UNIVERSITY OF MINNESOTA

College of Veterinary Medicine

VETERINARY CLINICAL SCIENCES

Informed Consent Form
Department of Veterinary Clinical Sciences
College of Veterinary Medicine
University of Minnesota
Study Title: Clinical evaluation of propranolol in combination with doxorubicin for the treatment of hemangiosarcoma
Principal Investigators:
Erin Dickerson, PhD; Antonella Borgatti, DVM, MS, DACVIM, DECVIM

Revised March 2020

You are being asked to allow your dog to take part in a study to determine the effects of adding the drug propranolol to chemotherapy standard of care for dogs with hemangiosarcoma. Please read this form carefully, initial the bottom of each page on this form, and sign and date the authorization on page 5.

Who is conducting this study? Drs. Erin Dickerson, Antonella Borgatti, and their colleagues at the University of Minnesota

Purpose: Hemangiosarcoma is a type of cancer that is difficult to treat because of its aggressive behavior and rapid progression after diagnosis. We have shown that a drug commonly used to treat heart disease, propranolol, can kill hemangiosarcoma cells in the laboratory. The drug has also been effective in reducing disease progression and increasing the survival time in people with angiosarcoma, a cancer very similar to canine hemangiosarcoma. We will study the tolerability and clinical benefit of propranolol in combination with doxorubicin chemotherapy. Propranolol will be tested at three dose levels: 0.8 mg/kg, 1.0 mg/kg, and 1.3 mg/kg. Each of these doses is thought to be in the effective range for propranolol. The study will also determine if higher doses work more effectively with chemotherapy. Your dog will start at one of these doses and may be increased to the higher doses depending upon how your dog tolerates propranolol. We will also study the pharmacokinetics (PK) of propranolol in the blood to determine if there is a correlation between blood PK and effectiveness of the treatment. Results of this study will be shared with the veterinary community and pet owners. Results will provide new information so that we can continue to improve upon treatments for this disease.

Propranolol has been used safely in people and dogs, but as with any experimental treatment, can carry unforeseen risks. As part of the study design, we are working to confirm the safe and effective dose of propranolol for the treatment of hemangiosarcoma. As part of this effort, two dogs are enrolled within each dose cohort of the study and evaluated for three weeks. Once both dogs enrolled are beyond this three-week evaluation period, study enrollment is again open. We realize that the study design may limit the enrollment opportunities for your pet; however, we have designed the study so that we can obtain the best information possible regarding safety and efficacy of propranolol in combination with doxorubicin for the treatment of hemangiosarcoma.

Selection of Participants:
Eligible dogs will have hemangiosarcoma restricted to the spleen which has been treated by surgical removal of the spleen (splenectomy) within 21 days prior to enrollment in the study. Dogs must weigh more than 15 kg (33 lbs) to be eligible for participation. Screening diagnostics required, and performed between 9-21 days following surgery, are: routine thoracic radiographs (chest x-rays), abdominal ultrasound, complete blood cell counts, serum chemistries, coagulation profile and urinalyses. These tests will help us determine eligibility. To be eligible, dogs must:

- Have no evidence of metastases
- Have adequate supply of red blood cells (≥ 22% packed red cell volume)
- Be free of concurrent kidney, liver or heart disease, or problems with blood clotting

In addition to the requirements above, to be enrolled:

- Dogs cannot have received cyclophosphamide or other chemotherapy.
- The use of anti-inflammatory medications (NSAIDs or prednisone) is acceptable.
- Because propranolol has not been tested for interactions with a variety of other drugs, the use of unapproved supplements is strongly discouraged at all times. Eligibility for the trial requires withdrawal of such unapproved supplements, including, but not limited to I'm Yunity, other coriolus or turkey tail mushroom preparations, Yunnan Baiyao, etc. at least 10-days prior to propranolol administration. If supplements have been used prior to enrollment, use must have been limited to an initial 24-hour period, such as at diagnosis. Use beyond an initial period of 24-hours will exclude your dog from enrollment in the study. Resumption of supplements will not be allowed at any time during the trial.

Procedures:

