Retrovirus Mediated Injection Of Barrett's Esophagus Lesions With Wild Type P53

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This will be a pilot study for proof of principle and safety of injected wild type p53 into esophageal dysplastic lesions via a retroviral vector.

A. Background

Barrett's Esophagus is defined as the replacement of the normal squamous epithelium of the esophagus with columnar epithelium. It is a peculiar form of healing that is the result of the constant exposure of the esophagus to acid that is refluxed from the stomach. Barrett's Esophagus is known to be a premalignant lesion and a major risk factor for Adenocarcinoma of the Esophagus. It is thought to be a step in the path from Metaplasia to Dysplasia to Carcinoma.

It is thought that as much as 20% of the general population suffers from GERD (Gastroesophageal Reflux Disease). In these patients, there is a high correlation between the subjective reporting of reflux symptoms in patients in whom short segments of Barrett's esophagus lesions are found.

Adenocarcinoma of the Esophagus has the fastest rising incidence of any cancer in the last 20 years. It is estimated that 1 adenocarcinoma of the esophagus will arise every 208 patient-years. The incidence of Adenocarcinoma of the esophagus has increased from 0.13 to 0.74 from 1935 to 1989.

The p53 gene is a Tumor Suppressor Gene. It acts by surveying the genome for DNA damage and inducing DNA repair at that site. In this way p53 acts as a checkpoint at the GI-S Junction of the cell cycle. If p53 is unable to facilitate the repair of DNA damage, it induces apoptosis, or programmed cell death. In this way p53 prevents the accumulation of mutations in the genome. As cancer is thought to be abnormal growth due to the accumulation of mutations, p53 prevents cancer. If there is a mutation in the p53 gene itself, the tumor suppression function is lost as genetic mutations are allowed to be promoted. Mutations of p53 are present in cancers from many tissue types, including the esophagus. In one study, 45% of all esophageal cancers were found to have mutant p53.

Because loss of p53 function is associated with oncogenesis, it is thought that restoring normal p53 can prevent cancer in a premalignant lesion, and perhaps even reverse cancer where it has already started. P53 has potent transforming activity in vitro, but it has yet to be proven in vivo studies.

B. Overview of Study Design

An outline of the study follows:

Step 1: Patients undergoing EGD (Esophagogastroduodenoscopy) will be assessed as all patients are for the presence of Barrett's Esophageal lesions. Biopsies will be taken of the areas and the sites of biopsies will be documented (distance from the GE junction to the biopsy site and the area of the lesion).

Based on the histology of the biopsy, patients will be offered the chance to participate in the study. Patients with Barrett's, Esophagus and documented p53 mutations are eligible.

Step 2: Patients who agree to enter the study will undergo another EGD. During this EGD the esophageal lesion will be injected with 10 ml of Retroviral Supernatant. The 10 ml will be evenly divided between 2 to 5 injections in the lesion depending on the size of the lesion, so as to evenly distribute the supernatant.

Step 3: Patients will undergo a third EGD 4 weeks from the therapy. At this time biopsies will be taken from the areas that were previously mapped out. These specimens will be analyzed for the presence of viral vector and for any evidence of cell death (apoptosis).

a. Assessment of Toxicity

Patients will be evaluated for toxicity according to the National Cancer Institute's Common Toxicity Criteria.

C. Subjects

All patients are eligible for the study. They must able to tolerate EGD and biopsy. They must also show evidence of p53 mutation in the studied lesion.

D. Medical Devices:

This study mill use standardized endoscopic equipment.

E. Location of Study

All aspects of the study will take place in the outpatient setting.

F. Alternative Therapies.

Patients will be allowed to continue all other therapies during the study period.

G. Compensation and Cost to Subjects:

There will be no compensation offered and no cost to the patient.

H. Minors and Research Subjects

Minors will not be involved in the study.

I. Radiation

There will be no radiation involved in the study.