Intra-marrow transplantation of Mesenchymal Stromal Cells to treat MyeloDysplastic Syndromes: A feasibility study

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Ethical review	Not approved
Status	Will not start
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON37006

Source
ToetsingOnline

Brief title
PMDS28 / Intra-marrow transplantation of Mesenchymal Stromal Cells in MDS

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Myelodysplastic syndromes

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: KWF aanvraag wordt ingediend (juni ronde)

Intervention

Keyword: mesenchymal stromal cell (MSC), myelodysplastic syndromes (MDS), transplantation

Outcome measures

Primary outcome

* The safety of intra-marrow transplantation of MSCs in low and int-1 risk IPSS

MDS patients.

Secondary outcome

* Efficacy (CR, PR, Hematological Improvement, SD, PD) 3 months after

intra-marrow MSC infusion

* Efficacy (CR, PR, Hematological Improvement, SD, PD) 12 months after

intra-marrow MSC infusion

* Overall survival measured from the date of first MSC infusion

* Probability of progression to AML after intra-marrow MSC infusion

* Number and duration of hospitalization as well as transfusion requirements

(red cell and platelet transfusion).

* Cytogenetic responses in CD34+ and CD45- cell fractions determined by FISH

analyses

* Determination of prognostic factors on response.

* Adverse events

Study description

Background summary

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by impaired peripheral blood cell production (cytopenias) and most commonly a hypercellular, dysplastic-appearing bone marrow. About 500 new cases are reported annually in the Netherlands. Based on the number of bone marrow blasts, cytogenetic abnormalities and the severity of the cytopenias, MDS patients can be categorized as lower-risk or higher-risk. Higher-risk patients tend to evolve in acute myeloid leukemia (AML) and are treated accordingly. Lower-risk patients usually die of bone marrow failure. Other than *best supportive care* (transfusions, antibiotics), no standard treatment is available for these patients.
Most investigations on MDS have focused on the hematopoietic stem/progenitor compartment, but various abnormalities have also been identified in the immune system and the bone marrow microenvironment in MDS patients. This insight has resulted in the successful use of immune modulatory (e.g. lenalidomide) and immune suppressive drugs (e.g. ATG and/or cyclosporine). However, only a subset of patients responds to these treatments, without a survival benefit. The armamentarium of immune regulatory agents has recently been expanded with mesenchymal stromal cells (MSCs) generated from healthy donors (*third party*). In contrast to conventional immune modulatory drugs, MSCs provide a more specific and more powerful modulation of the immune system. This is illustrated by our experience with MSCs for the treatment of steroid-resistant GVHD. In addition, MSCs provide another potential advantage: MSCs, derived from bone marrow stroma, produce bioactive molecules and regenerate the microenvironment, which is also considered to be crucial for the pathogenesis of MDS. Thus, both a specific and powerful immune modulation combined with a restoration of the microenvironment might provide a more sustained response to therapy, compared with usual therapies. This is in particular important, as in daily clinical practice, most patients with lower-risk MDS have few treatment options and die of their disease. To optimally modulate the bone marrow microenvironment we want to infuse third party MSCs directly into the bone marrow space, a procedure in our preliminary data shown to be feasible.
In this proposal we aim to study the safety and efficacy of intra-marrow transplantation of third party MSCs in lower-risk MDS patients. We hypothesize that intra-marrow transplantation of MSCs will re-establish normal hematopoiesis in lower-risk MDS patients.

Study objective

This proposed study has three main objectives:

1. To determine the feasibility of intra-marrow transplantation (IMT) of MSCs in lower risk MDS patients (a Phase I/II study):
Although we have experience with application of (unrelated) MSCs and intra-marrow infusion of transplants, we will start this project with a Phase I dose escalation safety study in 9 patients with lower-risk MDS and a treatment indication (symptomatic cytopenia). Subsequently, we will treat 20 additional patients to study feasibility and safety. All relevant clinical parameters for

patients suffering from MDS, including peripheral blood counts and transfusion dependency, will be monitored.

2. To assess the impact of IMT of MSCs on the bone marrow microenvironment
The bone marrow microenvironment will be studied prior to and 3 months after intra-marrow transplantation of MSCs. MSCs will be isolated and expanded for 2-3 passages for subsequent analyses. Additional studies, using conventional cytogenetics and FISH, should identify the impact of intra-marrow MSC transplantation on clonal composition of both CD34+ hematopoietic stem/progenitor cells and CD45- MSCs. In addition, the origin of CD45- MSCs (patient versus donor) in the bone marrow microenvironment 3 months after intra-marrow MSC transplantation will be investigated.

