

A Safety and Efficacy Trial of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene in Combination with Adjuvant Chemoradiotherapy for the Treatment of Adenocarcinoma of the Pancreas

Scientific Abstract

Background

Cancer of the pancreas is the tenth leading cause of cancer in the United States with an estimated incidence of 29,500 new cases in 1999. It is also one of the most lethal malignancies and is currently the fifth leading cause of cancer death with an estimated number of deaths in 1999 similar to the incidence rate. The death rate in pancreatic cancer is exceeded only by lung, colorectal, breast, and prostate cancer. Despite recent advances in the overall understanding of pancreatic cancer at the molecular level, improved imaging techniques to identify disease at an earlier stage, improved surgical techniques as well, as a growing body of literature that supports the role of adjuvant therapy, the 1-year survival is still on the order of 20% with a median survival of 15 to 19 months for resectable disease and a 5-year survival of approximately 3% for all stages combined. Only one drug, Gemcitabine, is currently approved for this disease. This drug was approved by the FDA based on a significant improvement in quality of life only.

Objectives

1) To estimate overall survival and disease-free survival in patients with minimal residual disease treated with adjuvant chemoradiotherapy in sequence with the irradiated allogeneic GM-CSF-transfected pancreatic tumor cell lines versus chemoradiotherapy alone; 2) to estimate the association of specific *in-vivo* parameters of immune response with clinical responses in patients with minimal residual disease treated with combination chemoradiotherapy together with the irradiated, allogeneic GM-CSF-transfected pancreatic tumor cell lines (by postvaccination delayed-type hypersensitivity reactions to autologous tumor, and the degree of local eosinophil, macrophage, and T-cell infiltration at the vaccine site); and 3) to further identify and characterize toxicities reported in the phase 1 trial.

Patient Population

Sixty patients with Stage 1, 2, or 3 adenocarcinoma of the pancreas.

Study Design

Phase II open-label, single-dose.

Treatment Plan and Schedule

Following surgical resection of the pancreas, patients will receive a combination of 5-FU-based chemotherapy and local radiation in sequence with a pancreatic tumor vaccine

consisting of two irradiated, allogeneic pancreatic tumor cell lines transfected with the GM-CSF gene.

Patients will receive their first vaccination 8 to 10 weeks following surgery. Sixteen days after vaccination, patients will begin a 26-week course of adjuvant radiation and chemotherapy at Johns Hopkins. Four to eight weeks following completion of the last cycle, eligible patients will receive two additional vaccinations at 1-month intervals. Patients who continue to remain disease-free will receive a fourth "booster" vaccination 6 months following the third vaccination.

Dose

The vaccine consists of equal numbers (2.5×10^8 each) of Panc 6.03 and Panc 10.05 cells combined into a single vaccination. Vaccine cells frozen at 2.5×10^8 cells/vial will be thawed on the day of vaccination, washed twice with sterile saline, and irradiated. Vaccine cells will be resuspended to a concentration of 8.3×10^7 cells /0.7 mL. Each patient will receive 6 intradermal injections, in the right and left thighs and the nondominant arm.

Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) is defined as any grade 3 or 4 nonhematological toxicity excluding alopecia, grade 3 hematologic toxicity, and grade 4 hematological toxicity which does not resolve in less than 5 days. If a DLT (except alopecia) occurs, treatment will be stopped. Treatment may be restarted if the DLT resolves to < grade 2. If the toxicity continues at \geq grade 2 for 4 weeks then the patient will be removed from further treatment in the study.

Safety Evaluation

The toxicity data collected will be descriptive, characterized according to the National Cancer Institute Common Toxicity Criteria. Safety parameters, physical examination, hematology, and serum chemistry. Monitoring for adverse events• will be done using an internal and external monitoring system.

Product

Two allogeneic cell lines have been developed from neoplastic tissue harvested from the surgical specimens of patients undergoing pancreaticoduodenectomy at The Johns Hopkins Hospital. These cell lines have been characterized as 100% epithelial by cytokeratin staining (Jaffe et al, Human Gene Therapy 1998;9:1951-1971). In addition, these cell lines carry the same k-ras mutation as the original tumor specimen, which supports the conclusion that these lines are derived from malignant pancreatic tumor cells. The cell lines Panc 10.05 and Panc 6.03 were chosen because they contain the most common *k-ras* mutation at codon 12 found in greater than 90% of pancreatic cancer. Panc 10.05 and Panc 6.03 were genetically modified to secrete GM-CSF by plasmid DNA transfection (Jaffe et al, Human Gene Therapy 1998;9:1951-1971; Jaffee et al, Cancer J Sci Am 1998;4(3):194-203).

Summary of Trial to Date

We began recruiting patients into a phase II study January 30, 2002 (New Protocol Amendment was submitted in July 10, 2001 (Amendment BB-IND 7136/012). The phase II study is a safety and efficacy trial of 5×10^8 lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene in combination with adjuvant chemoradiotherapy for the treatment of adenocarcinoma of the pancreas. Since that time we have consented 36 patients. Of the 36 patients, 25 were found to be eligible for the study and received at least one vaccination. Of the 25 patients that received at least one vaccination, 15 (62%) remain on study with no evidence of disease recurrence. Six subjects have now received more than one vaccination. Of the five subjects that have received three vaccinations, 80% remain disease-free. One patient is currently disease free after receiving the second vaccination. Five subjects who had received one vaccination only had disease progression before receiving the second vaccination. One subject has had local recurrence after three months after receiving the third vaccination.

All patients experienced local vaccine related adverse events including redness, swelling, and pruritus. Other less frequent side effects observed that may be related to the vaccine include: headache, low grade fever, and diarrhea.

Three serious adverse events were recorded during this reporting period. Two subjects who received one vaccination are off study without evidence of recurrence. One patient with pre-existing coronary artery disease had a coronary event during radiation and chemotherapy treatment and died of this event. A second patient is recovering from a 5-FU toxicity related to adjuvant chemotherapy. One subject was hospitalized three months after receiving the third vaccination for pain control as a result of disease recurrence. These serious adverse events were not related to the vaccine therapy.