work will be performed by a board-certified veterinary medical oncologist at each visit to determine whether treatment can be administered. Treatment delays may be necessary, and if your dog's lymphoma has progressed, s/he will be removed from the study and standard rescue treatments will be discussed, including palliative care.

- If it is determined to continue on study, all injectable chemotherapy agents will be administered by licensed veterinary technicians that are trained in the proper handling of chemotherapy, following all guidelines as outlined by the ACVIM Consensus Statement for Chemotherapy Safety in Veterinary Medicine, and within a USP800-compliant chemotherapy suite. A intravenous catheter will be placed and removed for all injectable chemotherapy treatments. Your dog may need to be sedated for his/her and the staff's safety during administration. Your dog will be discharged the same day (outpatient treatment) for all visits with supportive care medications to prevent or treat nausea, vomiting, or diarrhea, should they occur.

- An oncology doctor is available afterhours and on weekends if you have concerns about your pet's health in between visits.

- The 3rd doxorubicin treatment visit at day 49 requires recheck of the imaging and re-evaluation of the lymphoma at ACCRC to determine the official response to treatment. Sedation may be required for imaging, even if your pet does not need sedation for chemotherapy treatments.

Study visit summary (*PD = progression of disease, or relapse, of the lymphoma)

Procedures by day	**-7**	**0**	**3**	**7**	**14**	**28**	**35**	**49**	**56**	**70**	**77**	**91**	**98**	**PD***
Diagnosis	x													x
Immunophenotype	x													
Thoracic radiographs, abdominal ultrasound	x							x						x
CBC	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry panel	x			x		x		x		x		x		x
Urinalysis	x			x		x		x		x		x		x
NPS or placebo		x												
Doxorubicin i.v.				x		x		x		x		x		
Blood and fine needle aspirate of lymph node		x	x	x		x		x		x		x		x

Follow-up

Your dog will need to return to the Oncology service once a month for an exam after all chemotherapy treatments have been completed. At each recheck visit, your pet will have a physical exam, and additional diagnostics if indicated. We ask that you keep the clinical oncology service and researchers informed on the status of your pet's health. If relapse (progression of the lymphoma) is suspected, it will be confirmed by fine needle aspirate and official pathologist review (cytology). At that time, we will collect one final blood and lymph node sample, and discuss additional treatment options and your dog's prognosis.

Risks and Benefits:

The goal of this study is to develop a novel therapy against lymphoma that involves modulating the immune system to allow conventional therapies (chemotherapy) or targeted therapies (immunotherapy) to work better. Most of the procedures performed in this study are routine clinical procedures. **The NPS therapy is the experimental procedure and not part of the standard treatment.** Side effects that may be seen in your pet during this study may include but are not limited to fever, tumor inflammation, tumor-site discomfort, systemic inflammation, risk for severe infection, and death. Although unexpected, there could be problems with the diagnostic procedures required for enrollment (lab-work, staging, biopsy) or with standard chemotherapy treatment (low white blood cell counts, fever, nausea, inappetence, diarrhea). These problems can be due to inflammation or infection and may result in bruising at the collection site or from known side effects of chemotherapy in dogs. Additionally, all animals going under general anesthesia are in risk of adverse effects that may result in death. We take stringent measures to minimize these risks by taking steps to prevent contamination of the biopsy site, and monitor continuously the vital functions of your pet when under general anesthesia and during the recovery period. We also closely monitor your pet's blood cell counts, temperature, and are in communication with you and your primary care veterinarian about how s/he is handling treatment. Reducing the dose of chemotherapy or delaying treatment may be necessary to improve your pet's well-being during his/her treatment.

Study Costs and Compensation:

The study covers the sedation and NPS (or placebo) treatment, the collection and analysis of blood and lymph node samples for determining immune response, and $250 per chemotherapy treatment visit. **The total compensation per patient enrolled is $1,430.** All other costs associated with screening, the chemotherapy treatment and monitoring visits, required imaging exams at day 49, and any medications or hospital visits necessary for managing side effects are out-of-pocket. All diagnostics or procedures not covered by the study are standard, and would be performed in any pet dog undergoing evaluation and treatment for lymphoma with chemotherapy. The out-of-pocket costs may vary during the study period. As of July 1, 2021, the screening costs are estimated to be $1000-1200, the costs of imaging are estimated to be $500-700. The cost of treatments vary based on your dog's weight, and management of side effects also greatly varies. Estimates of treatment visits will be calculated specifically for your dog and provided at the time of screening.

Confidentiality:
The data collected in the course of this study is confidential. In any publication or presentation of the study data, we will not include information that would make it possible to identify a research participant. Research records will be kept in a secure location; only researchers will have access to the records.
There is no study sponsor for this clinical trial

Statement of Consent:
In giving my consent by signing this form, I acknowledge that I have been informed of the purpose and nature of this study and its associated procedures, as well as any possible side effects.

I have read and understood the above information. I have been given the opportunity to ask questions and receive answers, and I consent to participate in the study. I further certify that I am the owner (or duly authorized agent of the owner) of _____ .
(Animal's name)

Owner or Agent Signature: _____ Date: _____

Owner or Agent Printed Name: _____

Attending Clinician Signature: _____ Date: _____

Attending Clinician Printed Name: _____

Please don't hesitate to contact us if you have any questions or concerns about this study.
The research and procedures have been reviewed and approved by the Virginia Tech Institutional Animal Care and Use Committee and the Virginia-Maryland College of Veterinary Medicine Clinical Research Review Committee.

If you have any questions or concerns regarding the study and would like to talk to someone other than the researchers, please contact:

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United States
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You will be given a copy of this form to keep for your records.