3. To assess the impact of IMT of MSCs on immune regulatory and effector cells
The immune profile (T-cell subsets, T-cell clonality, myeloid derived suppressor cells, dendritic cells) and bioactive molecules (e.g. cytokines) will be studied prior to and 1 and 4 weeks after intra-marrow transplantation. The aim of these studies is to investigate the impact of MSCs on the immune profile in MDS patients and to identify predictors for response to MSC therapy.

Study design

This is a phase I/II feasibility study. Patients with MDS (RCUD, RARS, RCMD and RAEB1) and an IPSS score of 0.5 or 1 and an indication for treatment (patients should have had at least one red blood cell (RBC) transfusion in the two months prior to inclusion due to a hemoglobin level < 6 mmol/l) are eligible.

Nine patients (classic 3x3 design) will participate in the phase I part and receive increasing doses of MSCs directly infused in the bone marrow cavity of the left or right spina iliaca post (intra-marrow). In the phase II study eligible patients will receive a fixed (safe) dose of MSCs in the left or right spina iliaca posterior superior. In addition, patients without response after the first MSC transplantation will be infused with the same dose of MSCS in the left and right spina iliaca posterior superior (dose and space escalation) (re-treatment. In addition, patients without response after the first MSC transplantation will be infused with the same dose of MSCS in the left and right spina iliaca posterior superior (dose and space escalation) (re-treatment).

Intervention

Nine patients (classic 3x3 design) will participate in the phase I part and receive increasing doses of MSCs directly infused in the bone marrow cavity of the left or right spina iliaca post (intra-marrow) and will be observed for 3 months.

For this study we will use fixed doses of MSCs: patients whose weight is below 80 kg will receive a lower dose compared with patients whose weight is higher than 80 kg. The reason to use fixed doses is because we assume, based on our previous experience with MSCs, that small deviations from the standard dose per kg will have negligible impact on the clinical effect and because fixed doses allow bed-side preparation of the cellular product which also has logistic and financial advantages.

The first 3 patients will receive about 0.1 x 106 MSCs/kg (in 20 ml) directly infused into the bone marrow cavity via either the left or right spina iliaca posterior superior. In fact: patients with a weight lower than 80 kg receive 7.5 x 106 MSCs (in 20 ml) and patients with a weight higher than 80 kg receive 10 x 106 MSCs (in 20 ml). If no toxicities are observed, the second set of 3 patients will receive about 0.5 x 106 MSCs/kg (in 20 ml) directly infused into the bone marrow cavity via either the left or right spina iliaca posterior superior. In fact: patients with a weight lower than 80 kg receive 40 x 106 MSCs (in 20 ml) and patients with a weight higher than 80 kg receive 50 x 106 MSCs (in 20 ml). If no toxicities are observed, the third set of 3 patients will receive 1 x 106 MSCs/kg (in 20 ml) directly infused into the bone marrow cavity. If no toxicities are observed after this last set of patients is treated, the Phase II study will be started at a dose level of about 1 x 106 MSCs/kg (in 20 ml). In fact: patients with a weight lower than 80 kg receive 75 x 106 MSCs (in 20 ml) and patients with a weight higher than 80 kg receive 100 x 106 MSCs (in 20 ml).

In the phase II part 20 patients will receive the optimal dose of MSCs (as determined in the phase I part of this study) directly infused in the bone marrow cavity of the left or right spina iliaca post (intra-marrow). We expect that the optimal dose will be about 1 x 106 MSCs/kg (in 20 ml). Since we will infuse fixed doses of MSCs: patients < 80 kg will receive 75 x 106 MSCs/kg (in 20 ml) and patients > 80 kg will receive 100 x 106 MSCs/kg (in 20 ml).

Intra-marrow infusion
Prior to the infusion the patient gets adequate pain relief using continuous morphine infusion (pump), conform the protocol which was used for our preliminary study on intra-marrow infusion of autologous stem/progenitor cells. In addition, prior to infusion of MSCs clemastine (1 or 2 mg) iv, paracetamol 1 g orally, morphine continuous iv and prednisone 25 mg iv will be given. After thawing the MSCs will be infused over 30 minutes into the bone marrow compartment via a Jamshidi needle in the spina iliaca posterior superior. Per infusion, a total volume of 20 ml will be infused. Infusion of the MSC transplant will be performed by a hematologist experienced in intra-marrow infusion. Post-infusion patients will be monitored according to routine practice.

