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
Grant Amount:	$334,306
Start Date: 7/1/2019	**End Date:** 6/30/2022
Progress Report:	End-Year 2
Report Due: 6/30/2021	**Report Received:** 6/29/2021

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Original Project Description:

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. The clinical trial is ongoing.

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

Report to Grant Sponsor from Investigator:

During the first 24 months of the trial, we have made progress toward our objectives. 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 treatment effect. 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 June 27, 2021, we have enrolled 14 dogs in the study and no dose limiting toxicities 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.

Propranolol and doxorubicin levels in the blood from eight of the dogs have been analyzed, and the analyses of samples from the others five dogs are pending. Samples from a sixth dog (dog #14 enrolled in the study) were collected just prior to the submission of our report, and the samples will be sent for analysis within the next 7-14 days.

Currently five dogs enrolled in the study are alive while nine dogs have succumbed to their disease.

Enrollment of dogs into the study was severely delayed by approximately six months due to the COVID-19 pandemic. Enrollment was halted at all three study sites (University of Minnesota, University of Pennsylvania, Purdue University) in early to mid-March. Although enrollment resumed at all three sites

in late June/early July, we were unable to enroll another dog until September 2020. The pace of enrollment has continued to increase since this time, likely due to the easing and/or lifting of travel restrictions related to COVID-19 throughout the country.

Our plans are to continue to screen and enroll dogs into the study with the goal of enrolling the remaining six dogs by December 31, 2021. We also plan to complete the analysis of drug levels (propranolol and doxorubicin) in the blood samples. Due to delays related to the pandemic, we plan to request an extension of the study in order to provide a complete follow up (up to one year) for all of the dogs enrolled.