1. Prior to enrollment, an echocardiogram will be performed to establish a baseline. This visit may be a part of the screening described above. Propranolol treatment (Day 1) will begin within 9 days from screening. If screening is more than 9 days before Day 1, it will have to be repeated.
2. Day 1: start of propranolol treatment: Drop off for half of the day. We will obtain a baseline blood pressure and a blood sample for baseline plasma level before starting propranolol. Owners will go home with oral propranolol to give as directed.
3. Day 4: the study team will call to check on your dog and to discuss escalating (increasing) the dose of propranolol. Owners do not need to come to the clinic for this.
4. Day 7: the study team will call to check on your dog and to discuss escalating (increasing) the dose of propranolol. If your dog is in the group receiving a higher dose of propranolol, the dose will be increased. If not, you will continue to give the dose started on Day 4. Owners do not need to come to the clinic for this.
5. Day 9: the study team will call to check on your dog and to discuss escalating (increasing) the dose of propranolol. If your dog is in the group receiving a higher dose of propranolol, the dose will be increased. If not, then you will continue to give the dose started on Day 4 or 7. Owners do not need to come to the clinic for this.
6. Day 11 (for a portion of the dogs):
    a. We will ask that we be allowed to collect small amounts of blood for pharmacokinetics (PK) after giving propranolol in the clinic. Owners will withhold propranolol in the morning and drop off their dog on Day 11. We will take a blood sample for baseline PK and plasma, give the propranolol dose, then take blood samples post-dosing at 0.5, 1, 1.5, 2, 4, 6, and 24 hours. We will place a sampling catheter in a leg. Dogs in this part of the study will spend the night and continue with Day 12. The cost of the overnight stay will be covered by the study.
7. Day 12 (first chemotherapy): Drop off for the day if not in the PK group above.
    a. Owners will withhold the propranolol dose in the morning. Before dosing, we will perform a blood pressure and collect blood for plasma levels. We will give propranolol, then repeat the blood pressure and blood collection for plasma levels. Note, dogs which were in the propranolol PK group on Day 11 will not

have blood collection after the propranolol dose on this day. Chemotherapy will begin, with 5 total doses of doxorubicin given on a standard schedule. Your oncologist will go over the schedule with you.

   a. Doxorubicin PK (for a portion of the dogs): We will ask that we be allowed to collect small amounts of blood for pharmacokinetics (PK) after giving the first doxorubicin treatment. We will take a blood sample at 5, 45, and 60 minutes after the chemotherapy is given.

8. Day 19: Blood pressure check as part of the post-doxorubicin CBC appointment.
9. Day 33±3: While at the clinic for the second chemotherapy visit, we will obtain a blood sample for a serum chemistry profile and take a blood pressure. Standard of care for chemotherapy includes blood for CBC, we will sample at the same time.
10. Day 54±3: Study Imaging and third chemotherapy visit. Physical exam, blood pressure, blood for CBC and serum profile, urine collected for urinalysis, thoracic x-ray and abdominal ultrasound. Chemotherapy following these procedures.
11. Day 75±3: Visit for physical exam, blood for CBC and serum profile. Fourth chemotherapy following these procedures.
12. Day 96±3: Study imaging and chemotherapy visit. Physical exam, blood for CBC, serum profile and coagulation profile, urine collected for urinalysis, thoracic x-ray and abdominal ultrasound. Fifth and final doxorubicin chemotherapy following these procedures.
13. 6-months, 9-months, 12-months: Physical exam, blood for CBC, serum profile and coagulation profile, urine collected for urinalysis, thoracic x-ray and abdominal ultrasound.

Discomfort and Risks: Propranolol has been used safely in people and dogs, but as with any experimental treatment, can carry unforeseen risks. The side effects and the risks of treatment with propranolol combined with doxorubicin may include low blood pressure, lethargy, weight gain, vomiting, diarrhea, heart problems, and increased susceptibility to infection. In very rare cases, death may result from treatment. Please contact the study team during normal business hours with any concerns, or the VMC Emergency Service at 612-625-9711 after hours.

Sedation may be needed for the imaging (thoracic radiographs and abdominal ultrasound) as well as for chemotherapy administration. There are no risks from the imaging itself. With sedation, there are risks including the very rare risk of unexpected death. We take every precaution possible to minimize risks with sedation.

Risks associated with the blood-drawing procedure include minimal discomfort when the needle goes into the vein. A bruise may form at the site. In most cases, this does not require further management. If the bruise creates discomfort, you may need to apply warm compresses over the site once or twice a day for 2-3 days.

Because we are asking you to provide personal information (name and address), there is a potential risk for loss of privacy. Every effort will be made to keep your research records confidential, but this cannot be absolutely guaranteed. A complete explanation of the protocols we will follow to protect your personal information is provided in the Confidentiality section below.

Benefits*:* This is an experimental study designed for the researchers to learn more about cancer treatment. The intent is to improve our delivery of care and the outcome for each participant and future cancer patients. We cannot guarantee that your dog will benefit from participation in this study, and there are risks as mentioned in the Discomforts and Risk Section.

