Leukocyte dynamics during immune reconstitution after stem-cell transplantation: in vivo labelling of dividing leukocytes using deuterated water

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In this study we aim to gain more insights into immune reconstitution of various leukocyte populations after SCT. By application of heavy water labeling we investigate if and how the production- and death rate of leukocytes changes after an SCT.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	White blood cell disorders
Study type	Observational invasive

Summary

ID

NL-OMON44941

Source
ToetsingOnline

Brief title
Leukocyte dynamics during immune reconstitution

Condition

- White blood cell disorders
- Immunodeficiency syndromes
- Haematological and lymphoid tissue therapeutic procedures

Synonym
immune reconstitution, recovery of the immune system

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Landsteiner Stichting voor Bloedtransfusie Research (LSBR) en Europese Unie

Intervention

Keyword: immune reconstitution, leukocytes, stable isotope labelling, stem-cell transplantation

Outcome measures

Primary outcome

The main parameter of this study is the amount of deuterium (label) that the various leukocyte populations have incorporated in their DNA by cell division at a given time. For this purpose blood withdrawals are done both in the period during which participants drink 2H2O (uplabeling phase) and in the period after stopping with 2H2O intake (downlabeling phase). Data obtained during uplabeling and downlabeling phases can be interpreted by mathematical models that describe the dynamics of leukocyte populations.

Secondary outcome

Deuterium enrichment in urine. This parameter will allow us to determine the level of deuterium in body water that was available to be incorporated into the various cell populations. This level can vary between individuals, dependent on how much normal (unlabeled) water was drunk by the participant. (ii) T cell excision circles and plasma levels of growth- survival- and inflammatory factors. (iii). The composition of the transplant. The presence of various leukocyte populations in the transplant can possibly influence the

reconstitution rate of these cell populations.

Study description

Background summary

When patients affected with hematological malignancies are treated with a stem cell transplantation, they often suffer from a severe and long-lasting deficiency of the adaptive immune system, which increases the patient*s vulnerability to infections and tumor relapses. At present it is still unclear why it takes so long for the adaptive immune system to recover from a stem cell transplantation (SCT). Following an SCT, the production- and death rate of lymphocytes may be disturbed, as the pre-SCT conditioning may severely damage the primary lymphoid organs (bone marrow and thymus). An alternative explanation for the slow reconstitution of leukocyte populations after SCT may in fact be the reflection of a slow production rate in the healthy situation. In this study we aim to gain more insight in immune reconstitution by determining the production- and death rate of various leukocyte populations after SCT. As we investigate the production- and death rate of these cell populations in healthy individuals in a parallel study, we will be able to detect possible differences in cell dynamics after SCT. More insights in leukocyte dynamics after SCT will facilitate the development of strategies to accelerate immune reconstitution, and thereby reduce infectious complications and tumor relapses in the clinic.

Study objective

In this study we aim to gain more insights into immune reconstitution of various leukocyte populations after SCT. By application of heavy water labeling we investigate if and how the production- and death rate of leukocytes changes after an SCT.

Study design

The study concerns longitudinal observational research with invasive acts. It is composed of temporary consumption of deuterated (heavy) water (2H2O) and prospective blood withdrawals and urine sampling for laboratory research. Blood is drawn 4 times in the period during which participants drink heavy water (uplabeling phase) and 6 times in the period that follows (donwlabeling phase). From the blood samples various leukocyte populations will be sorted after which in the DNA of these samples deuterium enrichment can be quantified using gas chromatography and mass spectrometry (GC-MS). Frequent sampling of urine makes it possible to correct, per time point, for the intake of unlabeled water by an

individual.

Study burden and risks

The frequent blood- and urine sampling and associated hospital visits make the burden of this study substantial. In addition, the questionnaires can be considered an incursion to one*s privacy. There is no direct advantage of participation. The necessary amounts of heavy water are not harmful. The total volume of withdrawn blood falls within the limits applied by Sanquin bloedbank. Participation hence comes with burden, but is safe.

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

(i) At least 18 years of age;
(ii) Ability to understand and voluntarily sign the informed consent form for this study and ability to follow the study protocol;
(iii) Treatment for hematological malignancy with an autologous stem cell transplantation for which
(iv) the autologous transplant consists of non-T cell depleted stem cells, that are isolated from peripheral blood, and mobilized with G-CSF (and possibly Plexirafor);
(v) sufficient kidney function, defined by serum creatinine level * 1.5 × upper limit of normal (ULN) and glomerular filtration rate > 30 mL/min (calculated by Cockcroft and Gault formula);
(vi) sufficient liver function, defined by total serum bilirubin * 1.5 × ULN;
(vii) serum aspartate transaminase (AST) and/or alanine transaminase (ALT) * 2.5 × ULN;
(viii) women of child bearing potential must agree to use an adequate and medically accepted method of contraception
(ix) patients starting the protocol 12-18 months post-transplantation should have a naive CD4+ T-cell count of at least 20/µl peripheral blood.

Exclusion criteria

(i) Infection with human immunodeficiency virus (HIV);
(ii) Active infection with hepatitis B or C or other active liver disease
(iii) Other active uncontrolled infections, like malaria, infectious mononucleosis, sexually transmitted diseases;
(iv) Medical condition, serious intercurrent illness, or other extenuating circumstance that, in the judgment of the Principal Investigator, could jeopardize patient safety or interfere with the objectives of the study;
(v) Uncontrolled or significant cardiovascular disease, including: A myocardial infarction within 12 months; Uncontrolled angina within 6 months; Current or history of congestive heart failure New York Heart Association (NYHA) class 3 or 4;
(vi) Body weight below 50 kg
(vii) Pregnancy or parent*s wish in the coming year;
(viii) Excessive alcohol consumption
(ix) Drug use
(x) Extreme sensitivity to sea- and/or car sickness.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-10-2012
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	03-01-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
CCMO	NL36260.041.11