RESEARCH PROGRESS REPORT SUMMARY

Grant 02534: Clinical Trial for Evaluation of Propranolol and Doxorubicin in the Treatment of Canine Hemangiosarcoma

Principal Investigator: Erin Dickerson, PhD

Research Institution: University of Minnesota Office of Sponsored Projects Administration

Grant Amount: $334,306.00

Start Date: 7/1/2019 **End Date:** 6/30/2023

Progress Report: Mid-Year 4

Report Due: 12/31/2022 **Report Received:** 12/31/2022

(The content of this report is not confidential and may be used in communications with your organization.)

Original Project Description:

Co-investigators: David R. Brown, PhD; University of Minnesota, Michael O. Childress, DVM, MS; Purdue University, Jennifer Mahoney, DVM and Pascale Salah; University of Pennsylvania

Canine hemangiosarcoma is a largely incurable cancer in dogs, and treatment approaches to improve outcomes have remained relatively stagnant over the past few decades. Treatment remains a challenge partly because the cancer is frequently detected at an advanced stage and because these tumors are often resistant to chemotherapies. Recently published reports showed that propranolol, a drug used to treat heart disease in humans and dogs, substantially increased the survival time of human angiosarcoma patients when used in combination with standard of care treatments. Propranolol was also shown to sensitize hemangiosarcoma cells to doxorubicin, providing a more effective way to kill tumor cells. Because angiosarcoma is strikingly similar to canine hemangiosarcoma, this multi-institutional clinical trial has been designed to determine the efficacy of propranolol in dogs with hemangiosarcoma when used in combination with surgery and chemotherapy. The main goal of the study is to establish whether propranolol in combination with doxorubicin following surgery improves outcomes for dogs when compared to the use of chemotherapy and surgery alone. The investigators will also evaluate the plasma concentrations of propranolol achieved during dosing to assess whether the levels of propranolol correlate to survival times. If successful, the findings from this approach will be rapidly conveyed to the veterinary community, and the guidelines provided to clinicians for the use of propranolol and doxorubicin for the treatment of canine hemangiosarcoma.

Publications:

None at this time.

Presentations:

An overview of the study was presented at the 12th Biennial AKC Canine Health Foundation National Parent Club Canine Health Conference (NPCCHC) held August 9-11, 2019 in St. Louis, MO

A summary of the study design and goals was given at the annual Veterinary Cancer Society meeting held November 4-6, 2021 (virtual meeting). The presentation was part of a special session on hemangiosarcoma.

A summary of the study design and pre-clinical data supporting the rationale for the study were presented to the Minnesota Veterinary Medical Association at their annual meeting, held February 10-11, 2022 (virtual meeting).

An overview and preliminary analysis of the study was presented at the College of Veterinary Medicine faculty, staff, and students at the University of Minnesota as part of the Grand Rounds seminar series on December 1, 2022 (virtual presentation).

Report to Grant Sponsor from Investigator:

Our overall objective is to determine a clinically optimal dose and estimate the efficacy of propranolol in dogs with hemangiosarcoma when given as an adjunct to chemotherapy. Specifically:

Objective 1: We will confirm the tolerability and estimate the clinical benefit of propranolol in combination with doxorubicin.

Objective 2: We will assess levels of propranolol in the bloodstream after long-term administration to dogs with hemangiosarcoma to determine if there is a correlation between drug levels in blood and overall survival. We will also determine if propranolol alters the blood levels (exposure) of doxorubicin in dogs receiving propranolol and compare these levels to those found in the published literature for dogs receiving doxorubicin. Collection of these data will allow us to better understand how these drugs may be working together.

We opened the trial on July 1, 2019. As of December 31, 2022, we have screened 51 dogs and enrolled 19 dogs in the study and no dose limiting toxicities within the initial 21-day assessment period have been observed. Based on these results, we are continuing to enroll dogs at the highest dose of propranolol (1.3 mg/kg) being tested. We did observe an adverse event in one dog at approximately

month 6 of the protocol that could be attributed to propranolol (2-3 episodes of fainting/collapse), which was resolved by reducing the dose of propranolol to 1.0 mg/kg.

Propranolol and doxorubicin levels in the blood from 18 of the dogs enrolled to date have been analyzed. Analysis of samples from dog 19 is pending.

Currently three dogs enrolled in the study are alive while sixteen dogs have died. Of the dogs that died, two dogs were euthanized due to health issues unrelated to recurrence of hemangiosarcoma. So far, five of the nineteen dogs have survived for more than nine months (26.3%). Of these five dogs, four have survived for more than one year (21.1%), and two of these dogs have survived for more than three years (10.5%).

We plan to enroll the final dog in the study within the next six months at either the University of Pennsylvania or Purdue University.

We also plan to complete the analysis of drug levels (propranolol and doxorubicin) in the blood samples. Analysis of the samples from eighteen dogs has been completed, and the analysis from dog nineteen is pending. We may need to request an additional no cost extension for the study depending on when the final dog is enrolled.