

Scientific Abstract

Clinical Protocol for Wild Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity via an Adenoviral Vector

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A discreet group of patients with preneoplastic lesions of the oral cavity exists for which we have no meaningful treatment other than conventional surgical approaches. Unfortunately, conventional surgery does not take into account the multifocality of these processes as well as the high incidence of recurrence and 2nd primary lesions involving aerodigestive tract sites. Biochemoprevention approaches in preneoplastic lesions of the oral cavity site have demonstrated disappointing results with more than 50% of patients progressing in our prospective trial of cisretinoic acid, alpha interferon and alpha tocopherol. Biomarker studies have suggested that those patients with mutant p53 and genetic instability were at greatest risk of progression. The objective of this research is to directly modify the precancerous cell to express large quantities of an exogenously introduced, normal tumor suppressor gene product that may reverse the premalignant process by inducing apoptosis in the cancer predisposed cells, allowing for re-population with normal genotype and phenotype epithelial cells. Our goal is to determine the transduction efficiency of adenoviral mediated wild type p53 gene transfer in premalignancies of the upper aerodigestive tract and to determine the efficacy of single agent adenoviral mediated wild type 5 3 gene transfer in reversing oral premalignancies.

Patient eligibility includes males and females 18 years of age and older with clinical evidence and histologically confirmed diagnosis of mild - severe dysplasia or carcinoma in-situ of the oral cavity. Patients may have received conventional treatment for a prior head & neck malignancy, but must have a life expectancy of at least 12 months and a Zubrod performance status of <2. Female patients of childbearing potential must have a negative serum pregnancy test. Male and female patients must agree to use barrier contraception while on study, and to avoid pregnancy for 1 year after treatment. Patients must have negative serology for the Human Immunodeficiency Virus. Adequate bone marrow function (peripheral absolute granulocyte count of 2,000/mm³ and platelet count of 100,000/mm³), adequate liver function (bilirubin <1.5 mg/dl), and adequate renal function (creatinine 1.5 mg/dl) are required for participation. All patients must sign an informed consent indicating that they are aware of the investigational nature of this study in keeping with the policies of the institution.

Patients will receive an Ad5 CMV p53 injection and oral rinse on day 1 followed by twice-daily oral rinses on days 2-5 in addition to lab work, research blood draws, and photo documentation for the completion of one cycle. The study cycle will be repeated on a monthly basis for a period of six months. This is a limited dose escalation study. A total of 12 patients will be entered into the phase I dose-finding trial with 33 patients anticipated to be entered into the phase II trial. Biopsies of normal and preneoplastic tissue are performed at pretreatment and two hours following the last A.M. oral rinse of the 1st and 6th cycles. Alternative biologic endpoints will also be monitored through the collection of serum and urine. Maximal transduction rate will be determined by immunohistochemistry of p53 and downstream gene products.