

I. SCIENTIFIC ABSTRACT:

Prostate cancer is the leading site of internal malignancy in men and the second most common cause of cancer deaths, an estimated 40,400 in 1995. Current therapies for localized prostate cancer include surgical removal of the prostate (radical prostatectomy) or local radiation therapy. Serum prostate specific antigen (PSA) is accepted as the most sensitive and specific indicator of recurrent or residual prostate cancer following therapy. Unlike radical prostatectomy, radiation therapy does not eradicate all PSA producing cells. PSA levels decline gradually after radiation therapy, reaching nadir levels one to two years after treatment. Failure to achieve a nadir PSA level within the normal range (<4 ng/ml) is indicative of residual or recurrent disease. In addition, a rising PSA correlates with treatment failure. Patients who develop a rising PSA subsequent to a normal PSA nadir are more likely to have a local relapse only, while patients who have persistent PSA elevation are at high risk of having metastatic disease. Although the detection of disease recurrence after radiation therapy for prostate cancer is relatively straightforward, the treatment of these patients is not. Salvage radical prostatectomy has been utilized in patients with a clinically localized recurrence of prostate cancer after radiation therapy. However, this procedure is associated with a significant complication rate. Approximately 5% to 15% will sustain rectal injuries, all but the reportable patient will be impotent, and up to one-half will have severe incontinence. In addition, final pathologic stage correlates poorly with preoperative clinical stage. We have found only 8 of 38 patients who had salvage surgery had truly organ confined cancer and the majority of patients developed evidence of disease recurrence following surgery. Because of the limited impact surgery has on this group of patients, new therapeutic options which include gene therapy should be evaluated to assess their impact on radiation recurrent prostate cancer.

Direct introduction of therapeutic genes into malignant cells *in vivo* may provide an effective treatment of solid tumors such as adenocarcinoma of the prostate. The herpes simplex virus thymidine kinase (HSV-tk) gene codes for an enzyme which phosphorylates the nucleoside analog ganciclovir (GCV) into an intermediate that is incorporated into newly synthesized DNA and terminates further replication, leading to cell 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 tumors where rapidly dividing tumor cells are adjacent to tissues made up largely of non-proliferating cells. Using human and animal models for prostate cancer we have demonstrated that adenovirus-mediated transfer of the HSV-tk gene resulted in sensitivity to ganciclovir of all cell lines tested *in vitro* and growth suppression of mouse prostate tumors *in vivo*.

This phase I study is designed to study the safety and efficacy of gene therapy for patients with locally recurrent prostate cancer after radiation therapy. These patients do not have any standard treatment which has been demonstrated to have a high degree of efficacy in eradicating the tumor with a reasonable degree of safety. Thus, the potential risks associated with the use of gene therapy in this group would appear reasonable. Tumors will be treated with transrectal ultrasound-guided intra-tumor injections of replication-defective adenovirus vector delivering the HSV-tk gene. Initial tests will use 1×10^8 particle forming units (PFU). Patients will be hospitalized for two weeks following virus injection at which time they will receive twice daily intravenous infusion of ganciclovir (5 mg/kg/dose; total 28 doses). Only one course of therapy will be administered. Each patient will be carefully monitored for cytopathic or toxic effects. Five patients will be tested with this low dose of virus. If there are no serious adverse side effects, the dose will be escalated to 5×10^8 PFU and then 2.5×10^9 PFU in a subsequent groups of 5 patients each, or until unacceptable toxicity is reached. Effectiveness will be monitored with serial measurements of serum PSA, digital rectal examination, transrectal ultrasound of the prostate, and prostate biopsy; and by comparing survival times to historical survival times for patients with radiation recurrent prostate tumors. The primary objective of this initial study is to determine whether the treatment is associated with significant toxicity.