Outcomes of conventionally-treated systemic sclerosis patients eligible for autologous haematopoietic stem cell transplantation

S.T. Panopoulos, M.G. Tektonidou, V.-K. Bournia, K. Laskari, P.P. Sfikakis

Joint Rheumatology Program, First Department of Propaedeutic and Internal Medicine, Medical School, National and Kapodistrian University of Athens, Greece.

Stylianos T. Panopoulos, MD, PhD
Maria G. Tektonidou, MD, PhD
Vasiliki-Kalliopi Bournia, MD, PhD
Katerina Laskari, MD, PhD
Petros P. Sfikakis, MD, PhD

Please address correspondence to:
Stylianos Panopoulos,
First Propaedeutic and Internal Medicine Department,
LAIKO'Hospital,
Medical School, National and Kapodistrian University of Athens,
17 Agiou Thoma Street,
Goudi 11527 Greece.
E-mail: sty.panopoulos@gmail.com

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ABSTRACT

Objective. *Autologous haematopoietic stem cell transplantation (HSCT) has exhibited superior efficacy compared to conventional immunosuppressives in rapidly progressive diffuse systemic sclerosis (SSc) patients, albeit still of limited availability. We examined disease outcomes of conventionally-treated real-world inception patients eligible for HSCT, according to HSCT criteria used in the ASTIS and SCOT randomised trials, and compared them to the outcomes of participants in these trials.*

Methods. *Overall and event-free survival rates in our inception cohort were analysed at 4.5 and 7 years after HSCT criteria fulfilment and compared to those reported in HSCT and control arms of ASTIS and SCOT.*

Results. *Forty-five of our 142 inception cohort patients fulfilled HSCT criteria within 4 years from disease onset and had comparable baseline characteristics to SCOT/ASTIS patients. Four patients underwent HSCT. The remaining 41 were treated with conventional DMARDs: cyclophosphamide (n=24), mycophenolate mofetil (n=17), rituximab (n=2), tocilizumab (n=3), methotrexate (n=6) or combinations and their 10-year survival was 56% vs. 76% in those with diffuse SSc not fulfilling HSCT criteria. Their survival rates at the time endpoints of SCOT and ASTIS (4.5 and 7 years, respectively) were comparable to the conventionally-treated SCOT/ASTIS control groups. Extrapolating from SCOT/ASTIS results, if all our patients had undergone HSCT promptly, their overall and event-free survival rates could have increased from 73/51% to 83/72% at 4.5 years, and from 63/39% to 76/72% at 7 years, respectively.*

Conclusion. *Wider availability and physician's early acknowledgement and referral of eligible patients for HSCT could significantly improve disease outcomes of rapidly progressive diffuse SSc patients.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disorder characterised by a wide spectrum of clinical phenotypes. Patients with rapidly progressive diffuse SSc have the highest morbidity and mortality rates (1). Three randomised clinical trials (RCTs) (2-4) have shown efficacy of autologous haematopoietic stem cell transplantation (HSCT) in SSc. In particular, ASTIS (3) and SCOT (4), two multicentre phase III RCTs, which compared HSCT to conventional therapy with intravenous cyclophosphamide (CYC), presented the most compelling evidence, demonstrating the superiority of HSCT regarding overall survival and prevention of major organ failure.

In this retrospective study, we aimed to: 1) identify the eligibility rate for HSCT in a real-world inception SSc cohort applying the HSCT criteria defined in ASTIS and SCOT; and 2) examine outcomes of conventionally treated patients eligible for HSCT, comparing our findings to those reported in ASTIS and SCOT.

Materials and methods

The data from all adult SSc patients included in our inception cohort between January 2000 and December 2012 and followed regularly (every 3–4 months) or died until April 2020, were retrospectively analysed. We identified patients eligible for HSCT according to the ASTIS and SCOT eligibility criteria: age between 18 and 65 years old; diffuse SSc (dcSSc); disease duration ≤4 years; modified Rodnan skin score (mRSS) ≥15; involvement of heart, lung, or kidney; no severe major organ involvement (ejection fracture <50% or forced vital capacity <45% or diffuse capacity for CO <40% of predicted or creatinine clearance <40 ml/min); prior treatment with cyclophosphamide ≤5 g intravenously or up to 2 mg/kg body weight orally for 3 months.

