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
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Progress Report:	Mid-Year 5
Report Due: 1/31/2024	**Report Received:** 1/31/2024

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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:

"Repurposing Old Drugs for New Cancer Treatments." Accessed May 5, 2023. https://www.dvm360.com/view/repurposing-old-drugs-for-new-cancer-treatments.

We are working a paper to present the results of the study.

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:

We have completed enrollment for the trial. We are currently analyzing the pharmacokinetic data obtained from the blood samples of dogs enrolled in the study. The project goals have not been modified.

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. Overall, we screened 60 dogs and enrolled 20 dogs in the study, and no dose-limiting toxicities were observed. Based on these results, we continued to enroll dogs at the highest dose of propranolol (1.3 mg/kg). 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. We completed enrollment in August 2023.

Propranolol and doxorubicin levels in the blood from 19 of the dogs enrolled to date have been analyzed. Currently, two dogs enrolled in the study are alive, while eighteen dogs have died. Of the dogs that died, two dogs were euthanized due to health issues unrelated to the recurrence of hemangiosarcoma. So far, 40% (8 dogs) of the dogs have survived for more than six months, 30% (6 dogs) have survived for more than 9 months, and 15% (3 dogs) have survived for more than two years.

Importantly, the dogs surviving > 2 years were diagnosed with hemangiosarcoma at age five, suggesting occurrence at the age of five or younger may be a predictor of a favorable outcome. Based on the lack of age-matched controls (splenectomy only or splenectomy + doxorubicin), we cannot attribute the survival of these dogs to treatment with propranolol + doxorubicin. However, our data support follow-up studies assessing age (5 years or less) as a predictor of long-term survival following splenectomy + doxorubicin.

We also obtained the archived tumor blocks from 14 dogs in the study. Using these samples we have analyzed the gene expression signatures of the tumors. Our data show that gene signatures associated cell division and immune responses differ between the long-term and the short-term survivors. Specifically, decreased levels of immune cell infiltration into the tumors and increased levels of genes associated with cell proliferation are associated with shorter survival times.

We are carrying out additional studies and analysis of other data sets to establish the importance of these signatures in treatment responses. Analysis of these signatures may also yield important information for the development of new treatment approaches to treat dogs diagnosed with hemangiosarcoma.