Upfront autologous hematopoietic stem cell transplantation versus immunosuppressive medication in early diffuse cutaneous systemic sclerosis: an international multicentre, open-label, randomized con-trolled trial

No registrations found.

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

Summary

ID

NL-OMON26075

Source
NTR

Brief title
UPSIDE

Health condition

Systemic Sclerosis

Sponsors and support

Primary sponsor: University Medical Centre Utrecht
Source(s) of monetary or material Support: ZonMW, Boehringer Ingelheim b.v., Miltenyi b.v, and the private funding partner

Intervention

Outcome measures

Primary outcome

The primary endpoint is event-free survival. Event-free survival is defined as the time in days from
the day of randomisation until the occurrence of death due to any cause or the development of
persistent major organ failure (heart, lung, kidney) defined as follows:
• Heart: left ventricular ejection fraction < 30% by cardiac MR (or cardiac echo)
• Lungs: respiratory failure = resting arterial oxygen tension (PaO2) < 8 kPa (< 60 mmHg) and/or resting arterial carbon dioxide tension (PaCO2) > 6.7 kPa (> 50 mmHg) without oxygen supply
• Kidney: need for renal replacement therapy

Note 1. When major organ failure has occurred, its persistence is to be confirmed by repeated evaluation after 3 months.

Note 2. Cardiac MR is considered the gold standard for assessment of LVEF.
LVEF measurements by cardiac echo (instead of cardiac MR) will be accepted when baseline and follow-up eval-uations have been performed by the same experienced echocardiologist.

Secondary outcome

- Progression-free survival, defined as the time in days since the day of randomisation until any of the following relative changes from baseline has been documented:
• death,
• ≥ 10% drop in (F)VC predicted and/or ≥ 15% drop in DLCO predicted,
• ≥ 15% drop in LVEF by echo or cardiac MR,
• ≥ 15% drop in body weight,
• ≥ 30% drop in creatinine clearance,
• ≥ 30% increase in skin score,
• ≥ 0.5 increase in SHAQ.

- Treatment related mortality is defined as any death during the study period following randomisation
that cannot be attributed to progression of the disease according to the consensus opinion of the
DSMB.

- Treatment toxicity will be assessed using WHO toxicity parameters (adverse events =/> grade 3) in consecutive 3-month periods following randomisation until two years follow-up.

- The area under the curve (AUC) of the CRISS over time, measuring the ‘predicted probability of being im-proved’ over 2 years.(22) This AUC is calculated based on 4 repeated measures (6, 12, 18 and 24 months) with back translation to the original scale between 0 and 1.

The CRISS is a composite score, measuring the CRISS is a two-step process:
Step 1: Subjects who develop new or worsening of cardiopulmonary and/or renal involvement due to SSc are considered as not improved (irrespective of improvement in other core items) and assigned a probability of im-proving equal to 0.0. Specifically if a subject develops either: 1) New scleroderma renal crisis, 2) Decline in forced vital capacity (FVC)% predicted ≥15% (relative), confirmed by another FVC% within a month, high resolution computer tomography (HRCT) to confirm interstitial lung disease (ILD; if previous high resolution computer tomography of chest did not show ILD) and FVC% predicted below 80% predicted, 3) New onset of left ventricular failure (defined as left ventricular ejection fraction ≤45%) requiring treatment, or, 4) New onset of pulmonary arterial hypertension (PAH) on right heart catheterization requiring treatment.
Step 2: For the remaining subjects, Step 2 involves computing the predicted probability of improving for each subject using a validated equation, using the ΔMRSS indicates the change in MRSS from baseline to follow-up, ΔFVC denotes the change in FVC% predicted from baseline to follow-up, Δ Pt-glob indicates the change in patient global assessment, ΔMD-glob denotes the change in physician global assessment, and ΔHAQ-DI is the change in HAQ-DI. All changes are absolute change.

