1. Scientific Abstract

Many malignancies are associated with somatic mutations in p53. Quantities of abnormal p53 protein are often markedly increased in tumor cells as a consequence of such mutations, and several studies have shown that cytotoxic T cells that recognize non-mutant epitopes in p53 can selectively kill malignant cells, but not normal cells. Therefore non-mutant p53 may be a reasonable shared antigen for tumor selective immunotherapy. One immunotherapeutic strategy that is being developed by numerous investigators is to use dendritic cells (DC's), which are potent antigen presenting cells, "loaded" with target tumor antigens. One method of "loading" DC's with target antigens is to use an adenoviral vector that contains the gene coding for the target antigen. It has been shown that DC's can be transduced with recombinant adenoviral vectors and effectively present the protein encoded by the transgene carried by the adenoviral vector, and that this does not decrease DC function or viability.

Recent studies have suggested that development of new immunity to select antigens is more robust in a host recovering from total or near-total ablation of mature immune cells, such as following lymphO-myeloablation and hematopoietic progenitor cell transplantation. Moreover, augmentation of the hematopoietic progenitor cell transplant with candidate memory T cells may accelerate development of immunity.

This is a phase I/II study involving patients with extensive-stage small cell lung cancer (SCLC), who will be treated conventionally to reduce the bulk of their disease, and then subsequently will have hematopoietic progenitor cells (HPC) and dendritic cell (DC) precursors harvested by apheresis. The subject patients will then be immunized with a series of three vaccines consisting of DC transduced with the wild type p53 gene using an adenoviral vector (Ad-p53 DC). Another apheresis will be collected following this first round of vaccines, from which non-regulatory T cells will be expanded *ex vivo*. Patient subjects will then undergo high dose cytotoxic therapy with the combination of ifosfamide, carboplatin and etoposide (ICE) and will receive autologous HPC transplantation. Following transplantation, expanded autologous T-lymphocytes will be returned. Finally, a second series of three DC vaccines will be administered. Patients will be followed for disease response will be monitored for evidence of immune responsiveness to p53.

SCLC has an extremely poor prognosis, even though initial responses to chemotherapy are frequent. Furthermore, mutations in p53 occur in approximately 90% of patients with SCLC, and of these, about 90% overexpress mutant p53 protein. This makes these patients suitable for the testing of the clinical efficacy of the Ad-p53 DC vaccine. Early responsiveness to chemotherapy suggests clinical value in the application of high dose cytotoxic therapy and HPC transplant, which affords the added advantage of potentially maximizing the immunologic response, particularly with the supplementation by excess T-lymphocytes.