A phase I/II post-cord blood HCT dendritic cell vaccination trial directed against WT1 for pediatric acute myeloid leukemia: the U-DANCE-anti-AML trial

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Ethical review	Not approved
Status	Will not start
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON44046

Source
ToetsingOnline

Brief title
U-DANCE-anti-AML

Condition

- Leukaemias

Synonym
AML: Acute Myeloid Leukemia/ cancer of blood and bone marrow

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: NWO (ZonMW),KiKa

Intervention

Keyword: Acute myeloid leukemia, cord blood stem cell transplantation, dendritic cell vaccination, pediatric, relapsed/ refroactory

Outcome measures

Primary outcome

The primary endpoints:

Part A: Safety: Occurrence of DLTs including aGvHD (according to Glucksberg criteria) from the first vaccination (t=0) until 84 days after the third CBDC vaccination

Part B: Activity: One-year WT1+ AML relapse-free survival rate from the time of the first vaccination as compared to historical controls.

Secondary outcome

Secondary endpoints (part A):

- Treatment emergent adverse events (TEAEs), those with initial onset or increasing in severity after the first vaccination.
- One-year cumulative incidence of WT1-specific immunity after the first vaccination.
- One-year overall survival rate, from the time of first vaccination
- One-year WT1+ AML relapse-free survival rate, from the time of first vaccination.
- One-year cumulative incidence of cGvHD (according to NIH criteria2) from the

first vaccination.

Secondary endpoints (part B):

- TEAEs, those with initial onset or increasing in severity after the first vaccination.

- One-year cumulative incidence of WT1-specific immunity after the first vaccination.

- One-year cumulative incidence of cGvHD (according to NIH criteria2) from the first vaccination.

- One-year overall survival rate from the time of first vaccination.

Exploratory endpoints (part B):

- Changes in general immune parameters between those samples taken before and those taken after the first vaccination until one year of follow-up.

- Expression of inhibitory (immune checkpoint) molecules on the AML in the case of relapse occurring after the first vaccination until one year of follow-up

Study description

Background summary

Development of novel (immune) therapies aimed at reducing relapse rates (currently 50%) is of utmost importance to improve survival chances in pediatric acute myeloid leukemia (AML) patients receiving stem cell transplantation, in this case cord blood transplantation (CBT).
We hypothesize that tumor antigen-loaded cord blood-derived dendritic cell (CBDC) vaccination combined with the intrinsic anti-leukemic and proliferative

capacity of the grafted CB T cells will result in fast proliferation and differentiation of tumor-specific CD8+ cytotoxic T lymphocytes (CTLs).
Wilms Tumor 1 (WT1) is an oncoprotein overexpressed in the majority of AMLs. As such, the CBDC vaccine will be loaded with tumor antigen using WT1 mRNA-electroporation and WT1 15-mer-peptide pool-pulsing. This loading strategy ensures MHC class I and II presentation without any HLA restriction and enables induction of both WT1-specific CD8 and CD4 responses, which is required for the induction of immunological memory and optimal anti-tumor immunity.

Study objective

Although DC vaccinations have been used in allo-HCT settings, no previous studies have been performed using a CBDC vaccine after CBT. This study will therefore be subdivided into 2 parts:

- Part A: to determine a safe dose of the vaccination, and
- Part B: to study its activity measured as the one-year relapse-free survival rate, based on an expansion cohort.

Part A primary objective:
- To assess the safe dose for CBDC vaccination after CBT defined using the occurrence of dose limiting toxicities (DLTs), including acute graft versus host disease (aGVHD). The DLT evaluation period lasts from the first vaccination, until 84 days after the third CBDC vaccination.

Part A secondary objectives:
- To assess the safety and tolerability of the vaccination strategy
- To assess the induction/increase of WT1-specific immunity in vaccinated individuals during one year of follow-up from the first vaccination
- To assess overall survival at one year after the first vaccination
- To assess WT1+ AML relapse-free survival at one year after the first vaccination
- To assess the chronic GvHD (cGvHD) occurrence during one year of follow-up from the first vaccination

Part B primary objective:
- To demonstrate an increase in the WT1+ AML relapse-free survival rate using a WT1-loaded CBDC vaccine, at one year after the first vaccination (using a historic cohort not receiving a CBDC vaccination as reference data for the Simon-2-stage design).

