Treatment of severe acute GVHD after allogeneic hematopoietic stem cell transplantation with steroids versus MSC and steroids.
A prospective double-blind placebo-controlled randomized phase III trial

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON29599

Bron
NTR

Verkorte titel
HOVON 112 MSC

Aandoening

graft-versus-host disease

Ondersteuning

Primaire sponsor: HOVON Data Center
Overige ondersteuning: Koningin Wilhelmina Fonds (KWF), HOVON, UMCU

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Proportion of patients in each treatment arm who experience a CRGVHD or PRGVHD (see Appendix B) at day 57, without treatment failure (initiation of secondary treatment,progression/relapse, or death)

Toelichting onderzoek

Achtergrond van het onderzoek

Background of the study:

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is an established and powerful treatment modality for patients with multiple hematological malignancies and inborn errors. In particular, the immunotherapeutic effect, known as the graft versus leukemia (GVL) effect, significantly reduces the rate of relapse in leukemia patients, receiving their allograft as consolidation therapy in first or subsequent remission However, GVL is strongly associated with the occurrence of acute and/or chronic graft versus host disease (GVHD). GVHD occurs in 35%-50% of the transplanted patients, still substantially limiting the outcome and the more widespread use of allo-SCT .Thus, allo-SCT strategies which separate GVHD from GVL effects and therapies which treat effectively GVHD are urgently needed. The core of acute GVHD treatment consists of immunosuppression, with 1-2mg/kg/d prednisolone as the standard first line treatment. Several studies demonstrate an overall complete response rate to prednisolone in approximately 40-50% of all patients, with a lower response rate and a higher recurrence in patients with more severe GVHD. One interesting alternative therapeutic option for patients with severe GVHD comes from recent data of the application of mesenchymal stromal cells (syn., Mesenchymal stem cells). The data strongly support the notion that MSC need to be studied in larger and more stringent randomized clinical trials for patients with acute GVHD. They could be more effective when administered early in GVHD treatment thus leading to a better survival. This is the rational for this Phase lll trial comparing steroids and MSC as first line therapy against steroids alone. The study includes selectively patients suffering from gut and/or liver grade II-IV GVHD in first-line, thus patients with an expected survival of less than 25%.

Objective of the study:

To improve the response rate to treatment of severe acute GVHD (grade II-IV with gut and/or involvement) by adding Mesenchymal Stromal Cells to standard high dose prednisolone.

Study design:

Prospective, multicenter, double blind, placebo- controlled, randomized

Study population:

Patients who received an allo-SCT for malignant or non-malignant disorders who develop severe grade II-IV acute GVHD involving gut and/or liver .

Intervention:

Patients are randomized for treatment with

-high dose prednisolone 2 mg/kg/day i.v. and placebo

-high dose prednisolone 2 mg/kg/day i.v. and MSC at day 1, day 8, and day 22 i.v.

Cyclosporine A + Mycophenolate prevention regimens will be (re)started or continued according to prevention schedule (Cyclosporine A through levels 0.20-0,35 mmol/l).

Primary study parameters/outcome of the study:

- Proportion of patients in each treatment arm who experience a CR-GVHD or PR-GVHD at day 57, without treatment failure (initiation of secondary treatment)

Secundary study parameters/outcome of the study (if applicable):

- Proportion of patients in each treatment arm who experience a CR-GVHD or PR-GVHD at indicated timepoints (until 2 years), without treatment failure (initiation of secondary treatment)

- Time to CR-GVHD or PR-GVHD

- Amount of immune suppression at indicated days

- Adverse events

- The (immunological) phenotype before and after application of MSC/placebo of responders and non-responders in both groups at different sites

- The immunological genotype of responders and non-responders as well as donors in both groups

- Quality of life

- Cost-effectiveness

- Relapse of the underlying disease (e.g. hematological malignancy)

- Progression-free survival

- Incidence and severity of chronic GVHD

- Overall survival

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Burden consists of repetitive infusions of MSC, additional blood draws, bone marrow apirate and biopsy of the skin or gut after resolution of GVHD. So far no severe side effects have been reported of MSC. Theoretical risks are support of leukemia-growth, and severe infection. However, considering the life-threatening nature of GVHD and the side-effects of steroids, we expect an overall-benefit in terms of improved survival and less use of steroids.

Doel van het onderzoek

Multiple small clinical trials support the notion that Mesenchymal Stromal Cells (MSC) need to be studied in larger and more stringent randomized clinical trials for patients with acute GVHD. This is the rationale for this Phase lll trial comparing steroids and MSC as first-line therapy against steroids alone.
The study objective is to improve the response rate to treatment of severe acute GVHD (grade II-IV with gut and/or liver) by adding MSC to standard high dose prednisolone.

Onderzoeksopzet

The patients will be evaluated at entry, day 8, 15, 22, 29, 57 and at 3, 4, 6, 12 and 24 months.
Beyond 2 years after registration patients will be followed according to local practice.
All patients will be followed until 10 years after registration.

Onderzoeksproduct en/of interventie

Patients will be randomized to either standard treatment consisting of high dose prednisolone plus placebo (arm A) or high dose prednisolone plus MSC (arm B).

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Any age;

- Previously treated with allo-SCT/ DLI;

- Grade II-IV acute GVHD involving gut and/or liver according to appendix A (confirmed by histology of involved tissues, however, the first infusion of MSC/placebo can be given without final histological confirmation);

- WHO performance 0-3;

- Negative pregnancy test (if applicable);
- Patients must be willing and capable to use adequate contraception during therapy (if applicable) ;

- Written Informed Consent by the patient and/or parent(s) or legal guardian(s).

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Patients with active, uncontrolled infection;

- Rapid progressive hematological malignancy;

- Patients pre-treated with prednisolone > 1 mg/kg for GVHD, for more than 72 hours prior to randomization/application of MSC/placebo;

- Known uncontrolled toxicity for DMSO;
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, cancer, etc.)

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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-12-2013
Aantal proefpersonen:	200
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	28-10-2013
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 41587
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL4077
NTR-old	NTR4228
CCMO	NL41506.000.13
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON41587

Resultaten

Samenvatting resultaten
N/A