Autologous Stem cell transplantation for progressive systemic sclerosis: a Prospective Non-Interventional approach across Europe

For the Autoimmune Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT)

Short name: The NISSc study

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Synopsis	
Protocol Title	Autologous Stem cell transplantation for progressive systemic sclerosis: a prospective non-interventional approach across Europe
Short name	NISSC
Sponsor	EBMT/ADWP
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Protocol Design	Open, multi-centers,prospective non-interventional study
Aim of the study	To assess the effectiveness of Autologous Hematopoietic Stem Cell transplantation for early severe or rapidly progressive Systemic Sclerosis (SSc)
Inclusion criteria	Autologous HSCT Age between 18 and 65 years at time of transplant. Established diagnosis of progressive systemic sclerosis according to ARA-criteria
Exclusion criteria	Pregnancy or inadequate contraception Severe concomitant disease Reduced lung function Previously damaged bone marrow Uncontrolled severe infection Severe concomitant psychiatric illnes
Primary Endpoint	Progression free survival
Secondary Endpoints	Safety Overall survival Response to treatment Improvement of QOL Relapse incidence TRM
Recruitment	50 patients
Recruitment period	3 years
Follow up duration	2 years
Follow up	Follow up: according to local standard protocol with documentation of disease activity/survival:on a quarterly basis for 2 years period according to CRF

Glossary of Abbreviations	
ADWP	Autoimmune Disease Working Party
AHSCT	Autologous stem cell transplantation
ATG	Antithymocyte globuline
CHD	Coronary heart disease
CYC	Cyclophosphamide
Dc	Diffuse cutaneous
DLCO	Diffussion lung capacity for carbone monoxid
EBMT	European Group for Blood and Marrow Transplantation
FACS	Fluorescence activated cell sorting
G-CSF	Granulocyte-stimulating factor
HIB	Haemophilus influenzae B
HRCT	High resolution computed tomography
i.v.	Intravenous
FVC	Forced Vital Capacity
Lc	Limited cutaneous
mRSS	Modified Rodnan Skin Score
MRI	Magnetic resonance imaging
p.o.	Per os
PBSCT	Peripheral blood stem cell transplantation
SSc	Systemic Sclerosis

Aim of the study

To assess the effectiveness of Autologous Hematopoietic Stem Cell transplantation (AHSCT) for early severe or rapidly progressive Systemic Sclerosis (SSc) as currently performed by different study protocols used across Europe in various EBMT centres through the careful recording and analysis of routinely collected clinical and biological data.

1. Rationale

Systemic Sclerosis is a heterogeneous disease, characterised by the excessive production and deposition of collagen in the skin, blood vessels and organs, with a limited (lc) and a diffuse cutaneous form (dc**)** [1.] Severe forms of SSc, especially the rapidly progressing diffuse cutaneous form with organ involvement appearing within the first 4 years of disease onset, are associated with significant mortality (approximately 40 – 50% 5-year survival rate) as a consequence of lung, heart and kidney involvement. [2-6]

The treatment of individual organ manifestations has been improved over the last few years with the introduction of new therapeutic substances. Treatment with endothelin receptor antagonists, phosphodiesterase inhibitors and intravenous or inhaled prostaglandins leads to a reduction in pulmonary arterial pressure with additional effects on the digital ulcers[7-12]. Proton pump inhibitors reduce reflux symptoms in patients with oesophageal motility disorders and ACE-inhibitors probably have a beneficial effect on renal involvement [13-14].

Although each type of immunosuppressive drugs has successively been tested for the treatment of scleroderma (Methotrexate [15-16], D-penicillamine [17], alpha-interferon [18], rituximab [19,20], mycophenolate [21-23.], imatinib [24-26], Cyclophosphamide [27-31]) none of them has proven any efficacy in prospective randomised trials. Therefater, metanalysis of randomized controlled trials and observational prospective cohort studies on cyclophosphamide effects on pulmonary function in SSC patients did not show any benefit from its use in this setting.

In this context, AHSCT for rapidly progressive SSc with internal organ involvement within the first 4 years of disease onset or for cyclophosphamide-refractory cases has recently emerged as the best proven effective therapy [32].

