A phase I/II trial to boost the graft-versus-tumor effect of Allogeneic Stem Cell Transplantation by vaccination with PD-L silenced, minor histocompatibility antigen UTA2-1 peptide-loaded Dendritic Cells

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Primary objectives: - To evaluate the toxicity and feasibility of a preemptive minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination.- To evaluate the effect of a minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination on...

Ethical review	Not approved
Status	Will not start
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON44197

Source
ToetsingOnline

Brief title
mHag UTA2-1-loaded PD-L silenced DC vaccination after allo SCT

Condition

- Plasma cell neoplasms

Synonym
bloed cell cancer, hematological lymphoid and myeloid malignancies

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

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

peptide-loaded, PD-L silenced donor DC vaccination

- To evaluate the effect of 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

-to evaluate the efficacy of the minor H ag UTA2-1 peptide-loaded, PD-L

silenced donor DC vaccination to induce a GvT effect.

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 allo SCT 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), B cell malignancies and in acute myeloid leukemia(AML). We now propose a vaccination strategy, in which above mentioned patients will be preemtively treated with a therapeutic vaccine consisting of donor DCs loaded with the peptides of UTA2-1 minor Hag. 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 mHag pulsed DC vaccionations of patients even combined with a DLI is clinically feasible, safe and induces peptide specific T cell responses.

Study objective

Primary objectives:

- To evaluate the toxicity and feasibility of a preemptive minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination.
- To evaluate the effect of a 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 in patients with meaurable residual tumor load.

Study design

A single center phase I/II trial with the primary goal to evaluate the safety and efficacy of a preemptve DC vaccination strategy after donor stem cell transplantation.
Study endpoints are CTC toxicity grade 3 and 4 , b. Acute and chronic GvHD, c.

Clinical response and duration of response , d. Immune effects including minor H ag UTA2-1-specific CD8+ T cell responses.

For clinical efficacy response criteria related to the different hematological malignancies will be applied.

Intervention

Suitable patients will be vaccinated with ex vivo cultured donor DCs that are a) silenced for 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 intervalsPatients 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 procedures include a total of 3 DC vaccinations, 3 times repeated with an interval of 2 weeks between each vaccination: 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. In addition, routine investigations at the out patient clinic weekly or two weekly are performed to monitor the general physical status and tumor load of the patients. This may include bone marrow investigations, immune phenotyping and imaging techniques like CT scans, MRI and/or PET scans.

Risks associated with the investigational product.

The major potential risk in therapeutic interventions after allo SCT is the induction of GvHD.
In our two previous phase I/II trials we combined unloaded or peptide loaded host or donor DC vaccinations with DLI. No GvHD or other toxicity was recorded in these trials. Since in the current trial we will use only hematopoietic restricted minor H ag UTA2-1 loaded on donor DCs in a preemptive way, thus without combining the vaccination with DLI, we expect no GvHD associated with DC vaccinations. However, in this trial the donor DCs will be silenced for co-inhibitory molecules PD-L1and PD-L2. Therefore (GvHD related) toxicity is still one of the major endpoints of the study since such a PD-L silenced, peptide loaded donor DC vaccination has never been applied before. Therefore, to avoid overlapping toxicities we will keep an interval of 6 weeks

between recruiting for the first 3 patients and starting the vaccination. This will allow interrupting the vaccination scheme in the following patients if an unacceptable toxicity occurs in the preceding patient

Benefit: DLI is the standard next treatment step for patients with residual disease after allo-SCT. This procedure is associated with a substantial risk of severe and sometimes fatal GvHD. If proven feasible and effective, (sustained) complete remissions may be achieved through DC vaccination 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. Patients with Multiple Myeloma (MM) or Chronic Lymphocytic Leukemia (CLL) or non

hodgkin lymphoma (any grade) or acute myeloid leukemia (AML)
2. Recipient and donor have a mismatch in UTA2-1 mHag in the Graft versus Tumor (GvT) direction (recipient mHag positive, donor mHag 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 4 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,
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:	22-01-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	19-02-2018
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	EUCTR2017-005167-40-NL
CCMO	NL63830.000.17