A Phase I/II study to assess safety of 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

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Phase I-II safety study on the development of a multimodal treatment protocol combining the advantages of CB with the advantages of haploidentical stem cells in a group HSCT requiring patients with an estimated high risk of transplant related...

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

Summary

ID

NL-OMON34968

Source
ToetsingOnline

Brief title
Cord+ Haplo HSCT

Condition

- Leukaemias

Synonym
cancer, malignancy

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

The cumulative incidence of transplant related death (transplant related

mortality: TRM, non-relapse mortality< 100 days Post HSCT)

The cumulative incidence of acute- GVHD (Grades II-IV: Gluckberg Criteria)

Secondary outcome

- 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/graft versus host disease)* and relapse (in malignancies). 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. Haplo-grafts have the advantage of early neutrophil engraftment but are associated with high rates of secondary graft-failure and poor T-cell reconstitution associated with viral infections.

Combining cord blood and readily available haplo-identical family donor-HSCT combines beneficial effects of both allogenic transplantations strategies, such as the in the long term excellent T-cell recovery after CB HSCT, and the NK-cell mediated anti-tumor activity of CB with the early haplo-mediated neutrophil recovery and the targeted anti-leukemia effect of NK (KIR mismatch) and **T-cells after selected haplo-HSCT. We propose therefore that this multimodal treatment protocol will be a preferable treatment option in a selected group of high risk patients, for different reasons, with either non-malignant or malignant indications who may profit for various reasons from this double grafting:
1) Early neutrophil recovery (patients with ongoing infection)
2) Swift (early / fast haplo-engraftment) and secure (CB-engraftment) in patients with difficult engraftment and ongoing disease: such as hemophagocytic lymphohistiocytosis (HLH) and osteopetrosis as well as patients without a well matched unrelated marrow/PBSC donor or cord blood donor with a sufficient number of nucleated cells available.
3) Multi-modal cellular therapy: Strong early (first 2-4 weeks) NK + **T-cells mediated (anti-tumor/ antiviral) activity from the haplo-graft and NK + **T-cellular activity (> 4 weeks) from the CB-graft without increasing the risk of aGVHD (high risk lymphoma / leukaemia patients without standard SCT-protocol).

Study objective

Phase I-II safety study on the development of a multimodal treatment protocol combining the advantages of CB with the advantages of haploidentical stem cells in a group HSCT requiring patients with an estimated high risk of transplant related mortality

1) Co-infusion of haplo-identical hemopoietic stem cells from a third party donor will reduce the neutropenic period (<14d) without being associated with an increase of transplant related complications, and will result in sustained full cord blood donor chimerism. It would make HSCT safer in patients with ongoing infection and would make cord blood transplantation an attractive option for more adult patients.
2) Boost the anti-tumor/anti-viral effect by implementing a multi-modal cellular therapy by combining the allo-reactive NK-cells and **-cells from the

haplo-graft with NK-cells and T-cells from the CB graft. To obtain this, the haplograft is purified by TCR**- and CD19-negative selection with conservation of innate cells such as NK cells and **T-cells, while depleting ** Tcells and B cells.

Study design

It is a single center study within the UMC Utrecht, including both adult and pediatric patients with and indication for allo-SCT. Patients will be included during a period of 3 years. According to Simon et al. (Optimal two-stage designs for phase II clinical trials) it was estimated that a minimum of 21 and a maximum of 43 have to be included. To our opinion in 3 years time a number of 43 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 11 patients and of the cumulative incidence of aGVHD after the first 100 days of the first 15 patients. In line with Simon the trial will be discontinued early if *5 out of 11 patients died of TRM or if * 7 out of 15 patients have aGvHD grade 2-4.

Intervention

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 18 of the protocol under "Safety of infusion of innate immune cells".

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Study burden and risks

Potential Risks
1) possible increased risk of aGVHD because of using donor cells from an additional donor and because of coinfusion of NK cells and gamma deltacells instead of mere Cd34+ cells.
It is however (see protocol) unlikely that coinfusion of CD34+ cells with NK and **T *cells in our protocol will result in an increase in > aGVHD gr ll in comparison to the cord- haplo with CD34+ positive selection or general MUD or uCB HSCT (patient outcome review WKZ). This is particularly true in this high risk group of patients, in which the expected GVHD and TRM are already higher on the basis of lower lansky scores, underlying disease or suboptimal donors available. [32, 33] Patient outcome review WKZ 2009). Stopping rules have been applied to asses an eventuel unacceptable increased cumulative incidence of aGVHD.
2)possible increased risk of cGVHD
As the effects of the haplodonor cells are only temporary, it is unlikely that this protocol will lead to a higher incidence of cGVHD. However, in case of an increase in aGVHD the cumulative incidence of cGVHD is also increased by triggerd alloreactivity and tissue damage triggering new alloreactivity.
3) engraftment syndrome.
with increased engraftment rate and fast recovery of neutrophils there is an increased risk of engraftment syndrome.

Potential Benefits
1) lower TRM and longer event free survival
By swift and secure engraftment, and hopefully less relapse due to NK- and gammadelta T-cell activity.
2)possible lower risk of aGVHD and cGVHD
By decreasing the risk of infection and associated tissue damage and triggered alloreactivity
3) creating a platform for future studies: further development of selection and expansion of specific cell fractions (such as gamma delta T cells, T regs, or modified T cell populations with specific anti-tumor/antiviral activity)

and use them for immune interventions at specific time points when needed.

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

All of the following five criteria:;1) All patients qualifying for allogenic hematopoietic stem cell transplantation (HSCT) (based on national or international study protocols) with a malignancy and either:

- Relapse after first transplant with a SIB or MUD/UCB donor
- Having NHL or HD (refractory, *2CR) for which no standard allo-transplantation protocols are

available, or ALL *CR2 if not eligible to other running SCT protocols.
- Having relapse AML/ refractory AML
- Problems finding a donor: 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) having a single matching (* 4/6) umbilical CB unit available with total NC count > 1,5 E7/kg [22]
3) Lansky / Karnofsky > 40
4) Age 0-65 * (*<= age * 65 and 364 days)
5) Signed Informed Consent

Exclusion criteria

- Lansky < 40
- No cord blood unit available wih <=4/6 match en a minimum cell dose of > 1,5 x 10E7 Nucleated cells /kg
-no informed consent

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	31-10-2010
Enrollment:	43
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Generic name:	Somatic cels allogenic

Ethics review

Not approved

Date:	22-02-2011
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
Other	ingediend, uitspraak volgt < 4wkn, inlog 8239
CCMO	NL31978.000.10