The timepoint of HSCT criteria fulfilment was defined in our cohort as "baseline". Follow-up data at 4.5 and 7 years from baseline were collected for these patients. Outcomes of interest included death and major organ failure (lungs, heart, kidney), as defined in ASTIS (3) and SCOT (4). Overall survival from disease onset was compared between conventionally treated eligible and non-eligible patients for HSCT in our cohort. Additionally, baseline clinical data and outcomes of conventionally treated, eligible for HSCT patients in our cohort were compared to the respective data of participants in ASTIS and SCOT. The study protocol was approved by the local ethics committee.

Survival curves were estimated by Kaplan-Meier analysis. Categorical and continuous data were compared using chi-square test and student t-test, respectively. A p-value <0.05 was considered statistically significant. All analyses were computed using SPSS version 24.0.

Results

Patients fulfilling HSCT eligibility criteria

In total, 45 patients out of 142 comprising our entire inception cohort, fulfilled HSCT criteria. Notably, no patient was non-eligible for HSCT due to severe major organ involvement, while 2 patients did not fulfill age criteria (>65 years old). Among these 45 patients, 4 (3 female, 4 dcSSc) underwent HSCT while 41 patients were conventionally treated (Table I). Regarding transplanted patients, mean age and mean disease duration at transplantation were 47.2±8.0 years and 28±14.0 months respectively, mean mRSS was 23±4.7, 4 had pulmonary fibrosis, none heart or renal involvement and after a mean follow-up of 42.5±24.9 months, no death or major organ failure has been recorded. Demographic and clinical characteristics of 41 patients eligible for HSCT who were conventionally treated are shown in Table I.

Comparison of survival between patients fulfilling or not HSCT criteria

Conventionally treated patients eligible for HSCT in our cohort had significantly lower 5- and 10-year survival compared to non-eligible patients with diffuse (n=21) or limited (n=76) subtype (73% *vs*. 90% or 93% and 56% *vs*. 76% or 85% respectively, both p<0.001) (Table I and Fig. 1). Importantly, in the subgroup of patients eligible for HSCT smoking history was found to be associated with increased mortality [(OR: 4.2, (95% CI 1.09-18.4), p=0.038)].

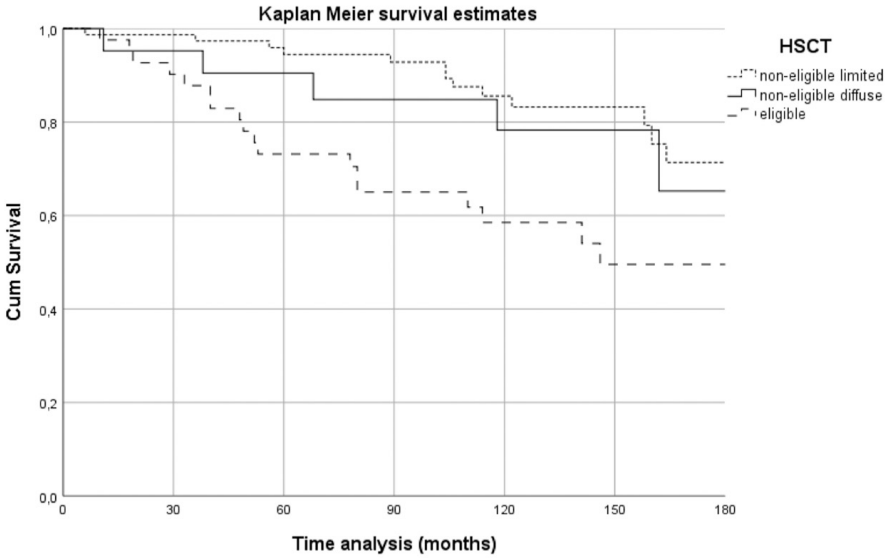
Comparison of disease outcomes between patients eligible for HSCT and participants of SCOT and ASTIS

Baseline demographics and clinical characteristics of patients eligible for HSCT in our cohort were comparable to the ASTIS and SCOT control groups (Table II). Disease outcomes of conventionally treated patients eligible for HSCT after 4.5 and 7 years of follow-up were also comparable to those in the control arms of the aforementioned trials. More specifically, overall survival in our group was 73% after 4.5 years and 63% after 7 years, consistent to that reported for control patients in SCOT (72% after 4.5 years) and in ASTIS (70% after 7 years). Furthermore, event-free survival in our cohort was comparable to the SCOT (51% *vs*. 49% after 4.5 years) but lower compared to the ASTIS control group (39% *vs*. 60% after 7 years).