Part B: secondary objectives:
- To assess the safety and tolerability of the vaccination strategy
- To assess the induction/increase of WT1-specific immunity in vaccinated individuals during one year of follow-up from the first vaccination
- To assess overall survival at one year after the first vaccination

- To assess the cGvHD occurrence during one year of follow-up from the first vaccination (as compared to our historic cohort not receiving a CBDC vaccination).

Part B: exploratory objectives:
- To assess general (non-WT1 specific) immune activation in each vaccinated individual during one year of follow-up from the first vaccination compared to the immune parameters before vaccination.
- To assess the expression of inhibitory (immune checkpoint) molecules on AML in the case of relapse during one year of follow-up from the first vaccination

Study design

This is a single-arm open-label phase I/II intervention study in pediatric AML patients using an advanced therapeutic medicinal product `(ATMP): cord blood-derived dendritic cell (CBDC) vaccine. Data from our historic cohort of pediatric patients with a WT1+ AML and receiving CBT will be used as control group for the primary objective in part B.

Intervention

CBDC-vaccination (day 0, day 14 and day 28):
Patients will receive three *Full length WT1 encoding* mRNA-electroporated and WT1 15-mer-peptide pool loaded CBDC-vaccinations starting at 8 weeks post-CBT every 2 weeks (hence week 8, 10 and 12). The CBDC vaccine will be split into two equal doses that will be administered intradermally and intravenously.

Study burden and risks

Potential burden:
* The intradermal injections may be experienced as painful (for this we will apply local anesthetics using *lidocaine-tetracaine* (Rapidan-plasters).
* Repeated intradermal injection may lead to local skin reaction characterized by erythema.
* Combined intradermal and intravenous vaccinations have been reported to cause signs of mild fatigue, fever, chills, anorexia and muscular pain starting as soon as time of vaccination but never lasting beyond two days after vaccination and always within grade 1-2
Since these vaccination related symptoms are generally mild, do not require medical interventions and are short lived their occurrence will not be considered as DLTs.

Additional risk of the CBDC vaccination:
* Induction of moderate / severe aGvHD (grade II * IV)
* Induction of cGvHD

Potential Benefits:
* Higher probability on continuous complete remission of AML
* Prolonged survival (Long-term stabilization of disease levels)

Taken together it is our opinion that the potential benefits (reduced relapse and enhanced survival) outweigh the potential risks (GvHD).

Group relatedness:
This study is developed to reduce the frequency of relapses in pediatric AML and hence cannot be studied in other populations.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

-Pediatric AML patients eligible for allo-HCT according to standard-of-care guidelines, with overexpression of WT1 mRNA in an AML sample (>50 copies WT1/10^4 copies ABL for PB, and >250 copies WT1/10^4 copies ABL for BM) taken at diagnosis and/or relapse after (re-)induction chemotherapy.;-Indication for CB-HCT according to the UMC Utrecht guidelines;-CB selection criteria: the 80% fraction of the unit should contain a minimum total nucleated cell number of 3x10^7 NC/Kg criteria for any match grade (before cryo-preservation). Preferable CD34+/Kg dose: > 1x10e5 in the 80% fraction;-The whole CB unit should contain more than 7.5x10^6 total CD34+ before freeze.;-Karnofsky/Lansky score *70 ;-Age limits for part A (safety run) only: *12 and *17 years of age, and <18 years for part B of the study. ;-Signed informed consent

Exclusion criteria

- Patients undergoing allo-HCT with stem cells derived from PBMCs or bone marrow;- Patients who are pregnant or breast-feeding or unwilling to use adequate contraceptive methods;- Known allergies to compounds used in the CBDC production process or the local anesthetic Lidocaine-tetracaine (Rapydan®) plasters;- Patients included in other intervention studies influencing the endpoints of this study

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	54

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic
Product type:	Medicine
Brand name:	CBDC vaccine

Ethics review

Approved WMO Date:	08-09-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	26-09-2016
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	EUCTR2015-000827-94-NL

Register	ID
Other	Nederlands Trial Register (registratie volgt nog)
CCMO	NL52641.000.16