

Intrathecal Gene Therapy for the Treatment of Leptomeningeal Carcinomatosis

Non-technical Abstract

Meningeal carcinomatosis is a complication of systemic cancer where malignant tumor cells seed the coverings of the brain and spinal cord (leptomeninges). The infiltrating tumor occurs in 5% to 20% of all cancer patients, and most adult cases are due to breast or lung cancer. Patients with leptomeningeal carcinomatosis present with a variety of neurological symptoms corresponding to involvement of cranial and spinal nerves, and infiltration into brain and spinal cord tissues. The prognosis is extremely poor. When maximal therapy is tolerated (intrathecal chemotherapy and whole-brain irradiation) mean survival is limited to 6-7 months and fewer than 15% of the patients are alive at one year. In an attempt to improve this grim prognosis of patients with leptomeningeal carcinomatosis, we have developed a novel approach for the treatment of this disease. This approach makes use of recombinant DNA technology to make the tumor cells sensitive to an antiviral drug called ganciclovir (GCV). Sensitivity to the drug is achieved by transferring a foreign gene into the malignant cells. This gene is the thymidine kinase gene from the herpes simplex virus. Cells that produce mouse viruses, which had been genetically engineered to contain the thymidine kinase gene, are injected into the subarachnoid space (intrathecal space; the space that is filled with cerebrospinal fluid and is in contact with the tumor cells in the leptomeninges). The viruses transfer the gene into the tumor cells and 7 days later the patient is treated with GCV, which leads to death of the tumor cells. Since the thymidine kinase enzyme which is normally present in mammalian cells has very low affinity for GCV, systemic toxicity related to this mechanism is not expected.

The proposed clinical trial will evaluate the distribution of retroviral vectors in the subarachnoid space, assess the safety of this approach, and evaluate its potential antitumor efficacy. As the study progresses, increasing numbers of producer cells will be injected into the ventricular system (cerebrospinal fluid-filled cavities in the brain) and the spinal subarachnoid space. Indications of antitumor efficacy will include monitoring of clinical symptoms, craniospinal MRI scans, and CSF analysis for the presence of tumor cells and tumor markers. A total of 20 patients will be enrolled in the various phases of the study.

This is the first clinical attempt to treat meningeal carcinomatosis by *in vivo*, intrathecal, genetic manipulation of the tumor's genome.