Table I. Demographics, clinical characteristics and outcome of inception SSc patients fulfilling or not criteria for HSCT.

	Patients eligible for HSCT (all diffuse SSc)	Patients non-eligible for HSCT	
		Diffuse SSc	Limited SSc
n.	41	21	76
Sex (female)	34 (83)	17 (81)	65 (86)
Age at diagnosis (years)	46.4 ± 12.5	47.9 ± 16	50.3 ± 14
Anti topoisomerase positivity	34 (83)$^{\#}$	15 (71)	37 (49)
Smoking status			
current	4 (10)	4 (19)	9 (12)
former	9 (21)	6 (28)	15 (20)
never	28 (69)	11 (53)	52 (68)
Pulmonary fibrosis	40 (96)$^{*/\#}$	13 (62)	33 (43)
Congestive heart failure	1 (2)	2 (10)	0
Pulmonary hypertension	9 (22)$^{\#}$	4 (19)	9 (12)
Renal crisis	3 (7)*	2 (10)	0
Digital ulcers	24 (58)	13 (62)	33 (43)
Mean mRSS$^{\times}$	23.2 ± 6.9$^{*/\#}$	14.3 ± 5.8	6.1 ± 2.2
Mean FVC$^{\times}$ (% of predicted)	77.2 ± 13.2$^{*/\#}$	90 ± 18.2	94.3 ± 14.6
Mean DLCO$^{\times}$ (% of predicted)	57 ± 9.6$^{*/\#}$	68.7 ± 15.9	76.9 ± 18.6
Immunosuppressive treatments administered n (%) / mean duration of treatment (months)			
CYC	18 (44) / 23 ± 16	3 (14) / 36 ± 21	5 (7) / 29 ± 18
CYC/MMF	6 (15) / 56 ± 8	1 (5) / 24 ± 0	2 (3) / 29 ± 2
CYC/MTX	0	1 (5) / 84 ± 0	3 (4) / 39 ± 9
MMF	9 (22) / 54 ± 30	4 (20) / 32 ± 20	2 (3) / 14 ± 4
MMF/MTX	0	1 (5)	3 (4) / 86 ± 40
RTX/CYC	0	1 (5) / 30 ± 0	1 (1) / 54 ± 0
RTX/MMF	2 (5) / 36 ± 0	0	1 (1) / 48 ± 0
MTX/ TCZ	3 (5) / 40 ± 18	0	3 (4) / 68 ± 28
MTX	3 (7) / 63 ± 6	6 (28) / 74 ± 18	30 (40) / 58 ± 32
Multiple treatments	0	1 (5) / 42 ± 0	1 (1) / 48 ± 0
No treatment	0	2 (10)	25 (32)
Deaths	20 (49)	6 (29)	13 (17)
5-year survival	30/41 (73)$^{*/\#}$	19/21 (90)	71/76 (93)
10-year survival	20/36 (56)$^{*/\#}$	13/17 (76)	46/54 (85)

Data shown as number (percentage) or as mean ± 1 standard deviation.
$^{*}p$<0.05 for comparison between eligible and non-eligible diffuse; $^{\#}p$<0.05 for comparison between eligible and non-eligible limited; $^{\times}$within the 1st year from disease onset.
SSc: systemic sclerosis; HSCT: autologous haematopoietic stem cell transplantation; FVC: forced vital capacity; DLCO: diffuse lung capacity for CO; mRSS: modified Rodnan skin score; CYC: cyclophosphamide; MMF: mycophenolate mofetil; RTX: rituximab; MTX: methotrexate; TCZ: tocilizumab.