- Change over years follow-up of the following parameters:
• modified Rodnan skin score by independent assessor
• Pulmonary involvement = diffusion capacity for carbon monoxide (DLCO and DLCO/VA), (forced)vital capacity ((F)VC), total lung capacity (TLC), residual volume (RV), mean pulmonary artery pressure by cardiac echo (or right heart catheterization), lung density measurement by thoracic CT
• Renal involvement = urine portion: creatinin/ protein ratio
Myocardial involvement= left ventricular function as measured by cardiac MR (at baseline and 12 months), ECG and cardiac echo (annually) and semiquantitative measurement of cardiac involvement with the cardiac score (based on the presence or absence of left axis deviation on ECG and moderate or large pericardial effusion on echo).
- Quality-of-life (EuroQol (EQ-5D-5L))
- Customized version (focussing on the important cost-drivers) of the iMCQ and iPCQ
- SHAQ incl visual analogue scales (VAS) for scleroderma-specific symptoms
- Gastrointestinal symptom scale (UCL-GIT 2.0)
- Sexual functioning (IIEF-5 and BMSFI (in men) and Sexual Function Questionnaire (SFQ-28))

Study description

Background summary

Rationale: This multicentre, randomized, open label trial aims to compare two treatment strategies used in usual care: upfront autologous HSCT versus usual care with (intravenous (i.v.) cyclophosphamide (CYC) pulse thera-py followed by mycophenolate mofetil (MMF) and HSCT as rescue option). HSCT has been implemented in (inter)national treatment guidelines for diffuse cutaneous systemic sclerosis (dcSSc) and is offered in clinical care and reimbursed

by national health insurance in several European countries. However, data and specific guidelines on the best timing of HSCT in the course of dcSSc are lacking. In particular, it is unclear whether HSCT should be positioned as upfront therapy or as rescue treatment for patients not responding to conventional im-munosuppressive therapy. Given the risks and costs associated with HSCT, it may be preferable to evaluate the patient's response to immunosuppressive therapy before proceeding to HSCT. Considering HSCT as a rescue treatment could significantly delay the need for a potentially harmful treatment and may be an efficient approach from a health economic perspective as HSCT is a highly specialized, resource intensive and expensive medical procedure. On the other hand, in the time frame needed to evaluate the effect of immunosuppressive therapy, pulmonary and cardiac involvement may develop, negatively influencing a patient's prognosis and possibly leading to a contra-indication for HSCT. We hypothesize that upfront HSCT results in less toxicity and medical costs in the long run. Therefore, we propose a multicentre randomized open label trial in chemotherapy naive patients with early dcSSc.
Objective: To determine the optimal treatment strategy in early dcSSc: the effect of HSCT as upfront therapy compared with that of immunosuppressive medication in early dcSSc, with respect to survival and prevention of major organ failure (referred to as 'event-free survival' which is considered as primary endpoint), safety and the impact on skin thickening, visceral involvement, functional status, and quality of life
Secondary goals are to evaluate (in both treatment arms) whether disease activity correlates with immunological parameters, including immunopathology of skin, immune reconstitution, and autoantibodies. We will also de-termine the cost-effectiveness of HSCT as first line treatment versus usual care and try to identify factors associ-ated with response to treatment.
Study design: This investigation is an international multicentre, prospective, randomized, open label trial com-paring two treatment strategies used in regular care: upfront autologous HSCT versus immunosuppressive thera-py with i.v. CYC pulse therapy followed by MMF and HSCT as rescue option.
Study population: Patients aged between 18 – 65 years with an established diagnosis of dcSSc according to the ACR/EULAR criteria. Patients disease duration (non-Raynaud's symptoms) should be ≤ 2 years and mRSS ≥ 15 (diffuse skin pattern) and /or clinically significant organ involvement (heart and lung involvement).
Intervention: One group (A) receives upfront autologous HSCT and the other group (B) receives 12 monthly i.v. pulses CYC (750 mg/m2), followed by at least 12 months of oral MMF (max 3 grams daily) at one year after start of treatment. From 6 months onwards, rescue HSCT is allowed in group B in case of severe progres-sion despite treatment, and immunosuppressive therapy can be initiated in case of disease progression or relapse in group A.
Main study parameters/endpoints: The main study parameter is event-free survival after randomisa-tion/treatment start.
Secondary efficacy endpoints: Overall Survival (OS), progression-free survival, number of participants that need rescue therapy (i.e. the alternative treatment) due to treatment failure. Treatment related mortality, treatment toxicity, and changes in mRSS, FVC, TLC and DLCO, nailfold microscopy, immunological markers in skin and blood, cardiac MR and 18FDG-PET. The CRISS at 12 months. Safety and tolerability outcomes according to CTC-criteria (CTCAE v5.0). Patient reported outcomes at 12 and 24 months include: Quality of life (EQ-5D), SHAQ, Gastrointestinal complaints (GIT 2.0), sexual functioning.