Cost to subject: You will be responsible for costs of surgery (splenectomy), anesthesia, initial oncology examination fee, and prescreening diagnostics (complete blood count, serum biochemical profile, coagulation profile, urinalysis, thoracic radiography, echocardiogram, and abdominal ultrasonography). At the VMC, these costs are equivalent to approximately $4,890 -

$5,995 for the surgery, $2,200 - $3,000 for doxorubicin chemotherapy, and $1,000-$1,900 for the prescreening diagnostics. **If your dog is eligible and enrolled in the study**, you will be partially reimbursed for some of these costs (see Compensation section below). **These costs are not subject to refund if your dog is not eligible to participate.**

Compensation: The study will reimburse owners of eligible and participating dogs up to $6,500 as follows: $1,000 for the prescreen diagnostics, $3,000 for chemotherapy and $500 for each visit for follow up and imaging (Day 54, 96, month 6, 9, 12 = $2,500 total for 5 visits). The study will also cover the cost of propranolol, up to $1,095 for 12 months.

Injury and Compensation: You should stay in contact with your oncologist and the clinical research team for the duration of the study and throughout your dog's treatment. Appropriate medications and care will be provided for your dog if he/she develops any severe side effects that require medical management. At least $500 will be available to help cover the costs of hospitalization related to propranolol. You will be responsible for any remaining costs or costs arising from side effects not related to propranolol treatment. The Veterinary Medical Center, and the University of Minnesota will not be responsible for compensation or care related to this research project beyond that described above.

Study Sponsor: This study is funded by a grant from the American Kennel Club Canine Health Foundation.

Confidentiality:
How will the identity of your sample and the information you provide be protected?
Your personal information will not be sold or disseminated to anyone not directly involved with this study. We will try to keep your research records confidential, but it cannot be guaranteed. Records that identify you (including your dog's medical record) and the consent form signed by you, may be looked at by the following people:

- Federal agencies that oversee human and animal subject research
- University of Minnesota Institutional Animal Care and Use Committee
- The investigator and research team for this study
- The sponsor or an agent for the sponsor
- Regulatory officials from the institution where the research is being conducted, to ensure compliance with policies or monitor the safety of the study

The results of this research may be presented at meetings or in published articles. However, your name will be kept private, and your dog will not be identified by name, family or kennel name. A complete accounting of your dog's care and results will be included in his or her medical record.

Where will information be stored?
Samples will be coded and tied to medical record identifiers. Computer records will only include the necessary information to allow sample tracking (hospital ID). Consent forms and coding information will be kept in a secure location in the office of the project coordinator. Even though every safety measure will be taken, there is a slight chance that someone who is not supposed to see information about you will accidentally see it.

If you have questions about injury related to the research, you may call Dr. Borgatti at 612-626-5786 or Dr. Dickerson at 612-626-5053.

Voluntary Participation and Study Withdrawal: Participation in this study is voluntary. You will not be penalized in any way if you elect not to participate and you can withdraw from the study at any time. To withdraw from the study, you can notify the investigators in person or writing by sending a letter to: Dr. Erin Dickerson, Animal Cancer Care and Research Program, University of Minnesota College of Veterinary Medicine, 1365 Gortner Ave, St. Paul, MN 55108 or by email at edickers@umn.edu If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

The investigators may decide to stop your participation without your permission for any reason. Also the sponsors may stop the study at any time.

Invitation for Questions: You may ask any questions you have now. If you have questions later, you may call Dr. Borgatti, Dr. Dickerson, or a member of the clinical research team (Clinical Investigation Center). You will be given a copy of this form to keep. Please do not hesitate to contact us if you have any concerns.

Investigators: Antonella Borgatti, D.V.M. – Office phone: 612-626-5786
Erin Dickerson, Ph.D. – Office phone: 612-626-5053

Clinical Research Technician: Amber Winter – Office phone: 612-624-1352
Email: alwinter@umn.edu
CIC Research Manager: Kathy Stuebner – Office phone: 612-624-2485
Email: stueb005@umn.edu

To speak to someone about your rights and about your dog as a research subject, please contact the **Institutional Animal Care and Use Committee:** 612-626-2126.

Authorization: I have read this form about the study or it was read to me, and my questions about its content have been answered. I have had an opportunity to ask questions about the project and understand that I can ask questions at any time. I understand the possible risks and benefits of this study. I know that participation in this study is voluntary. *I choose to allow my dog, named*

_____*, to participate in this study and to provide follow-up information as requested by the investigators*. Furthermore, I agree to donate to Drs. Erin Dickerson and Antonella Borgatti, of the University of Minnesota, tumor and other tissues removed from my dog during participation in this study. I understand that by signing this Consent Form, I give up all future claims to these tissues and any experimental results that may be derived from their investigational use. I know I can stop being in this study, and although I will forfeit any compensation, my dog can still get veterinary care. I will get a copy of this consent form (initial all the previous pages of the consent form). If I have any questions or problems which I feel are related to the study, I can contact the Principal Investigator whose name is on this form. By signing below I agree to participate in this research study.

I understand the above information and agree to participate in the study. Yes ☐ No ☐

_____ _____
Client Signature Date

_____ _____
Consent form explained by (Print Name) Date

_____ _____
Attending Veterinarian or Technician Date