C.2 Scientific Abstract.

Vaccination in Peripheral Stem Cell Transplant Setting for Multiple Myeloma: The Use of Autologous Tumor Cells with An Allogeneic GM-CSF Producing Bystander Cell Line

This study is designed to investigate the use of autologous, lethally irradiated myeloma cells admixed with a bystander cell (CG9962) engineered by plasmid gene transfer to secrete human granulocyte-macrophage colony-stimulating factor (GM-CSF) as a therapeutic vaccine. Phase I/il studies of vaccination with autologous, irradiated, cultured tumor cells, engineered by retroviral or adenoviral-mediated gene transfer to secrete human GM-CSF, have been performed in melanoma, renal cell carcinoma, lung, and prostate cancer. Phase I/II studies of allogeneic GM-CSF-modified tumor cell vaccines have also been performed in prostate and pancreatic cancer. These studies have revealed the consistent development of potent antitumor immunity without the induction of significant toxicity. We are now attempting to extend these principles to multiple myeloma in the setting of an autologous peripheral stem cell transplant. We are investigating the use of an allogeneic bystander GM-CSF-producing cell (CG9962) mixed with autologous tumor cells as the vaccine formulation. The final vaccine is referred to as Myeloma Bystander GVAX®.

Multiple myeloma is a disease with approximately 12,000 to 13,000 new cases a year. Current standard therapy is chemotherapy. Patients who have obtained a significant response to chemotherapy, and undergo an autologous peripheral stem cell transplant (ASCT) following high dose chemotherapy, have an enhanced disease-free and overall survival compared with standard dose chemotherapy treatment alone. In spite of this recent progress, only 25% of patients undergoing ASCT live longer than 5 years and only 5% are alive past 10 years. Clearly there is significant room for improvement in the current treatment of this disease, which is still largely considered incurable. We have designed a trial in which tumor-specific vaccines are combined with chemotherapy and ASCT for the treatment of multiple myeloma.

Objectives

The primary objectives of the study are to evaluate clinical and laboratory safety associated with administration of Myeloma Bystander GVAX and to determine the feasibility of generation of Myeloma Bystander GVAX. Secondary objectives are to evaluate in vitro and in vivo immunologic responses to vaccination as well as clinical responses including reductions in monoclonal protein (m-protein) levels, disease progression, and survival.

Patient Population

Up to 30 patients with de novo multiple myeloma to achieve at least 15 evaluable patients (receipt of at least 4 post transplant vaccines)

Study Design

Phase I/Il open-label, single-center study.

Treatment Plan and Schedule

Patients with multiple myeloma with > 30% bone marrow involvement and no more than once cycle of prior chemotherapy are eligible. Enrolled patients undergo myeloma cell harvest by large volume bone marrow aspiration under general anesthesia. Patients then receive standard chemotherapy and those with > 50% reduction in tumor burden are eligible to proceed with the study. Eligible patients receive a pre-transplant vaccination followed 14 days later by leukapheresis to collect "vaccine-primed" lymphocytes for reinfusion with the stem cell graft. Patients then undergo stem cell mobilization chemotherapy with collection of peripheral blood stem cells (PBSC) followed by high dose pre-transplant preparative chemotherapy (or chemoradiotherapy) and ASCT with reinfusion of the PBSC graft and the vaccine-primed lymphocytes. Eight post-transplant vaccinations are then given beginning 6 weeks post-transplant or at the time of hematopoietic recovery.

Dose

Patients are vaccinated at one of three dose levels depending on tumor cell yield from the bone marrow harvest. Each vaccination contains tumor cells admixed with CG9962 cells at a ratio of 5: 2 and vaccines are administered by multiple intradermal injections. Tumor cell dose levels are: 1 x $l0^7$ (4 x 10^6 CG9962); 4 x 10^7 (1.6 x 10^7 CG9962); and 1 x 10^8 (4 x 10^7 CG9962).

Endpoints

The primary endpoints of the trial are: 1) To evaluate clinical and laboratory safety associated with administration of Myeloma Bystander GVAX; and 2) To determine the feasibility of generation and administration of Myeloma Bystander GVAX. The secondary endpoints are: 1) To demonstrate the priming of tumor-specific immunity in response to vaccination with Myeloma Bystander GVAX using clinical and laboratory endpoints; 2) To characterize the kinetics of immune reconstitution and assess immunocompetence at regular intervals before and after transplant; 3) To demonstrate the ability to generate tumor-specific immune responses prior to transplant and to demonstrate adoptive transfer of immunity through the infusion of these "primed" lymphocytes as part of the peripheral blood stem cells (PBSC) graft; 4) To monitor tumor response; and 5) To monitor disease progression and survival.

Safety is being monitored by recording adverse events and laboratory evaluations. Feasibility is being assessed by the overall success rate of tumor harvest and autologous tumor cell processing. Immunologic response will be measured by DTH reaction to injections of irradiated, autologous tumor cells, in vitro monitoring of tumor-specific B and T cell responses, and overall monitoring of immune reconstitution. Clinical activity will be assessed by monitoring m-protein levels in the blood and urine and bone marrow plasma cell content as markers of disease burden. Disease progression and overall survival will be monitored, however, the study, is not powered to draw any meaningful conclusions about the relative impact of vaccination on disease progression or survival compared to historical data.

Product

Myeloma Bystander GVAX consists of two components, CG9962 cells and autologous, irradiated tumor cells mixed just prior to administration at a ratio of 5 tumor cells to 2 CG9962 cells. The CG9962 cell product was generated from a K562 erythroleukemia cell line engineered by plasmid transfection to secrete human GM-CSF. These cells are grown in suspension, irradiated at 10,000 rads to arrest cell growth, formulated in a dimethyl-sulfoxide (DMSO)-containing cryoprotectant and frozen in liquid nitrogen. Autologous tumor cells are obtained by bone marrow aspiration, processed to isolate mononuclear cells, irradiated at 10,000 rads, frozen in autologous serum and DMSO, and stored in liquid nitrogen. Tumor and CG9962 cells are thawed just prior to administration, mixed together, and injected intradermally without further manipulation.

Protocol Amendments

Three protocol amendments to the original protocol have been generated dated June 21, 2001, December 12, 2001, and October 18, 2002. The last amendment was generated during the reporting period of September 14, 2002 through September 13, 2004. Significant changes in this amendment included: 1) increasing the number of enrolled patients to not more than 30 patients to achieve at least 15 evaluable patients; 2) increase in the estimate of the maximum dose of GM-CSF administered at the highest vaccine dose from 68 to 200 mcg/24 hours; 3) broadening of the rules regarding regimens and number of cycles to be administered as induction chemotherapy; 4) addition of a post-transplant vaccine screen visit and an optional skin biopsy of the anergy panel (Candida) skin test site; 5) addition of long term follow up for late toxicities of gene therapy; 6) clarification of concomitant medications, adverse event reporting periods, safety laboratory parameters for proceeding with transplant, and toxicity stopping rules.

Trial Status

This phase I/lI study of Myeloma Bystander GVAX is currently ongoing. Enrollment has been completed and patient treatment and data analysis is in process. There are no plans to initiate any new trials with this vaccine product this year.