Improving Treatment Related Mortality over Time
Data from the Non-Interventional Trial on Autologous Stem Cell Transplantation in Systemic Sclerosis by the EBMT Autoimmune Diseases Working Party (ADWP)

European Society for Blood and Marrow Transplantation

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Background: Systemic sclerosis (SSc) is a rare heterogeneous autoimmune connective tissue disease with a high disease related mortality. Three randomized controlled trials (ASSIST, ASTIS, SCOT) that included 125 transplanted SSC patients overall, demonstrated that autologous hematopoietic stem cell transplantation (aHSCT) is superior to standard iv monthly bolus of cyclophosphamide. Since the 2012 EBMT guidelines (1), aHSCT has become the standard of care with a grade 1 level of evidence for selected patients (2) with severe progressive SSc (2).

The aim of this observational study was to describe the results of aHSCT for SSc in daily life and to identify risk factors for adverse events to make this approach safer.

Study design and patients: This prospective, open, multi-center, non-interventional study (NIS) analyzed routinely collected clinical data for all consecutive aHSCT performed in SSc patients.

Major organ exclusion criteria: severe heart failure with a LVEF<40% or pulmonary arterial hypertension with sPAP> 50 mmHg; reduced lung function with either FVC <50% or DLCO <30% of predicted values; kidney insufficiency with creatinine clearance <30ml/min; concurrent neoplasms or previously damaged bone marrow (leukopenia < 2 x 10^9/l ; thrombopenia < 100 x 10^9/l µl); severe concomitant psychiatric illnesses or uncontrolled severe infections.

Baseline characteristics were collected, including LVEF and sPAP as measured by echocardiography (ECHO), cardiac magnetic resonance imaging (MRI), right heart catheterization, standard and 24h Holter-electrocardiograph (ECG), lung function tests including FVC and DLCO in % of predicted values, high resolution computed tomography (HRCT) of the lung, and kidney function tests. All centers were asked to report the treatment regimen and days of hospitalization, the time to hematologic reconstitution and infectious and non-infectious complications during the first 100 days (D) after aHSCT.

Primary endpoint was ***progression free survival (PFS),*** defined as survival since baseline (1st day of mobilization) without death or evidence of SSc progression.

***SSc progression* = any of the following changes from baseline: death from SSc, >10% drop in FVC and/or >15% drop in DLCO, >15% drop in LVEF** by echo, >15% drop in body weight, >30% drop in creatinine clearance, >25% increase in mRSS.

***Response to treatment* =** number of patients achieving >25% improvement In mRSS and/or ≥10% improvement in FVC or DLCO as compared to baseline.

Results:

From 12/2012 to 02/2016, 80 consecutive pts underwent first aHSCT for severe SSc with a median time to neutrophil engraftment 11 (8-24) days and 9 (1-25) days to platelet recovery.

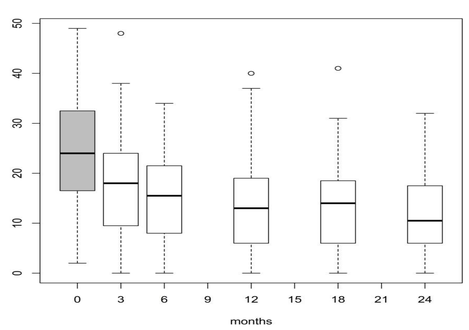
***PFS was 88.6% at 1 year and 67.4% at 2 years*. Response to treatment was 88.7% at year 2. Cumulative incidence of relapse/progression at 1 and 2 years was 10.1% and 26.3%.**

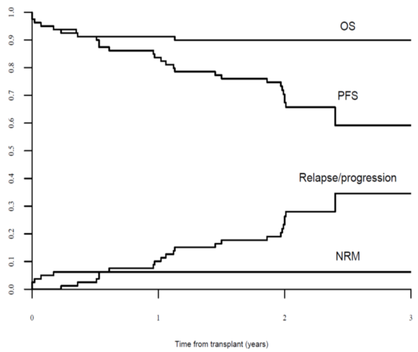
***Median mRSS decreased from 24.9 at baseline to 13.8 at month 12 and 12.4 at month 24. (p<0.001). Median FVC increased from 72.5% at baseline to 81.0% at month 12 and 85.5% at month 24 and the median DLCO remained stable* with 59.0% of predicted value at baseline, 57.6% at month 12 and 60% at month 24.**

By multivariate analysis, only CD34+-selection was associated with a better response to aHSCT (HR: 2.2; 95%CI: 1.3-3.7; p=0.003). The 100 days TRM was 6.25 % (n = 5 deaths): 4/5 from cardiac related event with 3 considered CYC related by the treating physician. During the 24 months of follow-up, 3 other patients died due to progressive disease, leading to an OS of 91.2% at 2 years.

Baseline characteristics of study patients (n=80)	
Age (years), median (range)	43 (20 - 62)
Sex (Female), n (%)	56 (70%)
Disease duration from diagnosis (months), median (range)	23.8 (5.3 - 103.7)
Modified Rodnan Skin score (mRSS), median (range)	24 (2 - 49)
Abnormal thoracic computed tomography (HCTR) N/available (%)	66/77 (85.7%)
FVC, % of predicted value	72 (43 – 132)
DLCO, % of predicted value	59 (34.3 – 120)
Abnormal 24h Holter ECG; N/available (%)	12/60 (20%)
Pericardial effusion (echo); N/available (%)	5/79 (6.3)
LVEF by cardiac echo (%)	65 (47 - 84)
PASP by cardiac echo (mm Hg)	29 (8 - 59)
Anti-nuclear antibody positive	74 (92.7)
Anti-Topoisomerase I (Scl70) positive	57 (71.3)
Anti-centromere positive	3 (4.2)

Treatment		N (%)
Mobilization		
	CYC 2 g/m²	45 (57.7)
	CYC 4 g/m²	23 (29.5)
	Other dose	10 (12.8)
	G-CSF, yes	78 (97.5)
CD34-selection		
	Yes	35 (43.8)
	None	45 (56.3)
Conditioning regimen		
	CYC 200 mg/kg	72 (90.0)
	CYC other dose mg/kg	4 (5.0)
	CYC 100mg/kg + Thiotepa 10mg/kg	4 (5.0)
ATG	Yes	80 (100)
TBI	No	80 (100)
GCSF administration after conditioning		34 (43.0)





Kaplan Mayer curves for :
Overall Survival (OS),
Progression Free Survival (PFS)
number of relapses/progression,
Non-relapse Related Mortality (NRM)

Conclusion : This NIS is the largest muticenter prospective study so far confirming the efficacy of aHCST in SSc : 80 severe patients achieved sustained skin fibrosis regression (↘ mRodnan skin score) and improvement (↗ FVC) or stabilization (DLCO) of lung function until 2 years after transplant. CD34+ selection was associated with better response to aHSCT, while previous retrospective EBMT study had found no difference (3). The 6.25% TRM observed in NIS has decreased compared to 10.1% TRM previously reported in the 75 patients treated by aHSCT in ASTIS trial (4), partly related to improved patient selection (2).

*1) **Snowden** JA et al BMT 2012 ; 2) **Farge D and Burt R et al , BMT 2017; 3) Oliveira MC et al BMT 2016; 4) Van Laar J and Farge D JAMA 2014***