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

Published: 19-09-2012
Last updated: 26-04-2024

- To investigate the feasibility and safety of administration of donor leukemia-reactive T cells- To evaluate the persistence of leukemia-reactive T cells after administration- To evaluate whether administration of leukemia-reactive T cells leads to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON37016

Source
ToetsingOnline

Brief title
Leukemia reactive donor T cells

Condition

- Other condition
- Leukaemias

Synonym
leukemia; lymphoma

Health condition

lymfomen

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Zon-MW

Intervention

Keyword: allogeneic stem cel transplantation, leukemia reactive donor T cells, mature B cel neoplasm

Outcome measures

Primary outcome

- 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 outcome

- 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.

- Time to next leukemia/lymphoma treatment.

Study description

Background summary

Patients with hematological malignancies can be successfully treated with

allogeneic hematopoietic stem cell transplantation (allo-SCT). The aim of this strategy is to replace the (malignant) hematopoietic system of the patient with cells of donor origin. The curative potential of this strategy is not solely caused by the cytoreductive treatment regimen preceding the transplant, but relies for an important part on the immune responses mediated by immune effector cells (e.g. T cells and NK cells) of the donor against the hematopoietic compartment from the patient including the malignant cells. One of the major challenges in the field of allo-SCT is to find a balance between the harmful induction of graft-versus-host disease (GvHD) and the beneficial graft-versus-leukemia/lymphoma (GvL) response, both mediated by donor T cells recognizing antigens expressed on cells of the recipient. The chance of inducing GvL and/or GvHD depends on the expression of the targeted antigens on hematopoietic and/or non-hematopoietic cells.
At the LUMC, allo-SCT is performed using grafts depleted of mature donor T cells to decrease the risk of inducing severe acute GvHD after transplantation. This strategy is successful, but obviously limits the induction of GvL responses, which is reflected by an increased incidence of (early) disease relapses after T cell depleted allo-SCT. In previous clinical studies we have shown that delayed application of mature donor T cells by conventional donor lymphocyte infusions (DLI) 6 months after the T cell depleted allo-SCT results in GvL responses with limited induction of acute GvHD. Earlier application of unselected mature donor T cells resulted in the induction of GvHD in a significant number of patients, thereby limiting the therapeutic applicability of unselected DLI for the treatment of early relapses occurring in the first months after the transplant. Moreover, efficient GvL responses after DLI are most efficiently induced in patients with chronic myeloid leukemia (CML) in chronic phase, whereas in patients with acute forms of leukemia (e.g. CML in accelerated phase or blast crisis, acute lymphoblastic leukemia (ALL), or acute myeloid leukemia (AML)), and in patients with less immunogenic forms of leukemia, like chronic lymphocytic leukemia (CLL), curative GvL responses are induced in only a minority of the patients.
In-vitro induction and selection of leukemia-reactive T cells may be an elegant strategy to overcome the problem of inefficient induction of GvL reactivity in-vivo and to select for T cells preferentially recognizing the malignant cells, thereby reducing the likelihood of concurrent development of GvHD. Previously, we reported the successful treatment of a patient with accelerated phase CML refractory to DLI who received in-vitro generated leukemia-reactive donor T cells resulting in a molecular complete remission. However, in this initial procedure no specific selection step was included, requiring extensive long-term in-vitro culture to enrich the leukemia-reactive T cells. This extensive in-vitro culture will hamper the in-vivo potential of the T cells. Therefore, in the current protocol we select the leukemia-reactive T cells based on surface expression of an activation marker, allowing us to limit the required in-vitro culture period. Moreover, the limited immunogenicity of leukemic cells of some patients hampered the proper in-vitro priming of GvL responses for these patients. Especially for the B cell malignancies (CLL, ALL, and mantle cell lymphoma (MCL)) it was observed that in-vitro manipulation was

pivotal to increase the immunogenicity of the malignant B cells. Pre-clinical work demonstrated that crosslinking of CD40 on the surface of the malignant B cells resulted in rapid and homogeneous upregulation of costimulatory and adhesion molecule expression, which significantly increased their immunogenicity and allowed successful induction of GvL responses in-vitro.
In the current protocol we will test the safety, tolerability and potential clinical efficacy of adoptive transfer of leukemia-reactive T cells in patients with relapsed or persistent mature B cell malignancies after allo-SCT or DLI. Malignant B cells present in peripheral blood or bone marrow samples of the patient are transformed ex-vivo into antigen-presenting cells (APC) using cytokines and CD40 crosslinking. Naïve donor T cells will be enriched from a leukapheresis product by depletion of regulatory T cells (Treg) and activated memory T cells, and will be stimulated with these malignant APC. Two weeks after this initial stimulation, the donor T cells will be restimulated with malignant APC and those T cells that are capable of recognizing the leukemic cells will be isolated based on their expression of the activation-marker CD137 after restimulation. Since the T cells in this leukemia-reactive T cell product are selected for reactivity against the hematopoietic (malignant) target cells, we anticipate that we have skewed the T cell repertoire in the direction of GvL reactivity, thereby diminishing the risk of inducing GvHD compared to the infusion of unmodified DLI. The leukemia-reactive T cell product comprises both cytotoxic CD4 or CD8 positive T cells and helper CD4 or CD8 positive T cells that do not exert a direct cytotoxic effect but will produce cytokines in response to stimulation with the malignant cells. Since it will be a combined response, we will define leukemia-reactivity of the T cells as their capacity to respond to the leukemic cells as demonstrated by the expression of the activation marker CD137 upon restimulation. It is anticipated that both cell types will contribute to the potential clinical effect of the treatment.

Study objective

- To investigate the feasibility and safety of administration of donor leukemia-reactive T cells
- 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

Study design

This is an open-label non-randomized phase I/II feasibility study to administer leukemia-reactive T cells to 20 patients with persistent or relapsed mature B cell neoplasm with blood and/or bone marrow involvement at least 3 months after allo-SCT or DLI, in a maximal dose of 1x10^6 adoptively transferred cells per kg bodyweight of the patient.
First, malignant cells will be collected from the patient and cryopreserved

under GMP conditions (if no cryopreserved malignant cells are available). Secondly, a leukapheresis product will be obtained from the donor.
The leukemia-reactive T cells will be generated from the PBMC from the leukapheresis product as summarized in the investigational medicinal product chapter of the protocol.
The leukemia-reactive T cells will be administered to the patient when the product meets the release criteria and the patient has no contraindications for administration of the cells. When the infusion of the leukemia-reactive T cell product is well tolerated by the patient, a second product will be generated and infused 6 weeks later.
Follow-up will be performed until 12 weeks after administration of the last T cell product or until subsequent DLI, whichever comes first. From then, routine follow up will be performed.

Intervention

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/kg 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 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.

Study burden and risks

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 contaminating non-leukemia-reactive T cells in the final product, harboring potential GvHD reactivity.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 allo-SCT or DLI;
- Possibility to collect > 5 x 10^7 mononuclear cells containing > 25% 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
- Pregnant or lactating women
- Severe psychological disturbances

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-06-2013
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	19-09-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-10-2012

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-003691-40-NL
CCMO	NL41794.000.12

Study results

Date completed:	25-08-2016
Actual enrolment:	4