

1.0 OBJECTIVES

- 1.1 To determine the response rate and response duration of patients with disseminated malignant melanoma to treatment with intratumoral gene therapy and concomitant low dose subcutaneous IL-2.
- 1.2 To evaluate the toxicities of this combination therapy regimen.
- 1.3 To correlate the antitumor response to evidence of gene expression and T cell infiltration of the tumor.

2.0 BACKGROUND

Human tumors are immunogenic and can induce effective anti-tumor responses. (1) Various approaches to immunotherapy including interferon (IFN), interleukin-2 (IL-2) and specific tumor vaccines, induce remissions in patients with a variety of cancers including melanoma, renal cancer, breast cancer, etc. (2 - 4) In these studies, complete or partial remissions have been observed in 10 to 35% of patients.

Gene therapy with gene-modified tumor cell vaccines offers the promise to improve upon these statistics. In animal models, vaccination protocols with gene-modified tumor cells have proven superior to non-modified tumor cells. Cells are transfected or transduced with genes encoding various immunomodulatory proteins including: IL-2, IL-4, IL-7, IL-12, IFN- γ , TNF- α or GM-CSF. (5 - 11) These cells do not grow when implanted into syngeneic mice and induce protection to subsequent challenge with wild type tumor cells. This protection is not induced by pre-immunization with wild type tumor cells. Also, the effect of immunization with gene-modified cells is abrogated by antibody to CD8 + cells suggesting the induction of tumor specific T cell mediated immunity.

In one experiment, Nabel and co-workers used the insertion of an allogeneic MHC class I antigen into murine tumor cells in vivo to induce an allogeneic response against the tumor. (12) In the course of the allogeneic response, an immune response was also induced against the tumor-associated antigens of the wild type tumor. Both transfected and non-transfected tumor cells were killed by a cytotoxic T cell response. Survival was prolonged.

This work was then translated into a clinical study. Five HLA-B7 negative patients with metastatic melanoma received intra-tumoral injection of the HLA-B7/B2M genes in a plasmid delivered via a cationic lipid vector. The HLA-B7 DNA, mRNA and HLA-B7 protein were detected in injected tumors from 4/5, 4/5, and 5/5 patients, respectively, and one patient had a partial remission. (13)

A Phase I study of the direct intratumoral injection of the HLA-B7/B2M genes was carried out in 17 patients with melanoma, 14 patients with renal cell carcinoma and 15 patients with colon cancer. (14 - 16) Of 14 evaluable melanoma patients, seven showed regression of the injected nodules and one also had regression of a non-injected nodule. Eleven of these patients received only one dose while three received 2 injections and three received 3 injections. There was no toxicity of the gene therapy and the only side effects were related to the mechanics of the injection procedure. A Phase II study based on these results will be conducted this year in patients with melanoma, renal cancer, breast cancer, colon cancer and non-Hodgkin's lymphoma.

There is evidence in animal systems that several cytokines can augment the immune response to a variety of antigens including microbial antigens and tumor antigens. Systemically administered cytokines including IFN- γ and IL-2 significantly augment the development of tumor immunity to tumor cell vaccines and induce a greater generation of CTL than tumor cells alone. (17 - 19)

The immunomodulatory doses and schedules of both IFN- γ and IL-2 have been well worked out in humans. (20 - 21) Therefore, their use as immunomodulators for tumor vaccines has a rational scientific basis. Furthermore, these immunomodulatory doses are relatively non-toxic. Long-term

subcutaneous IL-2 administration has proved safe, non-toxic and to improve the overall immune responsiveness of cancer patients. (22 - 33) --- --

Based on the above, we have hypothesized that a combination of intratumoral gene therapy plus systemic administration of immunomodulatory cytokines should induce more effective anti-tumor immunity and remissions in melanoma and should be safe and relatively non-toxic.

Therefore, this Phase II protocol will investigate the intra-tumor injection of the allogeneic HLA-B7 gene plus the systemic administration of a cytokine for the treatment of metastatic malignant melanoma. This protocol specifically will study intratumoral administration of HLA-B7 followed by IL-2 given systemically in a Phase II study. In particular, we are interested in determining if the subcutaneous administration of IL-2 enhances the development of systemic antitumor immunity and results in regression of non-injected nodules.

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects.