A phase I/II *minor histocompatibility antigen (mHag)-based Dendritic cell (DC) vaccination trial after allogeneic Stem Cell Transplantation (allo-SCT) to improve the safety and efficacy of donor lymphocyte infusions.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON37500

Source
ToetsingOnline

Brief title
mHag donor DC vaccination in haematological malignancy

Condition

- Plasma cell neoplasms

Synonym
bone marrow and lymphatic organs, cancers of the blood, hematological malignacy

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: KWF UU 2011-5136

Intervention

Keyword: DC vaccination, Donor lymfocyte infusion, hematological malignancy, minor histocompatibilty antigen

Outcome measures

Primary outcome

Primary endpoints are the evaluation of safety and efficacy, the occurance of

GvHD and the induction of a positive response to the combined DLI and DC

treatment

Secondary outcome

The immune effects of the combined modality including the induction of specific

mHag responses

Study description

Background summary

For many patients with a hematological malignancy donor stem cell transplantation is the only chance on a cure. The therapeutic effect of this therapy is due to so called killer cells (T lymphocytes) present in the donor transplant. These cells may recognize the cancer cells based on the presence of specific structures on the membrane (minor histocompatibility antigens: mHags) en subsequently kill them. Donor T cells (DLI) are frequently infused in patients that have not responded optimal to the donor stem cell transplant. However this procedure may be complicated with severe and sometimes fatal complications :Graft versus Host Disease. This is caused by the attack of the T cells on normal organs of the patient. Additionally in many patients the anti-tumor effect of the killer cells is too weak due to the lack of so called antigen presenting cells (Dendritic cells: DC). These DCs must stimulate the T

cells and activate them against the cancer cells. It is likely that the therapeutic effect of the infusion of donor T cells (DLI) is improved by co-infusion of donor DC*s that are loaded with suitable hematopoietic restricted mHags

Study objective

The objective of the study is to improve the T cell killing by treating the patient with in the laboratory cultured professional antigen presenting cells (DCs) which are loaded with specific antigens that are only present on blood and cancer cells of the patient (hematopoietic restricted) and absent on the healthy organ cells of the patient.

Study design

This is a phase I/II study with the primary goal to evaluate the safety and efficacy of a combined DLI and DC vaccination for relapsed or residual disease after donor stem cell transplantation and a previous DLI. Study endpoints are grade 4 CTC toxicity, late onset acute GvHD grade 3 and 4 en for efficacy response criteria related to the different hematological malignancies

Intervention

Suitable patients will be treated with a combined infusion of donor DC*s and DLI which are loaded with relevant mHags. Patients with minimal 1 relevant mismatch in the Graft versus Tumor direction are eligible (HA-1, HA-2, ACC1, ACC2, PANE1, LRH-1, CD19L, UTA2-1 or HB-1). The infusion of the DC*s will be repeated twice. Patients will be monitored for side effects, anti-tumor response , immune effcts and the development of specific anti-mHag responses. Positive outcome of the study may implicate that Donor DC vaccination will become standard for patients with relapsed and residual disease after donor stem cell transplant with the aim to improve the cure rate.

Study burden and risks

Burden associated with participation: The usual procedure for patients not responding to a first DLI is a second DLI containing a higher T cell dose. Patients included in the vaccination trial will receive the same T cell dose combined with the DC vaccination. For both categories of patients routine investigations at the out patient clinic weekly or two weekly are performed to monitor the general physical status status and tumor load of the patients. This may include bone marrow investigations, immune phenotyping and cytogenetics and imaging techniques like CT scans, MRI and/or PET scans.

Extra study procedures include: DC vaccinations 3 times repeated with an interval of 2 weeks. Blood sampling for evaluation of the immune effects: 40

ml of blood will be obtained at week -2 and at weeks 0, 1, 2, 4 , 6, 10, 14 and 20 after the first vaccination and DTH skin tests at 2 weeks after the third DC vaccination

Risks associated with the investigational product. Potential risk is the induction of GvHD. To minimize this side effect we will infuse the same T cell dose as given with the first DLI and maintain an interval of at least 10 weeks between the first and second DLI. In addition to avoid overlapping toxicities we will keep an interval of 4 weeks between recruiting in the first 3 patients and starting the DLI + vaccination. This will allow interrupting the vaccination scheme in the following patients in case unacceptable toxicity is observed in the preceding patient.
In a previous phase I/II trial of DLI combined with unloaded host DC*s no toxicity (GvHD) was recorded. (manuscript submitted). As in the current trial we will use only haematopoietic restricted mHags we expect but cannot exclude excessive toxicity. For this reason toxicity is one of the major endpoints of the study.

Benefit: A second dose escalated DLI is the standard next treatment step for patients not responding to a first DLI. This procedure is associated with a substantial risk of severe sometimes fatal GvHD. If proven feasible and effective, (sustained) complete remissions may be achieved in patients with an otherwise fatal outcome of their disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Patient with a measurable persistent disease after preceding DLI given for persistent or relapsed malignancy after allo-SCT. Reinduction chemotherapy in case of rapidly progressive disease (e.g. in AML) is allowed.
2. Recipient and donor with at least one relevant mismatch in mHags HA-1, HA-2, ACC1, ACC2, PANE1, LRH-1, CD19L or HB-1 in the Graft versus Tumor (GvT) direction (recipient mHag positive, donor mHag negative).
3. Recipient and donor positive for the relevant HLA, presenting the mismatched mHag(s).
4. Expression of the mismatched mHag in the lineage from which the malignancy has arisen.
5. Age 18-70 years
6. Absence of acute GvHD > grade 1 or extensive chronic GvHD
7. No prior or concomitant treatment for 8 weeks with immunosuppressive drugs such as prednisone, cyclosporine A and MMF.
8. WHO performance 0-2 (see appendix 1)
9. Absence of severe cardiac hepatic, renal, or metabolic disease
10. Written informed consent

Exclusion criteria

1. WHO performance 3-4
2. Presence of severe cardiac hepatic, renal, metabolic disease
3. Rapidly progressive disease, despite reinduction therapy
4. Life expectancy < 3 months

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):	23-05-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic
Product type:	Medicine
Brand name:	mHag peptide loaded DC vaccin

Ethics review

Approved WMO Date:	22-06-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-09-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-10-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	15-12-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-09-2015
Application type:	Amendment
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
Other	12402 NTR
EudraCT	EUCTR2012-002435-28-NL
CCMO	NL39604.000.12