Title: The treatment of canine brain tumors with Temozolomide incorporated into poly (lactic-co-glycolic acid) (PLGA) microcylinders

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Study description:
Many brain cancers are not accessible to surgical excision, and use of chemotherapy drugs is limited by the blood brain barrier. In an effort to deliver chemotherapy drugs directly into a cancer, novel polymeric microcylinders have been developed using poly (lactic-co-glycolic acid) (PLGA) as a biocompatible drug delivery system. These novel microcylinders have been designed to be amenable to stereotactic implantation, allowing for a minimally-invasive implantation procedure. The polymer can be adjusted for various degradation times, allowing the associated drug to be delivered over a prescribed period of time. Because the drug can be placed directly into the cancerous tissue, the blood brain barrier is bypassed entirely. This enables a high dosage of chemotherapy to be delivered into the cancer without the risk of systemic side effects associated with high-dose chemotherapy including myelosuppression or gastrointestinal upset.

Temozolamide is a chemotherapy drug that has been FDA approved for the treatment of glioblastoma multiforme (GBM) in humans, and was shown to provide a statistically significant benefit to 2-year survival and progression-free survival time in humans as part of multimodal therapy for GBM. Temozolomide has been demonstrated as safe in dogs with lymphoma, but there have been no studies evaluating its clinical efficacy for any type of brain tumor in dogs. The current objective is to study implantation of temozolomide and gadolinium-infused PLGA microcylinders in dogs with gliomas. Our preliminary studies confirm that PLGA microcylinders infused with both temozolomide and gadolinium are clinically well-tolerated in healthy dogs.

10 dogs diagnosed with a forebrain tumor using MRI images acquired at UGA or a referral practice and suggestive to be a glioma based on published characteristics will be enrolled in the study.

Inclusion criteria
- Dogs must be systemically well based on minimum data base, history and physical examination
- Dogs must judged to be only mildly neurologically affected by in-house neurologists based on (a) mentation level (b) normal cranial nerve function other than that associated with vision (c) absence of moderate or severe paresis (d) absence of moderate or severe ataxia (e) absence of compulsive demented behavior
- Dogs must be stable in terms of underlying seizure frequency, if any

Once deemed suitable for study enrollment, dogs will undergo anesthesia for surgery. A cerebrospinal fluid sample will be collected just prior to surgery. A biopsy of the brain tumor will be performed using a minimally invasive surgery technique (stereotactic guidance) involving a three dimensional
coordinate system to precisely locate the brain tumor. Afterward, temozolomide microcylinders impregnated with gadolinium, a common MRI contrast agent, will be placed using the same surgical technique to the extent necessary for adequate drug coverage of the tumor, which will vary based on tumor size and shape. Post-surgery, dogs will undergo a MRI to assess microcylinder placement prior to recovering from anesthesia. Dogs will be monitored in the ICU for a minimum of two days following implantation and will be discharged when it is clinically appropriate. Recheck examinations will be required at 30 days, and 3, 6, and 12 months after surgery for repeat MRI examinations. A small blood sample will be collected at these same time points for routine labwork. A repeat cerebrospinal fluid sample will be collected at 30 days post-implantation during the same anesthetic episode as the follow-up MRI.

If dogs appear to be deteriorating prematurely the owners may elect to pursue surgery and or radiation therapy at their expense.

The surgery and implantation procedure, MRI costs, post-operative hospitalization, blood and cerebrospinal fluid analysis, and repeat MRI examinations and associated costs will be covered by study funds as will any adverse events related to this course of treatment. The client will be responsible for costs associated with alternative treatments, such as radiation therapy.

**Duration of study:**
This study is currently OPEN. Study participation is 12 months duration following enrollment.

**Potential benefits to veterinary medicine:**
Results of this study may show that local delivery of chemotherapy to canine brain tumors and direct imaging of these novel microcylinders will lead to a treatment that is efficacious and safe.