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

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The goal of the proposed study is to test the null hypothesis that vaccination will not boost the cytotoxic T cell responses against UTA2-1 in >20% of the patients.

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON22602

Bron
NTR

Verkorte titel
UTA2-1DC

Aandoening

Multipel Myeloma (MM), Chronic Lymphocytic Leukemia (CLL), Non Hodgkin Lymphoma (NHL); Acute Myeloide Leukemie (AML)

Ondersteuning

Primaire sponsor: VU University Medical Center
Overige ondersteuning: ZON-MW

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

-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-L1/2 silenced donor DC vaccination on the immune
status of the recipient in correlation with the induction of UTA2-1 specific T cell responses after vaccination.

Toelichting onderzoek

Achtergrond van het onderzoek

Background of the study:

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. Furthermore allo SCT 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 allo SCT. 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 Hags). We have recently discovered the UTA2-1, a novel HLA-A2 restricted hematopoietic minor Hag antigen with a ~60% population frequency and high expression in multiple myeloma (MM), B cell malignancies and in acute myeloid leukemia (AML). We have recently shown that after a failed low dose Donor lymphocyte infusion (DLI) a second low dose DLI combined with vaccination of patients with DCs loaded with the peptides of minor Hags, including UTA2-1, is clinically feasible, safe and induces peptide specific T cell responses, but in a minority of patients. Furthermore these responses were not sufficiently robust to induce meaningful clinical responses in these DLI no responder patients, indicating that the vaccination strategy needs to be improved toward achieving better immune responses. Recently it became clear that the DC antigen presentation capacity can be significantly improved by knocking out the two important inhibitory molecules, PD-L1 and PD-L2. We therefore now propose an improved strategy, in which UTA2-1 positive patients, who underwent an allo transplantation from an UTA2-1 negative donor will be vaccinated with UTA2-1 loaded, PD-L1/L2 knocked out donor DCs, in a pre-emptive fashion, just after stopping the GvHD preventive treatment, where the tumor load is very low or barely detectable.

Objective of the study:

- 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

Study design:

A single center phase I/II trial with the primary goal to evaluate the safety and efficacy of a preemptive vaccination strategy with UTA2-1 loaded, PDL1/L2 silenced DCs 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.

Study population:

The treatment will be applied in patients with MM, chronic lymphocytic leukemia (CLL) B-cell Non-Hodgkin Lymphomas
and patients with acute leukemia (AML) who were previously treated with an allogeneic, UTA2-1 mismatched donor SCT. Hence, patient and
donor should be both positive for HLA-A2.1; but they should display and an incompatibility in the UTA2-1 antigen in the GvT direction (patient is positive and donor is negative for this antigen). Patients with ≥ grade 2 GVHD, extensive chronic GVHD and patients being treated with corticosteroids, chemotherapy or other immunosuppressive medications will be excluded.

Intervention (if applicable):

Suitable patients will be vaccinated with ex vivo cultured, UTA2-1 peptide loaded donor DCs that are furthermore silenced for PD-L1/L2 molecules via siRNA transfection DCs will be administered at a total dose of minimal 45 and maximal 90x10^6 DCs, in 3 servings with two weeks intervals. 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.

Primary study parameters/outcome of the study:

-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-L1/2 silenced donor DC vaccination on the immune
status of the recipient in correlation with the induction of UTA2-1 specific T cell responses after vaccination.

Secundary study parameters/outcome of the study (if applicable):

-to evaluate the efficacy of the minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination to induce a
GvT effect.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable):

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 outpatient 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, immunophenotyping 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 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.

Doel van het onderzoek

The goal of the proposed study is to test the null hypothesis that vaccination will not boost the cytotoxic T cell responses against UTA2-1 in >20% of the patients.

Onderzoeksopzet

eveyr 2 weeks until day +94, thereafter every month unitl 12 months, at progression and follow-up every 2 months for 5 years after registration

Onderzoeksproduct en/of interventie

Patients will be vaccinated with ex vivo cultured, UTA2-1 peptide loaded donor DCs that are furthermore silenced for PD-L1/L2 molecules via siRNA transfection DCs will be administered at a total dose of minimal 45 and maximal 90x10^6 DCs, in 3 servings with two weeks intervals.

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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 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 2 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

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. WHO performance 3-4
2. Presence of severe cardiac hepatic, renal, metabolic disease
3. Rapidly progressive disease,

4. Life expectancy < 3 months

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-08-2019
Aantal proefpersonen:	17
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	01-07-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL7846
Ander register	METC CCMO : (NL66760.000.18)

Resultaten