Study objective

We hypothesize that upfront HSCT results in less toxicity and medical costs in the long run.

Study design

first of July 2020

Intervention

Arm A. Upfront autologous HSCT
Autologous, non-myeloablative HSCT comprises the following consecutive steps:
a. Mobilisation: PBSCs will be mobilised using a regimen consisting of one-hour infusions of cyclophosphamide 2g/m2 on 1 day. Hyperhydration, alkalinisation of the urine and Mesna will be given in order to prevent haemorrhagic cystitis. The patients will receive filgrastim (G-CSF) 10 µg/kg/day subcutaneously for 5 days (or more when necessary). Administration of filgrastim commences 5 days after the last cyclophosphamide infusion. Mobilisation can be done either at a day care unit or inpatient admission, according to local practice.
b. Leukapheresis: Daily monitoring of full blood count will be mandatory during mobilisation to ascertain recognition of anaemia, neutropenia, thrombocytopenia and CD34+ counts. CD34 monitoring should be initiated at the latest if leukocytes increase up to 1000/µL during recovery from aplasia. Prompt start of leukapheresis is required at a CD34+ cell count of ≥20/µL. This is expected to occur on day 5 or 6 of filgrastim treatment. Leukapheresis will be performed on a continuous flow cell separator machine. PBSCs will be collected using a two arm venous access technique. The endpoint of each leukapheresis collection will be the processing of 10 to 20 litres of whole blood.
Leukaphereses will be performed with the goal to obtain at least 6 x 106 CD34+ cells per kilogram body weight. The primary goal is to obtain a target dose of 6 x 106 CD34+ cells/kg, but a minimum of 2 x 106 CD34+ cells/kg after selection. The apheresis product will be 4-5log T cell depleted. The CD34+ selected cells will be cryopreserved and stored in liquid nitrogen until reinfusion. In case of mobilization failure, the patient will be treated with daily s.c. filgrastim 20 µg/kg, or when locally available, plerixafor at day 5 from the start of the mobilization if circulating CD 34+ cells are lower than 20/mmc.
c. Prior to conditioning: Echocardiography should be repeated prior to conditioning to evaluate possible subclinical cardiac toxicity caused by cyclophosphamide administered during mobilization.
d. Conditioning: Conditioning is to be initiated as soon as possible after recovery, preferably within 6 weeks after successful harvest. The conditioning regimen consists of cyclophosphamide 50 mg/kg/day intravenously for 4 consecutive days (total 200 mg/kg) and rabbit antithymocyte globulin (rbATG, Genzyme). The first dose of cyclophosphamide will be given on day -5 (day 0 = day of infusion of PBSC). Hyperhydration, alkalinisation of the urine and Mesna will be given in order to prevent haemorrhagic cystitis. A total dose of 7.5 mg/kg intravenous rbATG will be administered over three days. Intravenous methylprednisolone 2 mg/kg will be given on the days ATG will be administered, to improve tolerability of the ATG.
d. Peripheral stem cell infusion: The interval between the last dose of cyclophosphamide and infusion of the graft will be at least 48 hours. On day 0 CD34+-selected stem cells are thawed

and infused according to local standard operating procedures. The number of CD34+ cells to be reinfused should be ≥ 2.0 x 106/kg, residual T cell content is targeted at ≤ 1.0 x 105 T cells/kg.(18)

Arm B. Cyclophosphamide followed by mycophenolate mofetil and HSCT as rescue option
Immunosuppressive therapy in arm B consists of 12 monthly intravenous pulses cyclophosphamide 750 mg/m2 (= 9 g/m2 cumulative) followed by at least 12 months of oral mycophenolate mofetil daily (3 grams as maximum daily dosage). Hyperhydration, alkalinisation of urine and mesna is recommended during the 12 monthly intravenous pulses cyclophosphamide, and will be given according to local protocols in order to prevent haemorrhagic cystitis.

