Co-infusion of haematopoietic stem cells from a haplo-identical donor and single unit unrelated cord blood in patients with a high risk of relapse: A Phase I/II study to assess safety and to investigate the biological mechanism of the anti-tumor response

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To study the safety of co-infusion of a alphabetaT-/CD19 B-cell depleted haematopoietic stem cells from haplo-identical donor and a single unit cord blood unit and to investigate the anti-tumor responses from both grafts.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON35879

Source
ToetsingOnline

Brief title
Haplo-Cord Study

Condition

- Haematological disorders NEC

Synonym
hematological malignancy, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Anti-tumor activity, Cord Blood Stem Cell Transplantation, Safety, Transplant related mortality

Outcome measures

Primary outcome

1) Safety: Transplantation related (non-relapse) mortality (TRM)

2) Biology: investigate the anti-tumor response mechanism from both grafts.

Secondary outcome

-acute GVHD (Gluckberg grade II-IV)

Engraftment: Neutrophils > 500K/uL for 3 consecutive days, Platelet (day 180 >

50 K) engraftment.

- Event Free Survival (>6mths follow up). Event defined as: death, CB

graft-failure (<25% donor CB chimerism) or relapse.

- Overall Survival

- Non-Relapse Mortality

- Chronic GVHD: limited and extensive (Shulman Criteria)

- VOD (Seattle Criteria)

- Mucositis * 3

Study description

Background summary

Although haematopoietic stem cells transplantation (HSCT) has become much safer over the last decade the major limitation remain *transplantation related mortality (TRM; e.g. due to viral reactivations/disease)* and relapse (in malignancies). Within the group of malignancies there is a subgroup of patients with a *very high risk (of relapse) profile* (e.g. relapse AML, refractory lymphoma, relapse after first allo-HSCT). Although this *very high risk group* may potentially benefit from allo-HSCT with the currently available *standard* transplant protocols the expected survival rates are very low <20%. Cord blood (CB) is emerging as stem cell source for HSCT because it has many advantages above the conventional bone marrow grafts. Disadvantages are however low stem cell count/kg for adults associated with prolonged neutropenia and a slower T cell recovery. T cell depleted haplo-grafts have the advantage of early neutrophil engraftment but are associated with higher rates of secondary graft-failure and poor T-cell reconstitution associated with viral infections. KIR-mismatching in Haplo-grafting is suggested to have anti-leukemic potential.

Study objective

To study the safety of co-infusion of a alphabetaT-/CD19 B-cell depleted haematopoietic stem cells from haplo-identical donor and a single unit cord blood unit and to investigate the anti-tumor responses from both grafts.

Study design

It is a single center study within the UMC Utrecht, including adult patients with and indication for allo-
SCT. Patients will be included during a period of 4 years. According to Simon et al. (Optimal two-stage designs for phase
II clinical trials) it was estimated that a minimum of 13 and a maximum of 37 have to be included. To our opinion in 4years
time a number of 37 should be feasible.
For all patients with an indication for allogenic HSCT, the best treatment option is discussed in a multidisciplinary meeting.
This treatment protocol will be considered as one of the options for eligible patients. When considered the best option, the
treatment proposal is discussed with the patient/ parents. Informed consent has to be obtained both for HSCT itself, for
immune reconstitution studies, and for the Cord+ Haplo HSCT protocol.
If informed consent is obtained, the best CB unit is ordered. After apheresis or bone-marrow harvest of the haplo-donor

graft, the cells are purified by the SCT lab using negative selection with anti-TCR**- and CD19-microbeads.
Just prior to transplant the Cord blood unit is thawed and infused immediately thereafter, followed by infusion of the
selected haplo-cells. All other treatment, both in- and outpatient care is the same as it is for other allogenic HSCT patients.
CRFs are filled out by the responsible doctors of the SCT ward and outpatient clinic on day 0; +1; +3; +10 days; +2 wks,
+4 wks, +6 wks, + 8 wks, + 10 wks, +12 wks: +100 dys; +4 months; +5 months; +6 months, +9 months, +1 year.
Main outcome parameters of this safety trial are aGVHD and TRM. Stopping rules on the two outcome parameters have
been defined , implying an interim analysis of TRM after the first 100 days of the first 13 patients and of the cumulative
incidence of TRM after the first 100 days of the first 13 patients. In line with Simon the trial will be discontinued early if
>4 out of 13 patients died of TRM

Intervention

For a group of patients with a very high risk malignancy: Instead of using a single donor, or no transplantation at all, a combination of a cord blood unit and selected cells from a haplo-identical family-donor are infused at the day of transplant. The selection procedure of the haplodonor allows mismatch NK-cells and gammadeltaT-cells in the graft for extra anti-tumor effect.