no. at risk							
Eligible	41	37	30	24	20	11	6
Non-eligible diffuse	21	20	19	15	13	9	4
Non-eligible limited	76	75	71	56	46	23	15

Fig. 1. Kaplan-Meier survival analysis of 41 conventionally treated SSc patients, eligible (fulfilling criteria) for autologous haematopoietic stem cell transplantation (HSCT), compared to 97 patients (21 diffuse, 76 limited) non-eligible for HSCT. Five- and 10-year survival were 73% and 56% in the HSCT eligible group *vs*. 90% and 76% in non-eligible patients with diffuse disease, and *vs*. 93% and 85% in non-eligible patients with limited disease ($p<0.001$ for both comparisons).

Based on the comparable baseline characteristics of our patients to the ASTIS and SCOT patient populations, we applied the results of the transplanted groups in these trials to our group. Therefore, based on the overall- and event-free survival of the transplanted groups in SCOT (83% and 72%, respectively) and ASTIS (76% and 72%, respectively), we may assume that if all patients eligible for HSCT in our cohort, who were conventionally treated, had undergone HSCT at baseline, overall survival in these patients could have increased from 73% to 83% after 4.5 years and from 63% to 76% after 7 years from baseline, respectively. Accordingly, event-free survival could have increased from 51% and 39% to approximately 72% after 4.5 and 7 years of follow-up. Thus, survival rates could have significantly increased in these specific patients, if HSCT had been chosen over conventional immunosuppressives.

Discussion

In the present study, patients with rapidly progressive disease fulfilling HSCT criteria comprised 65% of the dcSSc subgroup and 30% of our entire inception cohort. Notably, this specific patient subgroup in our cohort had a 5-year and a 10-year survival of 73% and 56% respectively, remarkably lower compared to the respected 90% and 76% survival of our patients non-eligible for HSCT with dcSSc, consistently to findings from the SCOT and ASTIS control groups, reflecting the frequently poor response of these patients to aggressive immunosuppressive regimens. Importantly, implementation of ASCT, as shown in 3 RCTs and in a recent multicentre study of 92 transplanted SSc patients (5), may significantly improve outcomes in this exact patient subgroup.

Only 4 patients in our cohort have undergone HSCT, 2 in 2015 and 2 in 2018, being alive to date without major organ failure, however the sample size is very small to allow conclusions. Globally, the overall number of HSCT performed in SSc from 1995 to August 2018, was 534 (40% of which during the last 7 years), according to the European group of Bone Marrow Transplantation (6). These numbers indicate that as mentioned previously, although during the first years from disease onset a significant proportion of patients will fulfil HSCT criteria, only very few, will be referred for HSCT in real-world settings. This steadily increasing, but still rather low number of performed HSCT, possibly reflects the limited awareness alongside the hesitance of physicians to select HSCT over conventional regimens despite the inclusion of HSCT in the 2016 EUSTAR treatment recommendations (7) for selected patients with rapidly progressive SSc at risk of organ failure, or it could also indicate a limited access to specialised HSCT centres.

Certainly, HSCT is not a panacea for patients with rapidly progressive SSc considering the transplant-related mortality risk estimated between 3% and 10% (3-5, 8, 9) or the possibility of post-transplantation disease relapse (4, 5), both related to procedural issues still remaining contentious among HSCT experts like the optimal mobilising and conditioning regimen (10), the selection or not of $CD34^+$ graft (8, 11) or the lack of unanimous HSCT eligibility criteria. Moreover, cumulative evidence has elucidated the negative effect of specific factors on HSCT efficacy like the presence of pre-existing cardiac disease indicating the necessity for a thorough pre-transplant cardiac screening in all candidates as suggested in a recent systematic review (12) or the impact of smoking. The latter was associated to poor post-transplantation outcomes in ASTIS and in our study was correlated with increased mortality in patients eligible for HSCT. Altogether, existing data indicate that HSCT is currently the only true disease-modifying treatment that has the potential to alter the natural course of the disease in patients with rapidly evolving disease, compared to all available conventional immunosuppressives. It is therefore very important to promptly identify, based on validated prediction models (13, 14), patients at high risk of organ failure who fulfil HSCT criteria and refer them to a specialised bone marrow transplantation facility in a timely manner.

