A phase I/II *minor histocompatibility antigen UTA2-1 loaded, PD-L silenced Dendritic cell vaccination trial after allogeneic Stem Cell Transplantation to improve the safety and efficacy of Donor Lymphocyte Infusions.

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Primary objectives:- To evaluate the toxicity and feasibility of a DLI-combined minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination in B cell hematological malignancies- To evaluate the effect of a DLI-combined minor H ag UTA2-1...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON43853

Source
ToetsingOnline

Brief title
minorHag loaded, PD-L silenced DC vaccine for hematological cancers

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
hematological B cell malignancies blood cell cancer

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZON-MW 95103005

Intervention

Keyword: Allogeneic stem cell trasplantation, Dendritic cells, Hematological malignancies, Minor Histocompatibility antigens, PD-L silencing, Therapeutic vaccination

Outcome measures

Primary outcome

The primary study parameters are

-To evaluate the toxicity and feasibility of a DLI-combined minor H ag UTA2-1

peptide-loaded, PD-L silenced donor DC vaccination in B cell hematological

malignancies

- To evaluate the effect of a DLI-combined minor H ag UTA2-1 peptide-loaded,

PD-L silenced donor DC vaccination on the immune status of the recipient in

correlation with toxicity and response, including the investigation of the

induction of UTA2-1 specific T cell responses after vaccination.

Secondary outcome

Te secundary study parameter is to evaluate the efficacy of the DLI-combined

minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination to induce

a GvT for B cell hematological malignancies.

Study description

Background summary

Allogeneic stem cell transplantation (allo-SCT) is the only curative option for a number of hematological malignancies including acute and chronic leukemia, lymphoma and myeloma, due to a donor T cell-mediated Graft versus Tumor effect (GvT). Unfortunately sustained complete remissions are only achieved in 30-60% of patients depending on disease category and disease characteristics. Donor lymphocyte infusions (DLI) are routinely applied in patients with relapsed or residual disease after allo-SCT. However, only a minority of patients responds to DLI. Furthermore DLI can cause severe and sometimes fatal side effects mainly due to Graft versus Host Disease (GvHD). Therefore strategies are urgently needed to improve the efficacy and safety of DLI.
An attractive strategy to improve the safety and efficacy of DLI is targeting donor T cells towards hematopoietic-system-specific minor histocompatibility antigens (minor H ags). We have recently discovered the UTA2-1, a novel HLA-A2 restricted hematopoietic minor H ag antigen with a ~60% population frequency and high expression in multiple myeloma (MM) and B cell malignancies. We now propose a vaccination strategy, in which patients with MM and B cell malignancies such as chronic lymphocytic leukemia (CLL) and Non-Hodgkin Lymphomas, who are not responding to a first DLI will be treated with a second DLI combined with a therapeutic vaccine consisting of donor DCs loaded with the peptides of UTA2-1 minor H ag. Since recent evidence indicates that co-inhibitory PD-L1/2 molecules present on DCs can negatively influence the generation of minor H ag T cell responses, we will also knock down these molecules on DCs by an innovative siRNA technology.
This approach is built on the following well established concepts:
i) Dendritic cells (DCs) are the best known professional antigen presenting cells, considered crucial for the development of an adequate immune response,
ii) minor H ags are the main targets of donor T cells inducing GvT,
iii) targeting donor T cells against hematopoietic minor H ags can induce a specific anti-tumor response without increasing the risk for GVHD.
iv) we have recently shown that DLI combined with minor H ag-peptide pulsed recipient- or donor-DC vaccination is clinically feasible, safe and induces peptide specific T cell responses (unpublished results).

Study objective

Primary objectives:

- To evaluate the toxicity and feasibility of a DLI-combined minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination in B cell hematological malignancies
- To evaluate the effect of a DLI-combined minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination on the immune status of the recipient in correlation with toxicity and response

Secondary objective:

- To evaluate the efficacy of the DLI-combined minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination to induce a GvT for B cell hematological malignancies.

Study design

A single center phase I/II trial with the primary goal to evaluate the safety and efficacy of a combined DLI and DC vaccination strategy tor relapsed or residual disease after donor stem cell transplantation and a previous DLI.
Study endpoints are grade 4 CTC toxicity, late ons et acute GvHD grade 3 and 4. For clinical efficacy response criteria related to the different hematological malignancies will be applied.

Intervention

Suitable patients will be treated with a combined infusion of DLI (same dose as the first DLI) with ex vivo cultured donor DCs that are a) stripped of PD-L molecules by means of a siRNA transfection methodology and b) loaded with peptides of the UTA2-1 antigen. DCs will be administered at a total dose of 45-90x10^6 DCs, in 3 servings with two weeks intervals; only the first administration will be combined with DLI. Patients will be examined for the occurrence of side-effects, anti-tumor effect, influence on the immune system and the development of specific immune responses against the UTA2-1 antigen. Upon positive results of the research this vaccination strategy can become a standard treatment for the treatment of appropriate patients with malignant hematologic diseases, with the ultimate aim to increase the chances of cure.

Study burden and risks

Burden associated with participation: The usual procedure tor patients nat raspondingtoa 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 are performed in weekly or two weekly intervals to monitor the general physical 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 mi of blood will be obtained at week -2 and at weeks 0, 1, 2, 4, 6, 10, 14 and 20 after the first vaccination.
Risks associated with the investigational product. Potential risk is the induction of GvHD. Ta 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 previous phase I/II trials of DLI combined with peptide loaded host or donor DC's, no toxicity (GvHD) was recorded. In the current trial we will use only UTA2-1, a strictly haematopoietic restricted antigen. Therefore we expect no GvHD, 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

Public
Vrije Universiteit Medisch Centrum

de Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

de Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

1. Patients with Multiple Myeloma (MM), Chronic Lymphocytic Leukemia (CLL), non hodgkin lymphoma (any grade),
2. Proven residual disease (including as determined by disease-specific or patient-specific PCR) minimally 6 months after allogeneic Stem Cell Transplantation (allo-SCT) and subsequent persistent or relapsed disease after a first therapeutic DLI
3. Recipient and donor have a mismatch in UTA2-1 mHag in the Graft versus Tumor (GvT) direction (recipient UTA2-1 positive, donor UTA2-1 negative).
4. Recipient and donor are positive for HLA-A*0201
5. Age 18-75 years
6. Absence of acute GvHD > grade 1 or extensive chronic GvHD
7. No treatment with immunosuppressive drugs such as prednisone, cyclosporine A and MMF at least 8 weeks prior to planned vaccination date.
8. WHO performance 0-2
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:	Will not start
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	28-10-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-03-2016
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	EUCTR2015-003554-41-NL
CCMO	NL53992.000.15