Post-transplant clinical evaluation
To determine response (CR, PR, hematological improvement (erythroid response,

platelet response, neuthophil response), stable disease and treatment failure) the Interantional Working Group (IWG) criteria will be used. In short: according to IWG an erythroid response is defined as a Hb increase by * 0.9 mmol/L (1.5 g/dL) or relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hb of * 5.6 mmol/L (9 g/dL) pretreatment will count in the RBC transfusion response evaluation. A platelet response is defined as an absolute increase of * 30 x 109/L for patients starting with >20 x 109/L platelets or an increase from < 20 x 109/L to > 20 x109/L and by at least 100%. A Neutrophil response is defined as an at least 100% increase and an absolute increase > 0.5 x 109/L. For these response criteria (erythroid, platelet and neutrophils) the responses must be at least 8 wk. In the IWG response criteria the pretreatment Hb should be < 6.8 mmol/L (11 g/dL), the pretreatment platelet count < 100 x 109/L and the neutrophils < 1.0 x 109/L.

Respons will be evaluated after 3 and 12 months. Those patients with a response after 3 months will be observed; those patients without a response after 3 months will receive re-treatment with the same dose, but infused in the bone marrow cavity of the left and right spina iliaca post sup (dose and space escalation). These patients will be evaluated again 3 months after the re-treatment.
All patients will be followed for a maximum of 2 years after intra-marrow transplantation.

Study burden and risks

There is a chance that the disease responds favorably to the direct infusion of MSCs in the bone marrow cavity. This would allow reduction of the amount of blood transfusions and infections.

A potential disadvantage of the study could be that the treatment has no effect despite the patient has undergone the procedure. The administration of MSC in the bone marrow cavity will presumably, despite optimal pain relief, still give slight pain. In our experience with direct infusion of autologous transplants in the bone marrow cavity this pain was well tolerated by our patients.

On standard evaluation points 3 and 12 months after MSC infusion, additional blood and bone marrow will be collected for scientific research. For routine bone marrow examination, bone marrow aspirates will be taken from the left and right side of the back of the iliac crest. At other moments of evaluation comparable blood tests will performed as would be done routinely if the patient did not participate in this study.

The information obtained from this study may, in the future, contribute to a

better treatment of patients with lower risk MDS.

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

* Subjects with a cytopathologically confirmed diagnosis of
(a) Patients with MDS RCUD, MDS RARS, MDS RCMD, MDS RAEB-1 and an IPSS * 1 (appendix C)
(b) An indication for treatment: patients should have had at least one red blood cell (RBC) transfusion in the two months prior to inclusion due to a hemoglobin level < 6 mmol/l,
Note: Subjects with thrombocytopenia or neutropenia are eligible.
* MDS RCUD, MDS RARS, MDS RCMD, MDS RAEB-1 and an IPSS * 1 and erythropoietin level <500 iU/l and progressive after first line erythropoietin treatment.
* MDS RCUD, MDS RARS, MDS RCMD, MDS RAEB-1 and an IPSS * 1 and 5q- cytogenetic

abnormality and progressive after first line lenalidomide treatment.
* WHO performance status of 0, 1 or 2 (see appendix F)
* Written informed consent

Exclusion criteria

* MDS RCUD, MDS RARS, MDS RCMD, MDS RAEB-1 and an IPSS * 1 and erythropoietin level <500 iU/l and not having received erythropoietin treatment
* MDS RCUD, MDS RARS, MDS RCMD, MDS RAEB-1 and an IPSS * 1 and 5q- cytogenetic abnormality and not having received lenalidomide treatment
* MDS RCUD, MDS RARS, MDS RCMD, MDS RAEB-1 and an IPSS * 1 who have been treated with immune suppressive drugs (e.g. corticosteroids, calcineurin inhibitors) during the last 6 months
* Impaired hepatic or renal function as defined by:
* ALT and/or AST > 2.5 x normal value
* Bilirubin > 2 x normal value
* Serum creatinin > 2 x normal value (after adequate hydration)
* Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, cancer, etc.)
* Cardiac dysfunction as defined by:
* Myocardial infarction within the last 6 months of study entry, or
* Reduced left ventricular function with an ejection fraction <50% as measured by MUGA scan or echocardiogram (another method for measuring cardiac function is acceptable)
* Unstable angina
* Unstable cardiac arrhythmias

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	29

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	19-09-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	27-09-2012
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	EUCTR2012-002390-64-NL
CCMO	NL40819.000.12