

SCIENTIFIC ABSTRACT

The goal of this project is to test the use of "suicidal lymphocytes" as a means of controlling graft-versus-host disease (GVHD) thereby expanding the population of patients able to benefit from the graft-vs.-leukemia effect (GVL) associated with allogeneic transplantation.

The ability to fully harness the immunologically mediated graft-versus-leukemia (GVL) effect noted after allogeneic marrow or stem cell transplantation is limited by the development of GVHD. Current therapies, designed to prevent or treat GVHD are sub optimal and the risk of GVHD remains a major barrier preventing many leukemia patients from undergoing allogeneic transplantation and benefiting from a GVL effect. A novel strategy to control GVHD is to selectively eliminate the GVHD initiating T-cell after infusion, instead of suppressing the function of all T-cells. This selectivity is generated by transducing T-cells ex-vivo with a retrovirus containing the herpes simplex virus-thymidine kinase (HSV-TK) gene. These "suicidal" lymphocytes are then infused into the patient. Should GVHD develop the "suicidal lymphocytes" are eliminated by the administration of ganciclovir (GCV) to which they are now sensitive.

Specific Aim: The protocol foresees inclusion of up to 20 patients ≥ 18 years old affected by hematological malignancies at high risk based on disease progression or presence of negative prognostic factors, who have received a stem cell transplantation from donor HLA mismatched (haploidentical) for 2 or 3 loci. The trial will use a double turnstile approach for accrual. Patients eligible for transplantation as defined below will be registered and begin therapy with the intention of receiving the planned DLI with the TK+ T-cells on days 42, 72 and 102 ± 7 days. At the time of each planned infusion, patients will need to meet a second set of inclusion and exclusion criteria, based on their condition post transplant, before receiving the planned DLI. Up to 14 patients in remission and up to 6 patients in relapse will be included in the DLI phase. Based on the data from the European phase I-II trial, 21 patients were transplanted and 13 received the DLI, suggesting that total accrual will approximate 30 patients.

Primary objectives of the trial are:

- Evaluation of clinical activity of HSV-TK+ lymphocytes in terms of immune-reconstitution after SCT
- Evaluation of the *in vivo* control of GvHD after administration of ganciclovir in patients treated with HSV-TK transduced cells
- Evaluation of GvL effect

The primary activity parameters for the evaluation of immune-reconstitution are:

- Number of circulating CD 3⁺ ≥ 100 /microliter
- Number of circulating CD 3⁺/CD 4⁺ ≥ 50 /microliter
- Number of circulating CD 3⁺/CD 8⁺ ≥ 50 /microliter

The primary activity parameters for the evaluation of the incidence/control of GvHD and Gvl effect are:

- Occurrence of GvHD and response to ganciclovir
- Number of circulating transduced cells after treatment with ganciclovir
- Evaluation of GVL effect by clinical, radiological, molecular, hematological and cytogenetical criteria