SUMMARY

Administration of leukemia-reactive donor T cells after allogeneic stem cell transplantation (allo-SCT) or donor lymphocyte infusion (DLI) to patients with persistent or relapsed mature B cell neoplasm with blood and/or bone marrow involvement.

Objectives

Primary Objective:
• To investigate the feasibility and safety of administration of donor leukemia-reactive T cells.

Secondary Objectives:
• To evaluate the persistence of leukemia-reactive T cells after administration.
• To evaluate whether administration of leukemia-reactive T cells leads to complete remission (CR), partial remission (PR) or mixed response (MR) within 12 weeks after last infusion.

Population

Patients with persistent or relapsed mature B cell neoplasm (see Appendix A) with blood and/or bone marrow involvement at least 3 months after last donor immune cell infusion (allo-SCT or DLI).

Inclusion criteria

• allo-SCT patient with a sibling or unrelated stem cell donor matched for at least HLA-A, -B, -C, and –DR alleles (8/8)
• Age 18-75 years
• WHO performance score 0-2
• Persistent or relapsed mature B cell neoplasm with blood and/or bone marrow involvement at least 3 months after last donor immune cell infusion (allo-SCT or DLI).
• Possibility to collect > 5 x 10^7 mononuclear cells containing ≥ 40% malignant B cells from blood or bone marrow of patient, or availability of patient malignant B cells cryopreserved at a GMP-facility
• Donor willing to donate PBMC, or cryopreserved donor PBMC available in an amount of ≥1 x 10^9 MNC/ total
• Written informed consent

Exclusion criteria

• Life expectation < 3 months
• End stage irreversible multi-system organ failure
• Acute GvHD overall grade ≥ II
• Treatment with corticosteroids in an equivalent dose of >0.5 mg/kg prednisone
• Expectation of necessity to administer chemotherapy within 3 months after administration of leukemia-reactive T cells
• Pregnant or lactating women
• Severe psychological disturbances
Sample size calculation
This is an exploratory study, so no power calculations can be made. We aim to administer leukemia-reactive T cells to 5-7 patients per year for a period of 3 years with a total of 20 patients.

Flowchart:

Collection and cryopreservation of patient malignant B-cells from blood or bone marrow

Leukapheresis of donor PBMC or thawing of cryopreserved donor PBMC's

Fulfilling in- and exclusion criteria

1st Generation of leukemia-reactive T-cells

3 weeks

1st infusion of leukemia-reactive T-cells (check contraindications §5.6)

3 weeks

Contraindication for 2nd infusion? (§5.8)

Yes → Follow up

No

2nd Generation of leukemia-reactive T-cells

3 weeks

2nd infusion of leukemia-reactive T-cells (check contraindications §5.6)

Follow up
Investigational product
The leukemia-reactive T cell product is a donor T cell population selected in-vitro, based on their reactivity against the malignant B cells (leukemia or lymphoma) of the patient. First, to increase their immunogenicity, the malignant B cells present in peripheral blood or bone marrow collection of the patient are transformed into malignant APC using cytokines and CD40 crosslinking. Naïve donor T cells are enriched from a leukapheresis product of the stem cell donor who donated the allogeneic stem cell graft by depletion of CD14+ monocytes and depletion of regulatory T cells (Treg) and activated memory T cells by depletion of CD25 positive cells. To generate leukemia-reactive T cells, these naïve donor T cells are stimulated with the malignant APC and cultured for 14 days. After a second stimulation with the malignant APC the leukemia-reactive T cells are isolated based on their expression of the activation marker CD137, followed by limited subsequent post-isolation in-vitro expansion. This T cell product will then be adoptively transferred to the patient.

Since the repertoire of T cells is determined by the specificity of the cells in the CD137+ fraction, the number of T cells in this fraction will be determined directly after the selection, and the portion of the leukemia-reactive T cell product that will be cultured and administered to the patient will be adjusted if necessary to stay below the defined accepted dose. Based on the results obtained in the currently used clinical protocol for unselected DLI given at 3 months after allo-SCT for patients with high risk leukemia, we anticipate that a dose of ≤0.3x10^6 of unselected donor T cells of unknown specificity per kg bodyweight of the patient can be administered with acceptable expected toxicity in case of a related donor. For unrelated donors the frequency of potential GvHD-inducing T cells is expected to be higher due to the higher number of genetic differences between patient en donor. Therefore, the tolerable dose of unselected T cells from unrelated donors is ≤0.5x10^6 T cells per kg bodyweight of the patient. The risk of GvHD induction by the leukemia-reactive T cell product is determined by the repertoire of T cells in the CD137+ fraction directly after isolation. Post-isolation expansion will not increase the GvHD risk. Therefore, the maximal number of T cells that may be administered to the patient is 1x10^6 cells per kg bodyweight of the patient. This number will be determined in the final leukemia-reactive T cell product after post-isolation expansion.

Before administration, the leukemia-reactive T cell product is centrifuged, washed and suspended in 100 ml NaCl 0.9% and 4% human albumin.

Investigational treatment
Leukemia-reactive T cells are a cell therapy product that will be administered to patients with persistent or relapsed disease from 3 months after allo-SCT or DLI. The maximal number of T cells that may be administered to the patient is 1x10^6 cells per kg bodyweight of the patient. This number will be determined in the final leukemia-reactive T cell product after post-isolation expansion. Post-isolation, the maximal dose of unselected donor T cells of unknown specificity in case of a related donor will be ≤0.3x10^6 per kg bodyweight of the patient and in case of an unrelated donor ≤0.15x10^6 per kg bodyweight of the patient. The cells will be administered intravenously at the department of Hematology of the Leiden University Medical Center (LUMC) during a clinical short stay with a maximum of 1 night. In
In case of contraindications for administration of leukemia-reactive T cells, administration will be postponed or cancelled. When the infusion of this leukemia-reactive T cell product is well tolerated by the patient, a second product will be generated and infused 6 weeks later.

**Risk/benefit**

The potential benefit of this treatment will be the induction of a curative Graft versus Leukemia/Lymphoma effect mediated by the donor T cells recognizing the malignant cells of the patient. A potential risk may be the administration of non-leukemia-reactive T cells in the final product, harboring potential GvHD reactivity.

**Contraindications for administration of leukemia-reactive T cells**

- Life expectation < 6 weeks.
- End stage irreversible multi-system organ failure.
- Acute GvHD overall grade ≥ II.
- Treatment with corticosteroids in an equivalent dose of >0.5 mg/kg prednisone.

**Study endpoints**

**Main study endpoints**

- The number of acute GvHD, other serious adverse events and deaths within 12 weeks after last infusion of leukemia-reactive T cells.
- The feasibility of generation of leukemia-reactive T cells for administration.

**Secondary study endpoints**

- Increase in number of leukemia-reactive T cells in blood and/or bone marrow at different time points after infusion of leukemia-reactive T cells.
- CR, PR and MR rate 12 weeks after last infusion of leukemia-reactive T cells.