Treatment of severe steroid-refractory acute GvHD with mesenchymal stromal cells.
A phase III randomized double-blind multi-center HOVON study.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27391

Source
Nationaal Trial Register

Brief title
HOVON 113 MSC

Health condition

graft-versus-host disease, steroid-refractory

Sponsors and support

Primary sponsor: HOVON Data Center
Source(s) of monetary or material Support: Koningin Wilhelmina Fonds (KWF), HOVON, LUMC

Intervention

Outcome measures

Primary outcome

Proportion of patients responding to treatment of acute GvHD grade II-IV (with gut and/or liver involvement) at day 29.

Secondary outcome

1. Overall survival

2. Progression-free survival

3. Duration of acute GvHD response

4. Time without systemic immunosuppression

5. Cumulative incidents of non-relapse mortality

6. Adverse events

7. Incidence of chronic GvHD

8. Quality of life

9. Immune reconstitution including monitoring of absolute T-cell subsets, B-cells, NK-cells as well as biomarkers of acute GvHD

Study description

Background summary

Allogeneic stem cell transplantation (SCT) is the only curative option for many patients suffering from hematological malignancies. Although providing cure for many patients, SCT may be accompanied by severe treatment-related side-effects, including acute Graft-versus-Host Disease (GvHD). Acute GvHD is a major cause of SCT-related morbidity and mortality. First line treatment consists of usually protracted immunosuppressive therapy with high dose corticosteroids often in combination with calcineurin inhibitors. A variety of second line immunosuppressive agents has been investigated for patients failing on corticosteroids, but no optimal treatment has emerged. Steroid-refractory acute GvHD has a high mortality rate and surviving patients often develop chronic GvHD, which severely reduces quality of life. Therefore, there is an urgent need for new and better treatment modalities. Several studies have indicated that third-party mesenchymal stromal cells (MSC) might be an effective therapy for steroid-refractory GvHD. MSC play a role in the regulation of hematopoiesis but

also have putative immunomodulatory properties. Pilot studies have yielded encouraging results suggesting that MSC treatment may induce responses in the majority of patients. We therefore propose a phase III prospective randomized double-blind multicenter study, comparing early treatment with MSC to placebo in patients with steroid-refractory acute GvHD.

The study will focus on:

i) improving the response rate to treatment with MSC,

ii) studying safety,

iii) assessing progression-free survival,

iv) assessing GvHD-free survival,

v) evaluating the possibility to reduce the time required for pharmacological immunosuppression,

vi) assessing the incidence of severe bacterial, viral and/or fungal infections,

vii) reducing the incidence and severity of chronic GvHD,

viii) evaluating the quality of life of patients receiving MSC compared with controls,

ix) developing a predictive score allowing the identification of patients with acute GvHD that will respond to MSC treatment.

Study objective

The hypothesis to be tested is that the outcome in arm B is better than in arm A.

Study design

Clinical, laboratory and QoL evaluations:

• At entry,

• At day 8, 15, 22 and 29,

• Thereafter at 6 weeks and at 2, 3, 6, 12, 18 and 24 months

All patients will be followed until 10 years after randomization.

Intervention

Eligible patients will be randomized to either standardized second line treatment only, consisting of mycophenolate mofetil (MMF) in combination with a placebo for MSC infusion, or MMF in combination with MSC at a dose of 2 x106 MSC per kg bodyweight IV. The first gift of MSC or placebo will be administered the day following randomization. The second gift will be administered 7 days after the first gift.
In addition, all patients will continue systemic treatment with steroids and a calcineurin-inhibitor.

Contacts

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Eligibility criteria

Inclusion criteria

•Grade II-IV acute GvHD with gut and/or liver involvement, confirmed by histology of involved tissues (in case of gut and liver involvement histology of either one of these tissues is

considered sufficient);

• Non-responsive to treatment with steroids and a calcineurin-inhibitor defined as:

- progressive disease or mixed response after 5 days of consecutive systemic treatment with steroids at a dose of 2 mg/kg and a calcineurin-inhibitor at therapeutic trough levels.

- stage 4 GvHD of gut and/or liver and deterioration of clinical parameters (gut) or increase of serum total bilirubin levels in umol/L (liver) after 5 days of consecutive systemic treatment with steroids at a dose of 2 mg/kg and a calcineurin-inhibitor at therapeutic trough levels

- stable disease after 10 days of consecutive systemic treatment with steroids at a dose of 2 mg/kg and a calcineurin-inhibitor at therapeutic trough levels.

- progressive disease after initial partial response of maximal 1 grade after 10 days of consecutive systemic treatment with steroids at a dose of 2 mg/kg and a calcineurin-inhibitor at therapeutic trough levels.

• Any age;

• Lansky / Karnofsky score of ≥20;

• Signed informed consent by the patient and/or parent(s) or legal guardian(s).

Exclusion criteria

• Use of prophylactic MMF, Myfortic or other systemic treatment for acute GvHD ≤ 6 days prior to development of acute GvHD grade II-IV with gut and/or liver involvement;

• Systemic treatment for acute GvHD other than steroids and a calcineurin inhibitor (budesonide is considered a local treatment);

• Previous treatment with MSC;

• Progressive or relapsing malignant disease in case of NHL, HL, CLL, MM, and ≥ 5% blasts in the bone marrow in case of AML, ALL, CML;

• Requiring ventilator or vasopressor support;
• Poor performance not expected to survive 14 days;

• Known seropositivity of HIV, Hepatitis B and C, HTLV;

• Known uncontrolled toxicity for DMSO;

• Known anaphylactic reaction to penicillin or streptomycin;

• Known pregnancy;

• Any psychological, familial, sociological and /or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2013
Enrollment:	150
Type:	Anticipated

Ethics review

Positive opinion

Date:	28-10-2013
Application type:	First submission

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
NTR-new	NL4076
NTR-old	NTR4227
Other	2012-004915-30 / NL42497.000.12 : HOVON 113 MSC
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A