Contacts

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Eligibility criteria

Inclusion criteria

1. Age between 18 and 65 years.
2. Fulfilling the 2013 ACR-EULAR classification criteria for SSc (appendix B).
3. Disease duration ≤ 2 years (from onset of first non-Raynaud's symptoms) and diffuse cutaneous disease with
- mRSS ≥ 15 and/or
- clinically significant organ involvement as defined by either:

a) respiratory involvement =
i. DLCO and/or (F)VC ≤ 85% (of predicted) and evidence of interstitial lung disease on HR-CT scan with clinically relevant obstructive disease and emphysema excluded.
ii. Patients with a DCLO and/or FVC > 85%, but with a progressive course of lung disease: defined as relative decline of >10% in FVC predicted and/or TLC predicted, or >15% in DLCO predicted and evidence of interstitial lung disease on HR-CT scan with clinically relevant

obstructive disease and emphysema excluded, within 12 months. Intercurrent infections excluded.

b) renal involvement = any of the following criteria: hypertension (two successive BP readings
of either systolic ≥ 160 mm Hg or diastolic > 110 mm Hg, at least 12 hours apart), persistent urinalysis abnormalities (proteinuria, haematuria, casts), microangiopathic haemolytic anaemia,
new renal insufficiency (serum creatinine > upper limit of normal); non-scleroderma related causes (e.g. medication, infection etc.) must be reasonably excluded.

c) cardiac involvement = any of the following criteria: reversible congestive heart failure, atrial
or ventricular rhythm disturbances such as atrial fibrillation or flutter, atrial paroxysmal tachycardia or ventricular tachycardia, 2nd or 3rd degree AV block, pericardial effusion (not leading to hemodynamic problems), myocardi-tis; non-scleroderma related causes must have been reasonably excluded.

4. Written Informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Pregnancy or unwillingness to use adequate contraception during study
2. Concomitant severe disease =
a) respiratory: resting mean pulmonary artery pressure (mPAP) > 20 mmHg (by right heart catheterisa
tion), DLCO < 40% predicted, respiratory failure as defined by the primary endpoint
b) renal: creatinine clearance < 40 ml/min (measured or estimated)
c) cardiac: clinical evidence of refractory congestive heart failure; LVEF < 45% by cardiac echo or cardiac
MR; chronic atrial fibrillation necessitating oral anticoagulation; uncontrolled ventricular arrhythmia; pericardial effusion with hemodynamic consequences
d) liver failure as defined by a sustained 3-fold increase in serum transaminase or bilirubin, or a Child-
Pugh score C
e) psychiatric disorders including active drug or alcohol abuse
f) concurrent neoplasms or myelodysplasia
g) bone marrow insufficiency defined as leukocytopenia < 4.0 x 109/L, thrombocytopenia < 50
x 109/L, anaemia < 8 gr/dL, CD4+ T lymphopenia < 200 x 106/L
h) uncontrolled hypertension
i) uncontrolled acute or chronic infection, including HIV, HTLV-1,2 positivity
j) ZUBROD-ECOG-WHO Performance Status Scale > 2

3. Previous treatments with immunosuppressants > 6 months including MMF, methotrexate, azathioprine, rituximab, tocilizumab, glucocorticosteroids.

4. Previous treatments with TLI, TBI or alkylating agents including CYC.

5. Significant exposure to bleomycin, tainted rapeseed oil, vinyl chloride, trichlorethylene or silica;

6. eosinophilic myalgia syndrome; eosinophilic fasciitis.

7. Poor compliance of the patient as assessed by the referring physicians.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	18-06-2020
Enrollment:	120
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Ethics review

Positive opinion

Date:	18-06-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 52909
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8720
CCMO	NL72607.041.20
OMON	NL-OMON52909

Study results