Indeed, several European [33-34] and North-American [35-37] open phase I-II studies using AHSCT for SSc showed rapid and durable fall in skin score [38], improved functional status, stable lung function and regression of fibrosis extent on skin histology [36,38] and on lung imaging [39]. Even normalisation of pathological capillary changes (nailfold capillary),[40-41] was shown. While gaining experience [42-43], Transplant-Related-Mortality (TRM) decreased to 3-5% [43], an acceptable risk regarding spontaneous disease evolution [2-6], Regular data registers on this activity have been published [34,42-43], while a center-effect related to centre activity was demonstrated [43-44]. Various treatment schemes for mobilisation and conditioning have been applied worldwide. Schemes with total body irradiation are avoided because of their high pulmonary toxicity [44]. The same applies for avoiding busulfan. In-vitro treatment of the stem cells before retransfusion (purging and/or CD34 selection) appears reasonable here to return as few autoaggressive T-cells as possible and to avoid early relapse of the autoimmune disease [45]. However, in-vitro manipulation is also associated with an increased susceptibility to infection.

Results of 3 adequate randomized trials conducted in the mean time with comparable eligibility criteria and control arms are emerging [46-48]. Two of them used either non myeloablative regimen (cyclophosphamide and rabbit ATG) with CD34+ selection for the European multicenter ASTIS (Autologous Stem Cell Transplantation International Scleroderma') trial, or without, for the American single center ASSIST trial in Chicago, and the third one the US multicenter SCOT trial used a TBI myeloablative regimen. Recruiting in these trials has been challenging, because SSc is a rare Autoimmune Disease (AD) (prevalence 7–50/Million) and AHSCT a well validated procedure, rather than a new drug to be tested. ASSIST[46], the first phase II study randomized trial comparing cyclophosphamide pulse therapy and AHSCT for SSc was stopped earlier due to the impressive short term clinical superiority (ASSIST) of AHSCT in 10 SSc patients, who showed rapid and significant regression of skin score, a strong predictor of outcome, and of volume of lung disease on CT scan plus improved functional status on SF 36, whereas 9 patients under cyclophosphamide (6 iv bolus monthly) progressed or failed to improve after one year. The ASSIST trial, originally designed to enroll 60 patients, allowed crossover for 8 controls who progressed, of whom 7 with no contraindication

could switch for AHSCT. All 17 AHSCT patients, without TRM, improved on the same parameters, with rather short follow-up: at least 2 years for 11 cases. Stopping rules for significant differences in outcome between the two arms, i.e. failure to achieve equipoise, allowed earlier trial termination and solved the dilemma of sustained randomization in ASSIST, the Chicago single center study. Initial results from the ASTIS phase III stem cell transplant trial recently presented at EULAR 2012, the Annual Congress of the European League Against Rheumatism 48, demonstrate that hematopoietic stem cell transplantation (HSCT) results in fewer deaths than IV cyclophosphamide in patients with poor prognosis early diffuse cutaneous systemic sclerosis.

In June 2012, about 1400 patients with autoimmune diseases treated by AHSCT have been reported to the EBMT data base, including 290 with SSc. In this context, use of AHSCT has become the best treatment option that can be proposed to patients with severe or rapidly progressive forms of SSc, as long as it will be performed after careful pretransplant evaluation of organ involvement 49, especially heart evaluation 50, respect of contra indications and performed in experienced centers.

Different protocols are used in the different centres, it is not yet clear which approach will be the most efficient and the safest 51. Every centre will follow its own local protocol for AHSCT which usually refers to the recent update of the EBMT Guidelines for HSCT in autoimmune disease 48. Patient selection for AHSCT treatment technique with regard to the risk/benefit balance has to be carefully addressed by standard patient pretransplant evaluation 52-53, whereas treatment local regimen, follow-ups evaluation, supportive medication and prophylaxis will be recorded and analysed.