In more detail: The intervention applies to the selection of the donor source and preparation of the grafts.
1) combining a cord blood unit with a minimum of > 1,5 x 10E7 NC/kg with coinfused cells form a haplo-identical
familydonor
2) preference of a KIR mismatch between haplodonor and recipient for recipients with a malignant indication for HSCT
(see protocol)
3) selection of the haplograft purified by TCR**- and CD19-negative selection leaving in the graft:
-5 x 10 E6/kg CD34+ /kg (in case of difficult apheresis minimum of 2.5 x 10E6/kg).
-Maximum number of T cells < 5x 10 E4/kg.
-NK cells and gamma delta T cells for extra antiviral and anti-tumor activity
4) Using conditioning regimens without ATG. This is explained on page 20 of the protocol under "Safety of infusion of
innate immune cells".

Study burden and risks

Potential Burden:
The protocol only comprehends the use of a different donor source (a combination of 2 donor sources). All other acts, measurements, follow-up and level of care are similar to off-study patients undergoing allogenic HSCT.

Potential Risks:
1) Potentially increased risk of aGVHD because of cumulative alloreactivity from 2 different donors: (1)CB + (2) the co-infusion of haplo-donor derived NK cells and gammadelta T-cells (together with CD34+ hematopoietic stem cells from the haplodonor).
2) Possible increased risk of cGVHD (associated with 1)
3) Possible increased risk of engraftment syndrome, due to speed of engraftment, and expected enhanced graft vs graft reaction (because of presence of NK and gammadeltaT-cells in the Haplo-graft).
4) Possible risk of rejection of the cord blood graft (or both the CB and the haplo-graft) due to increased graft-versus-graft reaction and augmented NK/gamma deltaT cell power of the haplo-graft.

Potential Benefits:
1) lower TRM due to swift and secure early engraftment, and lower virus-associated toxicity
2) Less relapse due to NK-(CB and Haplo), gamma delta T-cell (Haplo) and alpha betaT-cellular (CB) activity.
3) Potentially lower risk of aGVHD and cGVHD because it is expected that the CB will be the sustained engrafting donor (CB is associated with lower levels of GvHD) and NK and gammadelta T-cells from the Haplo-donor are suggested not to be associated with GvHD. In addition, due to the decreased risk of infections (early engraftement, anti-viral potential of NK and gammadelta T-cells), the combination of these to donors may result in reduced associated tissue damage. Reduced tissue damage may prevent the occurrence of allo-reactivity.

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

All of the following five criteria:
1) Patients with either:
A) No standard HSCT protocol available and any of the following malignancies: NHL or HD (refractory, *2CR); relapse AML, refractory AML, MDS/SAA, ALL *CR2
B) Relapse after first allo-HSCT with either SIB or MUD/UCB donor
C) With a leukemia/lymphoma, MDS/SAA indication, qualifying for HSCT but without donor available according to ongoing, open study protocols (only adults): no fully matched family donor or matched (9-10/10) unrelated donor available and / or no single or double unit cord blood available with sufficient cell numbers according to ongoing, open study protocols. ;2) With having a single matching (* 4/6) umbilical CB unit available with total NC count > 1,5 E7/kg [1]
3) Lansky / Karnofsky > 40
4) Age 18-65 * (*<= age * 65 and 364 days)
5) Signed Informed Consent

Exclusion criteria

- geen getekende toestemingsverklaring
- Lansky < 40
- No cord blood unit available wih <=4/6 match en a minimum cell dose of > 1,5 x 10E7 Nucleated cells /kg
- Creatinine clearance < 40 ml/min
- cardiac dysfunction (SF < 45%) (Ejection fraction < 45%), unstable angina, or unstable cardiac arrhythmias

-Pulmonary function test VC, FEV1 and/ or DOC< 50%

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-10-2011
Enrollment:	37
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	12-09-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-11-2011
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	EUCTR2010-019529-33-NL
CCMO	NL36740.000.11

Study results

Date completed:	27-06-2013
Actual enrolment:	5