Allogeneic hematopoietic cell transplantation with HLA-matched donors : a phase II randomized study comparing 2 nonmyeloablative conditionings

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The present project aims at comparing two nonmyeloablative regimens currently used in 2 major HCT centers in the US for patients with HLA-matched related or unrelated donor: the one from the Seattle group consisting of 2 Gy TBI with fludarabine (90...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON32010

Source
ToetsingOnline

Brief title
Minitransplant-Random TBI vs TLI

Condition

- Leukaemias
- Leukaemias

Synonym
minitransplantation / GvHD

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: allogeneic, minitransplant, TBI, TLI

Outcome measures

Primary outcome

Primary endpoints:

To compare the incidence of grade II-IV acute GVHD between the 2 groups

Secondary outcome

Secundairy endpoints:

1. to compare hematopoietic (whole blood and T cell chimerism) engraftment and

to evaluate the incidence of graft rejection in the 2 groups

2. to compare the incidence of grade I-IV and III-IV acute GVHD in the 2 groups

3. to compare the incidence of chronic GVHD in the 2 groups

4. to compare the quality and timing of immunological reconstitution in the 2

groups

5. to compare the incidence of bacterial, fungal and viral infections in the 2

groups

6. to compare relapse rate, nonrelapse mortality, progression-free survival and

overall survival in the 2 groups

Study description

Background summary

Alloreactivity of donor immunocompetent cells present in the graft against the host tumor play a major role in eradicating malignancies after allo-HCT (graft-versus-tumor (GVT) effect). The GVT effect is so potent that standard treatment for disease relapse after conventional HCT consists of donor lymphocyte infusions (DLI) that induce complete remissions (CR) in 20-70 % of the cases, depending of the underlying malignancy.
Based on studies in a murine model, the Stanford group has developed another non-myeloablative regimen that favoured the presence of a high proportion of NK-T regulatory cells, and thus was associated with a low incidence of acute GVHD. This regimen consists of total lymphoid irradiation (TLI; 8 Gy) and ATG (Thymoglobulin, 7.5 mg/kg total dose), and postgrafting immunosuppression with MMF and CSP. First results in 37 patients indicated that this regimen was indeed associated with a low incidence of grade II-IV acute GVHD (1 of 37 patients) despite a high rate of stable engraftment, while graft-versus-tumor effects were apparently preserved 23. .

Study objective

The present project aims at comparing two nonmyeloablative regimens currently used in 2 major HCT centers in the US for patients with HLA-matched related or unrelated donor: the one from the Seattle group consisting of 2 Gy TBI with fludarabine (90 mg/m²) versus the one from the Stanford group combining 8 Gy TLI with ATG

Study design

The study is a multicenter, randomized phase II study, comparing two conditioning regimens. Sixty patients with HLA-matched donors will be randomized between the TBI or the DLI regimen. There will be a stratification between centers.

Intervention

The conditioning regimens used will be either the one developed in Seattle (TBI arm) or the one developed by the Stanford group (TLI arm). These 2 regimens have been extensively reported in major medical journals and are routinely used in our centers.

Study burden and risks

The irradiation load is low in both arms

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

Diseases:
Hematological malignancies confirmed histologically and not rapidly progressing:
- AML in CR (defined as * 5% marrow blasts and absence of blasts in the peripheral blood);
- MDS with * 5% marrow blasts and absence of blasts in the peripheral blood;
- CML in CP;
- MPS not in blast crisis and not with extensive marrow fibrosis,
- ALL in CR;
- Multiple myeloma not rapidly progressing;
- CLL;
- Non-Hodgkin*s lymphoma (aggressive NHL should have chemosensitive disease);
- Hodgkin*s disease with chemosensitive disease.;Clinical situations
· Theoretical indication for a standard allo-transplant, but not feasible because:

- Age > 50 yrs;
- Unacceptable end organ performance;
- Patient*s refusal.
· Indication for a standard auto-transplant:
® perform mini-allotransplantation 2-6 months after standard autotransplant.;Other inclusion criteria
· Male or female; fertile patients must use a reliable contraception method;
· Age £ 75 yrs;
· Informed consent given by patient or his/her guardian if of minor age.;Donors:
· Related to the recipient (sibling, parent or child) or unrelated;
· Male or female;
· Any age;
· 10 of 10 (HLA-A, -B, -C, -DRB1, and -DQB1) HLA allele matched;
· Weight > 15 Kg (because of leukapheresis);
· Fulfills criteria for allogeneic PBSC donation according to standard procedures;
· Informed consent given by donor or his/her guardian if of minor age, as per donor center standard procedures.

Exclusion criteria

Patient:
· Any condition not fulfilling inclusion criteria;
· HIV positive;
· Non-hematological malignancy(ies) (except non-melanoma skin cancer) < 3 years before nonmyeloablative HCT.
· Life expectancy severely limited by disease other than malignancy;
· Administration of cytotoxic agent(s) for *cytoreduction* within three weeks prior to initiating the nonmyeloablative transplant conditioning (Exceptions are hydroxyurea and imatinib mesylate);
· CNS involvement with disease refractory to intrathecal chemotherapy.
· Terminal organ failure, except for renal failure (dialysis acceptable)
a. Cardiac: Symptomatic coronary artery disease or other cardiac failure requiring therapy; ejection fraction <35%; uncontrolled arrhythmia, uncontrolled hypertension;
b. Pulmonary: DLCO < 35% and/or receiving supplementary continuous oxygen;
c. Hepatic: Fulminant liver failure, cirrhosis of the liver with evidence of portal hypertension, alcoholic hepatitis, esophageal varices, a history of bleeding esophageal varices, hepatic encephalopathy, uncorrectable hepatic synthetic dysfunction evinced by prolongation of the prothrombin time, ascites related to portal hypertension, bacterial or fungal liver abscess, biliary obstruction, chronic viral hepatitis with total serum bilirubin >3 mg/dL, and symptomatic biliary disease;
· Uncontrolled infection;
· Karnofsky Performance Score <70%;
· Patient is a fertile man or woman who is unwilling to use contraceptive techniques during and for 12 months following treatment;
· Patient is a female who is pregnant or breastfeeding;

· Previous radiation therapy precluding the use of 2 Gy TBI or 8 Gy TLI;;Donors:
· Any condition not fulfilling inclusion criteria;
· Unable to undergo leukapheresis because of poor vein access or other reasons.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-02-2009
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ATG
Generic name:	thymocytenglobuline
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	fludara
Generic name:	fludarabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-11-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-12-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2007-002548-12-NL
CCMO	NL22777.068.08