Vaccination with minor histocompatibility antigen-loaded donor DC vaccines to boost graft-versus-tumor immunity after allogeneic stem cell transplantation (a phase I study)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON40014

Source
ToetsingOnline

Brief title
MiHA-loaded DC vaccination after allogeneic SCT

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
blood cell cancer, hematological malignancies

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: KWF en ZonMW

Intervention

Keyword: dendritic cells, minor histocompatibility antigens, stem cell transplantation, vaccination

Outcome measures

Primary outcome

The primary study parameters are to evaluate the safety, toxicity, development

of GVHD and the immunological response by appearance of MiHA-specific CD8+ T

cells following vaccination with monocyte-derived donor DC electroporated with

mRNA encoding hematopoietic-restricted MiHA in patients who had undergone

allo-SCT with stem cells from HLA-matched, MiHA-mismatched donor.

Secondary outcome

The secondary study parameters are to evaluate the clinical effect of MiHA-DC

vaccination in case of detectable minimal residual disease and mixed chimerism.

Study description

Background summary

Allogeneic stem cell transplantation (allo-SCT) is a potent treatment and sometimes the only curative treatment for aggressive hematological malignancies. The therapeutic efficacy is attributed to the graft-versus-tumor (GVT) response, during which donor-derived CD8+ T cells become activated by recipient minor histocompatibility antigens (MiHA) presented on dendritic cells (DC). Consequently, these alloreactive donor T cells clonally expand, acquire effector functions and kill MiHA-positive malignant cells. However, in a substantial number of patients persistence and recurrence of malignant disease is observed, indicating that insufficient GVT immunity is induced. This is reflected by our observation that not all patients develop a productive CD8 T

cell response towards mismatched MiHA between the recipient and donor. A promising strategy to induce or boost GVT immune responses is pre-emptive or therapeutic vaccination with ex vivo-generated donor DC loaded with MiHA that are exclusively expressed by recipient hematotopoietic cells and their malignant counterparts. In contrast to pre-emptive donor lymphocyte infusion (DLI) with polyclonal donor T cells, this MiHA-DC vaccination approach has less risk of inducing GVHD and the potency to induce more efficient GVT-associated T cell immunity.

Study objective

The primary objectives of our study are to evaluate safety, toxicity and capability of inducing T cell responses of vaccination with, monocyte-derived donor DC electroporated with mRNA encoding hematopoietic-restricted MiHA in patients who had undergone allo-SCT with stem cells from HLA-matched, MiHA-mismatched donor. The secondary objective is to evaluate the clinical effect of vaccination in case of detectable minimal residual disease and mixed chimerism.

Study design

This is a phase I/II study in a series of 10 allo-SCT recipients. Eligible patients include MiHA-mismatched patients who do not develop aGVHD * grade 2 or extensive cGVHD after stopping cyclosporine A, and have no or limited MiHA-specific T cell response (defined by *1.0% of total CD8+ T cells). These eligible patients will receive pre-emptive MiHA-DC vaccination.

Intervention

Eligible patients will receive one cycle of donor DC vaccination consisting of maximal 3 immunizations, given at 2 week intervals. MiHA mRNA-electroporated donor DC will be infused intravenously (2.5x105/kg body weight).

Study burden and risks

Participating patients will visit the outpatient clinic weekly or two-weekly for standard physical examination and blood sampling from the first DC vaccination until 4 and 12 weeks after vaccination, respectively. For follow-up, peripheral blood will be collected from patients pre-study, at day 0, 7, 14, 21, 28, 42, 63 and 84 during and after DC vaccinations. The total amount of blood that will be taken for study purposes will be maximally 282 ml in a three month period. Two extra bone marrow aspirations will be performed (day 42 and 84 after first DC vaccination). Theoretically, the risk of MiHA-DC vaccination is the development of a strong T cell response inducing GVHD or an anaphylactic reaction. However, as the MiHA HA-1, LRH-1 or ARHGDIB are expressed only by hematopoietic cells we do not expect severe acute GVHD.

Furthermore, because CD8+ T cell responses against these hematopoietic-restricted MiHA occur in allo-SCT patients by nature, we do not expect a systemic anaphylactic reaction. Indeed in a previous post-transplantation vaccination study with recipient-derived DCs expressing endogenous MiHA, the toxicity was limited to low-grade fever and chills, but none of the patients developed GVHD (Levenga et al. BBMT 2010). Finally, when MiHA-DC vaccination indeed yields a productive immune response, with increasing donor chimerism and/or reducing residual disease, there is no need for a DLI thereby decreasing the risk of acute GVHD. In addition, DC-induced MiHA-specific CD8+ T cell responses could be associated with a lower relapse rate.

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

* Patients with AML, myelodysplasia (MDS), ALL, CML (accelerated or blast phase), CLL, MM or malignant NHL, who underwent HLA-matched allo-SCT
* Patients positive for HLA-A2 and/or HLA-B7
* Patients positive for HA-1, LRH-1 and/or ARHGDIB transplanted with corresponding MiHA-negative donor
* Patients >18 and <65 years of age
* WHO performance 0-2
* Witnessed written informed consent

Exclusion criteria

* Life expectancy < 3 months;* Severe neurological or psychiatric disease;* Progressive disease needing cytoreductive therapy;* HIV positivity;* Patients with acute GVHD grade 3 or 4;* Patients with extensive chronic GVHD;* Patients with active infections (viral, bacterial or fungal) that requires specific therapy. Acute anti-infectious therapy must have been completed within 14 days prior to study treatment;* Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure or symptomatic ischemic heart disease;* Severe pulmonary dysfunction (CTCAE III-IV);* Severe renal dysfunction (serum creatinine > 3 times normal level);* Severe hepatic dysfunction (serum bilirubin or transaminases > 3 times normal level);* Patients with known allergy to shell fish

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-01-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	23-08-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	28-11-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-12-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-08-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-09-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	27-10-2014
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

ID: 29214
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-002879-34-NL
CCMO	NL41183.000.12
OMON	NL-OMON29214