Table II. Baseline demographic and clinical characteristics and disease outcomes of a real-world systemic sclerosis inception patient cohort eligible for HSCT and of the SCOT and ASTIS control groups.

	Patients eligible for HSCT	SCOT control group	ASTIS control group
n.	41	39	77
Mean age (years)	47.7 ± 12.5	46.9 ± 10.4	43.3 ± 11.5
Female sex	34 (83)	29 (74)	49 (64)
Race (white)	41 (100)	31 (79)	62 (80)
Mean duration of scleroderma at baseline (months)	23 ± 12.7	29 ± 16.0	20 ± 15.6
Smoking status			
current or former	13 (31)	10 (26)	43 (56)
never	28 (69)	29 (74)	34 (44)
DMARDS use in previous 6 months	28 (68)	25 (64)	-
Previous use of cyclophosphamide ≤3 months*	5 (12)	17 (44)	17 (22)
Mean modified Rodnan skin score	24.5 ± 7.2	30.8 ± 10.5	25.8 ± 7.9
Pulmonary fibrosis	40 (96)	37 (95)	59 (87)
Mean FVC (% of predicted value)	77.2% ± 13.2	73.8% ± 17.0	81.1% ± 17.6
Mean DLCO (% of predicted value)	57% ± 9.6	52.7% ± 8.2	57.7% ± 14
Renal crisis	3 (7.3)	-	2 (2.6)
Mean left ejection fracture (%) by cardiac echocardiography	59.7 ± 4.5	59.9 ± 4.3	65.7 ± 7.8
Mean creatinine clearance (mL/min)	88.6 ± 35.4	124.9 ± 54.3	76.5 ± 26.0
Mean ESR (mm/1st hour)	34 ± 20.3	32.2 ± 24.9	-
Antitopoisomerase antibody positive	34 (83)	-	62 (81)
Disease outcomes			
Follow-up time points (years)	4.5/7	4.5	7
Death or respiratory, renal or cardiac failure	20 (49) / 25 (61)	20 (51)	31 (40)
Death from any cause	11 (27)/15 (37)	11 (28)	23 (30)
Major organ failure	11 (27)/13 (32)	14 (36)	8 (10)
Respiratory failure#	10/12	13	3
Renal failure/dialysis	0/0	0	3
Heart failure (EF<30%)	1/1	1	2
Pulmonary hypertension	8 (20)/9 (22)	5 (13)	-

Data shown as number (percentage) or as mean ± 1 standard deviation.
*before fulfillment of HSCT criteria; #according to the criteria defined in the SCOT and ASTIS trials. HSCT: autologous haematopoietic stem cell transplantation; DMARDS: disease-modifying anti-rheumatic drugs; FVC: forced vital capacity; DLCO: diffusing lung capacity for CO; ESR: erythrocyte sedimentation rate; EF: ejection fracture.

The main strength of our study is that it derives from a real-world inception cohort of SSc patients followed-up in a dedicated academic centre, possibly reflecting the general SSc population. The fact that 60% of our patients were administered CYC *versus* 100% in ASTIS and SCOT may limit the direct comparison of disease outcomes. However, the second most commonly used DMARD in our patients was MMF, previously recognised as equally efficient to CYC in SSc RCTs (15). A limitation of our study is the extrapolation of the results of transplanted patients in ASTIS and SCOT to our cohort. However, a) since patients included herein are inception cohort patients with regular follow-up and all their baseline characteristics were almost identical to those of ASTIS and SCOT participants, b) given the very limited evidence on the outcomes of patients eligible for HSCT from the existing literature, we believe that our results may add helpful information for clinicians affronting the challenges of treating patients with rapidly progressive SSc.

To conclude, SSc patients eligible for HSCT, with disproportionately high mortality and major organ failure rates, can represent up to 65% of the diffuse subset and 30% of the entire SSc population. Although HSCT has been associated to favourable outcomes for these patients, so far, only a few actually undergo such a procedure, denoting that physicians should seriously consider promptly providing this treatment option to selected SSc patients, upon fulfilment of the eligibility criteria for HSCT.

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