RESEARCH PROGRESS REPORT SUMMARY

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

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Research Institution: University of Minnesota

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

Grant Amount: $334,306

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

Progress Report: Mid-Year 3

Report Due: 12/31/2021 **Report Received:** 12/31/2021

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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.

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.

Report to Grant Sponsor from Investigator:

We opened the trial on July 1, 2019. As of June 27, 2021, we have enrolled 18 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. The dog continues to do well and remains in the trail.

Propranolol and doxorubicin levels in the blood from all of the dogs enrolled to date have been analyzed.

Currently six dogs enrolled in the study are alive while twelve dogs have succumbed to their disease. Two of the dogs have survived for two years or more, and six dogs have lived longer than six months.

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, and we expect to enroll the final two dogs in the study by early 2022.

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. The request for the extension will be based on the date for the final dog enrolled.