2. Inclusion/ exclusion criteria

Inclusion criteria:
a. Autologous HSCT
b. Age between 18 and 65 years at time of transplant.
c. Established diagnosis of progressive SSc according to ARA-criteria

Exclusion criteria:
- Age <18 years at transplant
- Pregnancy or inadequate contraception
- Severe concomitant disease
  - Severe heart failure with Ejection Fraction < 40% by cardiac echo
  - Pulmonary arterial hypertension with systolic PAP > 50mm Hg
  - Kidney insufficiency: creatinine clearance <30ml/min
  - concurrent neoplasms or myelodysplasia
- Reduced lung function
  - FVC < 50% of normal
  - DLCO < 30%
- Previously damaged bone marrow
  - Leukopenia < 2,000/mmm3
  - Thrombopenia < 100,000/ mmm3
- Uncontrolled severe infection (Hepatitis B/C, HIV, Salmonella carrier, syphilis, tuberculosis)
- Severe concomitant psychiatric illness (depression, psychosis)

4. Study endpoints

4.1. Primary end point:
Progression free survival (PFS), defined as survival since Baseline (the 1st day of mobilisation) without evidence of progression of SSc.

Progression is defined as any of the following changes from baseline:

- Death from SSc
- $\geq$ 10% drop in FVC and/or $\geq$ 15% drop in DLCO (of predicted values),
- $\geq$ 15% drop in LVEF by echo or MUGA,
- $\geq$ 15% drop in body weight,
- $\geq$ 30% drop in creatinine clearance,
- $\geq$ 25% increase in modified Rodnan skin score (mRSS)
- $\geq$ 0.5 increase in SHAQ.

4.2. Secondary end points:
- **Safety**

Treatment related toxicity throughout the study period using WHO toxicity parameters (expressed as maximum grade toxicity per organ system, see appendix)
Incidence of Adverse Events (AE) and Serious Adverse Events (SE)
Neutrophil and platelet engraftment, defined as first day after transplantation with absolute
neutrophil count > 500 cells/µL and >20.000 platelets/µL without platelet transfusion, respectively

- **Overall Survival**

- **Response to treatment**

Response to treatment within 1 year following autologous HSCT, defined as
- 25% improvement in mRSS and/or
- ≥10% improvement in DLCO or FVC

as compared to baseline without need of further immunosuppression

- **Improvement in Quality of life** assessed by SHAQ evolution (Scleroderma Health Assessment Questionnaire)

- **Relapse incidence (RI)** is defined as any of the following changes after prior response to treatment on quarterly follow up as defined above:
  - Worsening of mRSS > 25%
  - New/Worsening of organ manifestation
  - Lungs: Decrease in lung function tests with drop of $\geq$ 10% in FVC and/or $\geq$ 15% drop in DLCO (of predicted values) *and/or* increase of interstitial lung disease (HR-CT scan and/or bronchoalveolar lavage and/or biopsy of the lungs) with clinically relevant obstructive disease and emphysem excluded necessitating the reintroduction of immunosuppression.
  - Heart: congestive heart failure, atrial or ventricular rhythm disturbances such as recurrent episodes of atrial fibrillation or flutter, recurrent atrial paroxysmal tachycardia or ventricular tachycardia, 2nd or 3rd degree AVblock, pericardial effusion; non-scleroderma related causes must have been reasonably excluded by an experienced cardiologist
  - Kidney: urinalysis abnormalities (proteinuria, hematuria, casts), new/worsening of renal insufficiency (serum creatinine > upper limit of normal/rise >25%); non-scleroderma related causes (e.g. medication, infection etc.) must be reasonably excluded reintroduction of immunosuppression for any of the above

- **100-day Treatment related mortality (TRM)** defined as any death during 100 day following transplant that cannot be attributed to progression or relapse of the disease.

5. Statistical method

Fifty (50) patients are expected to be included within 36 months recruitment period.
The probabilities Progression -Free survival (PFS) is the primary study end-point. Safety, Overall Survival (OS), Response Rate (RR), Relapse Incidence (RI) and Treatment-Related Mortality (TRM) are the secondary endpoints. The PFS is defined as time interval from mobilisation to eitherrelapse, progression or death, and will be calculated using the Kaplan-Meier estimate. Engraftment, RR and RI will be calculated using cumulative incidence curves in a competing risks setting, death being treated as a competing event. RI will be calculated only for responder patients from the date of response. For studying possible impact of prognostic factors (mRRS, CVF, DLCO, age, geographic origin, sex, smoking status, proteinuria,creatine clearance) on PFS, univariate analyses will be done with the use of log-rank test for OS and PFS while Gray's test will be applied for RI and TRM. Multivariate analyses will be performed using Cox proportional hazards model.
Statistical analyses will be performed with SPSS 19 (Inc., Chicago) and R (R Development Core Team, Vienna, Austria) software packages.

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