

Scientific Abstract

Primary CNS malignancies are responsible for approximately 12,000 deaths annually in the United States. There has been little change in the outcome for adults with malignant brain tumors over the past few decades, despite improvements in surgical techniques and advances in radiation therapy. These tumors are uniformly fatal one to two years after diagnosis. The morbidity and mortality of this disease arises from the effects of a locally invasive, non-metastasizing lesion. The patients may suffer from seizures, paralysis, incoordination, aphasia, confusion, memory loss, sensory deficits or visual loss, depending on the regions of the brain affected. In addition, they usually require large doses of corticosteroids early and late in their illness, and may experience disabling side effects of this treatment, such as edema, proximal myopathy, diabetes, fungal infections or deep vein thrombosis. Few patients in the older age group are able to work after the diagnosis. Most of the patients are incapable of self-care for several months before death. The localized transfer of new genes into cancer cells potentially permits the expression of proteins with specific biologic functions that may provide a means to alter the biology of tumor growth through a variety of mechanisms including increasing tumor immunogenicity, inducing the local expression of toxic agents, and sensitization of tumors to chemotherapeutic agents. Gene therapy with the transfer of the drug susceptibility gene Herpes virus thymidine kinase (HSV-TK) has shown promise in a number of animal models, including CNS tumors. This study will evaluate the use of adenovirus-mediated transfer of the HSV-TK gene into primary human brain tumors followed by systemic treatment with ganciclovir. The goals of this phase I study is to evaluate the overall safety and efficacy of this treatment and to gain insight into the parameters that may limit the general applicability of this approach. In this phase I study, patients with recurrent gliomas will receive stereotactic-guided injections of the virus into the brain tumor, followed by intravenous ganciclovir for 14 days. Patients eligible to undergo a palliative debulking procedure will receive the same treatment followed by resection on day 7. At the time of resection a second dose of virus will be administered intra-operatively into the residual, unresectable portion of the tumor, and intravenous ganciclovir will be continued for additional 14 days. Tissue removed at the time of resection will be analyzed for evidence of adenovirus infection, thymidine kinase expression and signs of inflammation. The size and metabolic activity of all tumors will be followed by volumetric MRI scans and Positron Emission Tomography Scans, respectively. Patients will be enrolled in groups of three, with each group receiving successively larger doses of adenovirus. This study will quantify the toxicity of this therapy, and provide evidence as to the duration of transgene expression and virus induced inflammation.