

Scientific Abstract

GM-CSF secreting leukemia cell vaccinations after allogeneic non-myeloablative peripheral blood stem cell transplantation in patients with advanced myelodysplastic syndrome or refractory acute myeloid leukemia

This pilot trial will investigate the use of autologous, irradiated myeloblasts engineered by adenoviral mediated gene transfer to secrete human granulocyte-macrophage colony stimulating factor (GM-CSF) as vaccinations in patients with advanced myelodysplasia (MDS) or refractory acute myeloid leukemia (AML) after allogeneic non-myeloablative stem cell transplantation. A total of up to 24 patients will be vaccinated on this study beginning 30-45 days post transplant. Each vaccine dose, consisting of 1×10^6 to 1×10^7 irradiated, GM-CSF secreting autologous myeloblasts, will be injected subcutaneously weekly times three, and then every two weeks times three.

Allogeneic hematopoietic stem cell transplantation is a potentially curative therapy for some patients with hematologic cancers, primarily through an immune-mediated graft-versus-leukemia effect. The application of less toxic, non-myeloablative conditioning regimes renders a larger number of patients eligible for transplantation. However, disease relapse remains the most frequent cause of treatment failure for patients with AML or MDS after non-myeloablative stem cell transplantation. One strategy to augment the efficacy of transplantation involves cancer vaccinations. Indeed, our pre-clinical experiments in murine tumor models demonstrated that vaccination with irradiated tumor cells engineered to secrete GM-CSF, following T-cell depleted allogeneic bone marrow transplantation, stimulated potent anti-tumor immunity without the exacerbation of graft-versus-host disease.

In this pilot clinical trial, we will investigate the feasibility, safety, and biologic activity of GM-CSF secreting autologous tumor cell vaccines for patients with refractory MDS or AML following non-myeloablative allogeneic stem cell transplantation. Vaccines will be manufactured using an E1, E3 deleted adenoviral vector (serotype 5) engineered to express GM-CSF from myeloblasts harvested prior to allogeneic non-myeloablative stem cell transplantation. Patients will initiate vaccination between days 30 to 45 post-transplantation, after stable neutrophil engraftment has been achieved. Standard clinical and laboratory measurements of toxicity and graft-versus-host disease will be made. Immunologic activity will be assessed through analysis of vaccination site reactions, the development of delayed-type hypersensitivity to irradiated, autologous myeloblasts, and laboratory assays of anti-leukemia antibody and T cell responses. An ongoing Phase I study of this immunization strategy in non-transplanted MDS and AML patients has demonstrated that vaccination can stimulate anti-leukemia immunity without inducing any significant toxicity.

The overall goals of the pilot trial are to determine:

- 1.1 Feasibility, as measured by ability to generate sufficient vaccine and initiate vaccination between day 30-45 following transplantation
- 1.2 Safety, as measured by grade III-IV acute GVHD, or CTC grade ≥ 3 non-hematologic toxicity attributable to vaccination
- 2.1 Biologic activity of vaccination
- 2.2 Disease-free and overall survival