

A Phase I/II Study of Hepatic Infusion of Autologous CC49-Zeta Gene-Modified T Cells in Patients with Hepatic Metastases from Colorectal Cancer.

Scientific Abstract:

Adenocarcinoma of the large bowel affects approximately 15% of the population of the Western world and is the second most common cause of cancer and cancer-related deaths in the United States. In the United States alone, 155,000 new cases of colorectal cancer are diagnosed per year resulting in 61,500 annual deaths. This cancer spreads by direct extension through the bowel wall, hematogenous metastases, regional lymph node metastases, perineural spread, and intraluminal metastases. The most common site of distant metastases is the liver with lung, bone and brain metastases occurring much less frequently. Approximately 75% of patients have liver metastases at the time of death. Despite a modest improvement in the 5-year survival rate of colon cancer patients from 41% to 54% over the past 30 years, a significant unmet medical need for more effective therapy still exists for this disease.

The proposed protocol will evaluate the intra-hepatic delivery of CC49-zeta gene-modified T cells in patients with hepatic metastases from colorectal cancer. Rather than isolating and expanding rare, MHC-restricted, tumor antigen-specific T cell clones, a method has been developed to rapidly generate large numbers of antigen-specific, MHC-unrestricted T cells using retroviral-mediated gene transfer to insert a tumor-targeting gene into primary CD8⁺ and CD4⁺ T cells. The tumor-targeting gene, CC49-zeta, encodes a genetically-engineered, MHC-unrestricted, chimeric receptor directed against a tumor antigen present on most colorectal carcinomas. The DNA introduced into the cells encodes a receptor that is made from an antibody that recognizes a tumor-specific marker expressed on colon cancer cells, linked to a signaling chain derived from the human T cell receptor. The genetically-modified cells can be expanded *ex vivo*, resulting in the rapid generation of large numbers of high affinity tumor-specific T cells. This approach has been used to generate genetically-modified T cells specific for TAG-72, a tumor-associated antigen expressed on a wide range of adenocarcinomas.

The study is a phase I/II, open label, inpatient dose escalation of autologous CC49-zeta gene-modified CD4⁺ and CD8⁺ T cells administered via the hepatic artery in patients with hepatic metastases from colorectal cancer.