Single-cell analysis of somatic mutations to understand and improve blood formation after hematopoietic stem cell transplantation

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anaemias nonhaemolytic and marrow depression
Study type	Observational invasive

Summary

ID

NL-OMON54736

Source
ToetsingOnline

Brief title
Tracing stem cells after transplantation

Condition

- Anaemias nonhaemolytic and marrow depression
- Immunodeficiency syndromes
- Leukaemias

Synonym
Hematopoietic stem cell transplantation; bone marrow transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Subsidie vanuit het Oncode-instituut (tav dr. R. Boxtel) en onderzoekssubsidies tav dr. M. Belderbos

Intervention

Keyword: Clone, Hematopoietic stem cell transplantation, Somatic mutations, Whole genome sequencing

Outcome measures

Primary outcome

Our main study endpoints are:

- The total number of somatic mutations acquired after HSCT in the HSCT

recipient and his/her donor;

- The frequency of HSC clones contributing to production of each of the mature

blood lineages in the HSCT recipient and donor.

- The impact of donor age on the number of HSC clones that contribute to

post-transplant hematopoiesis, and the genomic integrity of these cells

Secondary outcome

Secondary study outcomes are:

- Identification of potential causes of HSC mutagenesis upon HSCT, assessed by

mutational signature analysis

- Insight into the cellular and molecular pathways that guide HSC

(non-)engraftment

Study description

Background summary

Hematopoietic stem cell transplantation (HSCT) is a last-resort curative therapy for patients suffering from various, otherwise lethal, diseases. Despite the widespread use of HSCT in patients, the number of engrafting HSCs and the mechanisms guiding their long-term contribution to hematopoiesis remain elusive. Maintaining long-term HSC integrity is especially relevant in children, who are now expected to survive for several decades after successful HSCT. In the current project, we hypothesize that blood formation in human allo-HSCT recipients is supported by a limited number of HSCs, and that the proliferative stress posed upon these cells accelerates HSC mutagenesis, ultimately predisposing to premature stem cell senescence and second malignancy.

Study objective

We aim to quantify the contribution of individual HSCs to blood (re-)generation in pediatric HSCT recipients and their donors, and to unravel the consequences of transplantation on HSC long-term genomic integrity.

Study design

This is an observational, fundamental study. We will use an innovative laboratory method, which employs single cell analysis of naturally occurring genetic mutations to retrospectively reconstruct the number of HSCs clones, their quantitative contributions to each of the mature blood lineages and their mutational burden in human allo-HSCT recipients and their donors. The proposed research involves collection of 10 mL venous blood of the HSCT recipient and his/her donor.

Study burden and risks

This study requires pediatric recipients and their donors, as their post-transplant survival exceeds that of adult HSCT recipients by several decades, posing unique challenges on the integrity and longevity of the engrafted HSCs. In addition, as clinical HSCT regimens differ between children and adults (e.g. use of irradiation, chemotherapy dose), results obtained in adult HSCT recipients cannot be translated directly to children,
We believe that the studies proposed here will provide unique insights into the clonal behaviour and mutagenesis of transplanted human HSCs, which will contribute to improved clinical HSCT protocols. In addition, knowledge on the mechanisms that damage and/or protect HSC integrity may benefit our understanding and treatment of blood diseases in general.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Patients (n=30):
- Recipients of an allogeneic hematopoietic stem cell transplantation (HSCT) from an umbilical cord blood donor (n=10), adult haplo donor (n=10), or healthy sibling donor (n=10)
- Age at HSCT <18 yrs
- First HSCT
- >95% donor chimerism at the time of blood sampling
- Currently alive
- No major HSCT-related complications (see exclusion criteria),

Healthy subjects (n=20):
- Healthy donors of the sibling and haplo-HSCT recipients described above.

Exclusion criteria

- Major HSCT-related complications, such as >grade 2 graft versus host disease.
- Secondary graft failure
- Objection to be notified about actionable findings from whole-genome sequencing.
- Failure of the HSCT recipient, donor and/or their legal representatives to understand the patient information and informed consent form (either due to intellectual disability or to language problems). Of note: For sibling and haplo transplants, we will only include subjects in whom both the HSCT recipient and his/her donor (and, if applicable, their caregivers) agree to participate in the current study.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-10-2019
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	08-05-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-01-2023
Application type:	Amendment
Review commission:	METC NedMec

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: 23273
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL68140.041.19
Other	NL7585, Nederlands Trial Register
OMON	NL-OMON23273