

SCIENTIFIC ABSTRACT

The primary goal of this proposal is to utilize ADV/HSV-tk in a Phase I clinical trial in patients with high risk clinically localized prostate cancer (stage T1c and T2b/c) as neo-adjuvant therapy prior to radical prostatectomy to learn the toxicity profile of this *in situ* treatment approach. These patients are at high risk for local and systemic recurrence of their tumors. Adenovirus-mediated (ADV) transduction of the Herpes Simplex Virus thymidine kinase gene (HSV-tk) and ganciclovir (GCV) therapy has been shown to impact on a variety of experimental cancers. In a mouse model of prostate cancer, ADV/HSV-tk+GCV resulted in significant growth suppression of the treated primary tumor, in the inhibition of spontaneous metastatic activity, and in the inhibition of further development of pre-existing micro-metastases, indicating the induction of systemic anti-tumor activity. Prostate tumors will be injected with the escalating doses of vector in 3 patient tiers beginning at 1×10^9 pfu with the plan for 10 fold increases in the absence of toxicity to reach 1×10^{13} pfu. All patients will receive a 7 day course of GCV during which time patients will be monitored for toxicity through routine blood tests and for virus shedding within the blood. Patients will be discharged home following the completion of GCV to be readmitted 7-10 days later for the pre-scheduled prostatectomy. Since all patients will undergo lymph node dissection and removal of the prostate following treatment valuable information can be gleaned from an analysis of these tissues. These studies will determine the presence and spread of vector, yield an estimation of the transduction efficiency of vector and gage the induction of cytotoxicity and apoptosis within both benign and cancerous portions of the prostate. Several investigators have implied a role for the immune system in some of the activities relating to HSV-tk mediated cytotoxicity both locally and systemically. The production of cytokines within treated tumors and the catalogue of tumor infiltrating lymphocytes (TILs) will be ascertained to understand the role of the immune system in the treated tumor. Attempts will be made to document anti-tumor activity within the TIL, lymph node-derived lymphocytes, and peripheral blood mononuclear cell (PBMC) populations through chromium release assays. Likewise the induction of immune activity against both the adenovirus and the transgene will be performed using PBMCs, Lymph node-derived lymphocytes, and TILs, the results of which have far reaching ramifications for adenoviral mediated gene therapy. Therefore, this study will not only provide important information regarding the potential toxicity and efficacy of this treatment but also answer some important questions regarding the potential anti-tumor immunological activity incited by adenovirus mediated gene therapy and immunological activity induced against the adenovirus and/or transgene.