SCIENTIFIC ABSTRACT OF PROPOSED STUDIES

We propose to study whether immunization with cytokine secreting tumor cells will induce host anti tumor responses in cancer patients. Our first protocol will be a phase I study in melanoma patients and will address whether allogeneic HLA-A2 matched melanoma cells expressing a recombinant human IL-2 gene can be used as vaccine without causing major toxicity. Furthermore, to determine whether such a vaccination protocol is applicable for non-melanoma tumors a similar approach will be used in renal cell carcinoma patients. Toxicity studies will be done in stage IV renal carcinoma patients vaccinated with HLA-A2 matched IL-2 secreting renal carcinoma cells. Serologic and cellular host antitumor responses will be assessed in both groups.

Autologous tumor cell lines are difficult to establish and not available for many patients. There is substantial experience at MSKCC and at other institutions that has established the general safety of immunization using irradiated allogeneic tumor cells. The choice of allogeneic HLA-A2-positive tumor cells in our initial studies is based on the following considerations, first, HLA-A2 molecules expressed on allogeneic cells are capable of presenting identical peptides derived from the same tumor associated antigen to HLA-A2 positive effector populations. Second, the use of a single established well characterized immunizing cell line bypasses the necessity to introduce the cytokine gene into autologous tumor cells for each patient. Growing autologous tumor cells in tissue culture can be a difficult and time-consuming procedure and the success rate for establishing autologous tumor cell lines can be quite low. Third, since approximately 40% of North Americans are HLA-A2 positive, a tumor vaccine produced from HLA-A2 matched allogeneic tumor cell lines could be used in a substantial subpopulation of melanoma patients and renal carcinoma patients.

Evidence exists that tumor specific cytotoxic cell precursors are present in melanoma, renal cell carcinoma, lung and breast carcinoma patient. These effector cells have been found in PBMC and can be expanded in vitro and in vivo. Several laboratories, including our own have shown in animal studies that introduction of cytokine genes into tumor cells is feasible and that such modified tumor cells induce potent host anti-tumor responses. Presumably, by allowing the tumor cells to present both the antigenic peptide by the MHC- class I molecule and the second signal in form of the secreted IL-2, allows a substantial clonal expansion of tumor specific effector cells. By having access to systemic circulation in vivo these effector populations have access to residual tumor at distant sites.