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 Brian Husbands, DVM

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: $310,970

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

Progress Report: Mid-Year 1

Report Due: 12/31/2019 **Report Received:** 12/22/2019

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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:
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 6 months that the project has been active, we have made progress toward our objectives. Based on our experiences during this time, we have made some minor adjustments to the day-to-day running of the clinical trial and reporting of results. 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, and as of December 15, 2019, we have screened 10 dogs and enrolled three dogs in the study. Dogs that were not enrolled did not meet enrollment criteria (e.g. evidence of metastatic disease) or the owner declined enrollment. The first dog was enrolled in mid-September, the second in October, and the third dog in November.

Overall, propranolol has been well-tolerated by all of the dogs; no dose limiting toxicities were noted in the three dogs enrolled. One dog did have gastrointestinal upset that was attributed to the chemotherapy (doxorubicin) used in the study. Propranolol and doxorubicin levels in the plasma from two dogs has been analyzed, and analysis of samples from the third dog is pending. Our plans are to continue to screen and enroll dogs in 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.