Scientific abstract

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the US with 20,000 deaths per year (Lillemoe et al, 2000). Approximately 40% of patients have metastases at diagnosis and a median survival of only 3-6 months. Another 40% have locally advanced unresectable disease which is usually treated with chemotherapy and radiation with equally dismal results.

Surgery is the only potentially curative therapy for pancreatic cancer at this time but is only applicable for approximately 20% of patients who have localized disease. Conventional chemotherapy and radiotherapy are relatively ineffective. Over the last decade there have been advances in the development of cancer gene transfer, especially in terms of suitable vectors. On the whole, replication-incompetent adenoviruses are the vectors of choice due to their low pathogenicity, ability to carry large therapeutic genes and a proven track record.

Direct introduction of therapeutic genes into malignant cells in vivo may provide an effective treatment of solid tumors such as adenocarcinoma of the pancreas. The herpes simplex virus thymidine kinase (HSV-tk) gene codes for an enzyme which phosphorylates the nucleoside analog gancyclovir (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 GCV and synthesis of DNA. Non-dividing cells may express HSV-tk and phosphorylate GCV 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 pancreatic cancer we have demonstrated that adenovirus-mediated transfer of the HSV-tk gene resulted in sensitivity to GCV in vitro and in growth suppression of mouse pancreatic tumor in vivo.

Adenoviral-mediated gene transfer, combining the herpes simplex virus thymidine kinase gene (AdV-tk) with GCV, has been evaluated as a treatment modality for numerous tumors in the laboratory and in the clinics. As a single modality, gene transfer has shown some promising local and systemic results. Clinical studies have proven that it is beneficial to combine gene transfer with chemotherapy, radiation and surgery.

Based on lack of significant toxicity of AdV-tk + prodrug in combination with radiation or chemotherapy in previous clinical trials for other tumor types, severe toxicity is not expected in this trial.

However, given the extremely poor prognosis of patients with pancreatic cancer and the promising results seen in preclinical trials, it is justified to assume limited risk to examine this novel approach in patients with pancreatic cancer.

Since this approach has not yet been studied in pancreatic cancer, the first phase of the trial will be a dose-escalation study followed by expansion to a phase 2 study at the maximum tolerated dose (MTD) level if all levels are well tolerated.

This is a phase 1/2, open-label, single arm gene transfer clinical trial of AdV-tk + valacyclovir in combination with standard chemoradiation for newly diagnosed patients with unresectable pancreatic cancer. The rationale for this research is based on preclinical studies demonstrating local and systemic anti-tumor effects of AdV-tk/prodrug gene transfer, which is accentuated in combination with chemoradiation, and the poor prognosis with current standard therapeutic approaches for pancreatic cancer.

The primary objective is to test safety of AdV-tk + valacyclovir in combination with standard chemoradiation for pancreatic cancer. The secondary objectives are to

evaluate clinical efficacy and immune reactivity. The first phase of the trial will be a dose escalation with 3 patients per dose group. Four dose levels of AdV-tk, ranging from $3x10^{10}$ to $1x10^{12}$ vector particles in half-log increments, will be evaluated. Once the maximum tolerated dose is reached or the highest dose level is completed without significant toxicity, the trial will continue to phase 2 and will accrue up to a total of 40 evaluable patients at that dose level.

Patients will have intratumoral injection of AdV-tk via endoscopic ultrasound, which is performed for diagnostic biopsy in these patients, followed by 14 days of the oral prodrug, valacyclovir. Intensity modulated radiation therapy (IMRT) will be delivered via helical tomotherapy. Radiation will begin within 48 hours and up to 72 hours after the injection with 1000cGy X 2 to a target that includes the pancreatic mass that has been recently injected. The patient will subsequently receive 5 FU chemotherapy and IMRT within 7 days of the vector injection. The new target volume will include the pancreatic mass with a margin along with N1 and N2 lymph nodes as described by the Japanese nodal staging system. Target will be outlined utilitilizing the Anatom-e targeting system. The patient will be treated to 4500cGy in 180cGy fractions with a subsequent boost of 540cGy. Patients unable to have IMRT performed with helical tomotherapy (for technical reasons) will have IMRT performed with the *varian clinac*, and if this is not feasible, patients will have three-dimensional conformal radiation (3DCRT) performed utilizing the previously described target volumes.

AdV-tk gene transfer is a promising approach, which may be incorporated as an adjuvant to standard chemoradiation therapy with a non-overlapping toxicity profile and may improve the treatment of pancreatic cancer.