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: Evaluating a new chemotherapy protocol (THOP) as the first-line therapy in dogs with 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 pet in a clinical research study. Your participation is voluntary, and you may withdraw your pet from the study at any time by notifying the Principal Investigator. There is no penalty if you choose not to participate.

Study Purpose:
Lymphoma is one of the most common cancers diagnosed in dogs. The current standard of care for treatment is a chemotherapy protocol that uses multiple drugs: doxorubicin, vincristine, cyclophosphamide, and prednisone. This protocol, the UW-19, requires weekly clinic visits for 19 weeks, and is the most effective treatment available: >85% of dogs experience a complete clinical remission (all enlarged lymph nodes return to normal size). However, canine lymphoma is rarely cured: <10% of dogs are alive at two years after diagnosis. Half of dogs treated with the UW-19 will have a complete remission for longer than 8-10 months. However, the remission time is measured from the date of diagnosis to the date of cancer progression, which includes the 5 months of treatment, resulting in 3-5 months of life in remission *after* finishing the treatment protocol. Multiple attempts to reduce the treatment time using the same combination of drugs have failed. Our team proposes a different strategy: replacing the least effective drug in the UW-19, cyclophosphamide, with a more effective drug, temozolomide. We will reduce the total treatment time from 19 weeks to 15 weeks by giving temozolomide at the same time as doxorubicin. Temozolomide has been shown to be synergistic with doxorubicin, and to be effective in dogs whose lymphoma does not respond, or stops responding, to standard of care protocols, like the UW-19. ***The objective of our study*** is to determine the efficacy and side effect profile of THOP, a new multi-agent doxorubicin-based chemotherapy protocol, as the first-line treatment in dogs with diffuse large B-cell lymphoma (DLBCL). THOP (temozolomide, doxorubicin, vincristine, prednisone) is a new combination of chemotherapy drugs that replaces cyclophosphamide with temozolomide and capitalizes on the synergy between doxorubicin and temozolomide: reducing the treatment time by 4 weeks and the overall cost of treatment by more than $1,000. ***We expect the results of this study to show*** that the THOP treatment protocol will result in similar response rates to current standard of care with minimal toxicity.

Study Design/Procedures:
This is a prospective, single-arm, open-label pilot study of THOP chemotherapy treatment in dogs with diffuse large B-cell lymphoma (DLBCL) that have not received any other treatment. All dogs enrolled will be treated with the THOP chemotherapy protocol at the ACCRC, under the direct supervision of a board-certified veterinary medical oncologist and by chemotherapy-trained licensed veterinary technicians (prospective, single-arm). The researchers, technicians, and owners will know that all dogs are being treated with THOP (open-label). A small number of dogs will be enrolled in order to collect data to appropriately design larger studies in which dogs are randomly assigned treatment with either THOP or the current standard of care (pilot study).

If you agree to participate in this 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.

Eligibility criteria / Screening visit

To be eligible for enrollment, your dog must have an official diagnosis of multi-centric diffuse large B-cell lymphoma. S/he must be at least 1 year of age and weigh at least 10 kg (22 lb). Your dog cannot have received any conventional chemotherapy treatment for lymphoma. 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*. You must agree to return to the ACCRC for all required appointments within 2 days of the scheduled visits. You must agree to sedation for chemotherapy treatments if this is required for safety reasons by the attending oncologist. You must agree to administer temozolomide (chemotherapy) at home strictly following the administration instructions.

(b) Treatment

Once your dog is enrolled in the study, there are (15) protocol clinic visits, (11) of which are required to be at the ACCRC. There are include (10) chemotherapy treatments, (1) imaging visit, and (15) blood draws. 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 begin THOP chemotherapy treatment as soon as possible, but within 1 week.

- 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) with supportive care medications to prevent or treat nausea, vomiting, or diarrhea, should they occur.

- Temozolomide will be dispensed as tablets/capsules to be given by you, at home, for 5 days on doxorubicin treatment weeks. Temozolomide can cause significant nausea and correct timing of treatment with nausea-prevention medications is critical. Additionally, temozolomide must be given on an empty stomach. You will be provided with chemotherapy-approved gloves and instructions on how to give your pet his/her treatment.

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

- The CBC-only weeks 3, 12, and 15 can be performed with your regular veterinarian, along with getting his/her weight and temperature.

- CBC-only week 6 requires imaging for official evaluation of response to treatment. This will include chest x-rays and abdominal ultrasound at ACCRC. Sedation may be required for imaging, even if your pet does not need sedation for chemotherapy treatments.

Study visit summary

Procedures by week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Vincristine i.v.		x			x			x			x			x		
Doxorubicin i.v.			x			x			x			x			x	
Temozolomide oral, at home once a day for 5 days			x			x			x			x			x	
Prednisone oral, at home once a day for 7 days		x			x			x			x			x		
CBC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry panel	x		x			x			x			x			x	
urinalysis, immunophenotype, and diagnosis	x															
Thoracic radiographs, abdominal ultrasound	x						x									

Follow-up

Your dog will need to return to the Oncology service once a month for an exam after all 15 weeks 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 discuss additional treatment options and prognosis.

Risks and Benefits:

Our goal is to develop a new chemotherapy protocol that is as effective as the current standard of care while decreasing the treatment time and financial impact. Our goal is to give your dog the best quality of life for as long as possible; maximizing the amount of 'normal' life your dog has with you and your family.

All of the procedures performed in this study are routine clinical procedures and treatments. The doses of all of these drugs are known in dogs, and all of these drugs have been shown to be effective treatment against lymphoma in dogs. The benefits of this trial for your pet is treatment with effective drugs against lymphoma, at doses and a treatment schedule that are known to be safe and well-tolerated.

The investigative aspect of this trial is that this combination of drugs, THOP, has never been used as first-line treatment for canine lymphoma. We do not know how effective this treatment is, or for how long it is effective. THOP is not the current standard of care as the first-line treatment in dogs diagnosed with diffuse large B-cell lymphoma. One of the risks of enrolling in this trial is forgoing first-line treatment with the known standard of care, UW-19, which has been shown to induce a complete remission in 85% of dogs for a median duration of 8-10 months (as measured from the date of diagnosis to the date of relapse). It is possible that the response rate and/or response duration is below anticipated. It is also possible that the side effects are greater with this protocol than has been previously documented in dogs treated with these drugs. We address these concerns by frequent exams and lab work to identify progression of the cancer and/or unacceptable side effects; we will discuss alternative treatment options if either of these scenarios occur.

Study Costs and Compensation:
Enrollment in the study will provide the temozolomide at no charge, a compensation of approximately $1,000 if the protocol is completed as planned. The imaging exams at week 6 will also be covered by the study, which typically cost $650-700. All other costs associated with THOP treatment and monitoring are out-of-pocket, including the screening (eligibility) tests, clinic or hospital visits for medical management of side effects, and follow-up visits. All diagnostics or procedures are standard, and would be performed in any pet dog undergoing evaluation and treatment for lymphoma with chemotherapy; there are no additional tests or procedures required due to study involvement. The out-of-pocket costs may vary during the study period, and the cost of treatments vary based on the drug that is given and your dog's weight. Estimates of screening tests and the treatment visits will be calculated specifically for your pet and provided at the time of enrollment consideration.

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.

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