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 and Antonella Borgatti, DVM, MS

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

Research Institution: University of Minnesota

Grant Amount: $334,306

Start Date: 7/1/2019 **End Date:** 6/30/2022

Progress Report: End-Year 1

Report Due: 6/30/2020 **Report Received:** 6/26/2020

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

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.

Presentations:

A description of the study design was presented at the 2019 AKC CHF National Parent Club Canine Health Conference, August 9-11, St. Louis, Missouri.

Report to Grant Sponsor from Investigator:

During the first year that the project has been active, 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 the circulating drug levels of propranolol after long-term administration to dogs with hemangiosarcoma to determine if there is a correlation between plasma drug concentration and treatment effect. We will also determine if propranolol alters the plasma 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 23, 2020, we enrolled six dogs in the study. Importantly, we were able to enroll dogs in all three dose cohorts (0.8 1.0, 1.3 mg/kg), and no dose limiting toxicities were noted in any of the dogs enrolled.

Propranolol and doxorubicin levels in the plasma from four of the dogs has been analyzed, and analysis of samples from the fifth and sixth dogs are pending.

The study has been delayed by approximately four 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. Enrollment has now resumed at the University of Minnesota as of June 22, 2020; enrollment is expected to resume at the University of Pennsylvania and Purdue University in July.

Our plans are to continue to screen and enroll dogs into the study with the goal of enrolling another 8-10 dogs within the next 6 months. We also plan to complete the initial analysis of drug levels in the plasma samples during this time.