

I. SCIENTIFIC ABSTRACT:

Scientific Abstract

There are 15,000 new cases of primary brain tumor with 11,000 deaths annually in the United States, and brain tumors are the second leading cause of cancer death in children and young adults. The most common primary brain tumor is the glioma which has a range of expression of malignancy extending from low grade glioma to glioblastoma multiforme (GBM). The current best therapy of malignant gliomas involves surgical removal followed by irradiation therapy and chemotherapy. Diffuse infiltration of tumor into adjacent normal brain tissue, limited penetration of chemotherapeutic agents through the blood-brain barrier, and the limited regenerative capacity of the brain all reduce the efficacy of conventional therapy. Even with aggressive surgical and radiation therapies patients with GBM have median survival times of 9 to 10 months. Median time to tumor progression for patients with recurrent glioblastoma multiforme is approximately 12 weeks and for patients with anaplastic astrocytoma it is approximately 20 weeks. Hence, the prognosis for this disease is bleak and compels investigation of new therapeutic avenues.

Direct introduction of therapeutic genes into malignant cells *in vivo* may provide an effective treatment of solid tumors including tumors of the central nervous system (CNS). Of these strategies, conferring drug sensitivity holds the greatest promise for clinical application in the near future. The gene coding for the herpes simplex virus thymidine kinase (HSV-tk) enzyme is the leading therapeutic gene. Thymidine kinase phosphorylates the nucleoside analog ganciclovir (GCV) into a phosphorylated intermediate that is incorporated into newly-synthesized DNA of dividing cells. The incorporated analog hinders further DNA replication leading to the cell's death. Since normal mammalian cells do not possess this enzyme, cytotoxicity depends on the successful introduction and expression of the HSV-tk gene, phosphorylation of ganciclovir, and synthesis of DNA. Non-dividing cells may express HSV-tk and phosphorylate ganciclovir but are not harmed since they do not synthesize DNA. This approach is especially suitable for the treatment of gliomas where rapidly dividing tumor cells invade adjacent tissues made up largely of non-proliferating cells. Several techniques have been used to introduce therapeutic genes to neural and non-neural tissue. Of these, viral transduction is currently the most efficient method. Vectors based upon retrovirus, herpes virus and adenovirus are the most common gene therapy. The adenovirus-based vectors have advantages over the other virus vectors that make them leading candidates for somatic gene therapy. We have demonstrated using two glioma animal models that adenovirus-mediated transfer of the HSV-tk gene and GCV treatment resulted in ablation of the tumors and significant increases in life spans.

This phase I study is designed to study the safety and efficacy of gene therapy for patients with CNS tumors. Patients with malignant CNS tumors refractory to all potentially curative therapy will be treated with stereotactic intra-tumor injections of replication-defective adenovirus vector delivering the HSV thymidine kinase gene. Initial tests will use 1×10^8 virus particles. Ganciclovir will then be administered intravenously at 10 mg/kg/day for 14 days. Only one course of therapy will be administered. Each patient will be carefully monitored for one month for cytopathic or toxic effects by several methods including MRI scans. Five patients will be tested with this low dose before another group of patients are treated with 5×10^8 particles and monitored closely for 1 month. This will be repeated until the target dose of 1.5×10^9 particles is reached or significant toxicity is detected. Effectiveness will be monitored by MRI and/or CT scans and by comparing survival times to the historical survival times for patients with recurrent brain tumors. The primary objective of this initial study is to determine whether the treatment is associated with significant toxicity.