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REVIEW

Life after Autologous Hematopoietic Stem Cell Transplantation for Systemic Sclerosis

Daniela A Moraes[1]
Maria Carolina Oliveira[2]

[1]Division of Clinical Immunology, Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil; [2]Center for Cell-Based Therapy, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

Abstract: Stem cell transplantation has been investigated as treatment for severe and progressive systemic sclerosis (SSc) for the past 25 years. To date, more than 1000 SSc patients have been transplanted worldwide. Overall and event-free survival have increased over the years, reflecting stricter patient selection criteria and better clinical management strategies. This review addresses long-term outcomes of transplanted SSc patients, considering phase I/II and randomized clinical trials, as well as observational studies and those assessing specific aspects of the disease. Clinical outcomes are discussed comparatively between studies, highlighting advances, drawbacks and controversies in the field. Areas for future development are also discussed.

Keywords: systemic sclerosis, stem cell transplantation, long-term outcomes, progression-free survival

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by tissue fibrosis, pronounced alterations in the microvasculature and frequent abnormalities in cellular and humoral immunity.[1] Combined pathogenic mechanisms of inflammation, fibrosis and microvascular damage affect the skin and internal organs, including the lungs, heart, gastrointestinal tract and kidneys.[2] Conventional treatment includes systemic immunosuppression, vasodilators and more recently, antifibrotic therapy.[3] However, a subset of patients with severe and progressive disease is refractory to these approaches. A meta-analysis from 2012 showed that despite newly available medications, more standardized treatment protocols and strategies to enable early diagnosis, mortality in SSc had not decreased in 40 years.[4] In fact, none of the available conventional treatments reverse the natural course of the disease or demonstrate prolonged benefit.[5] Currently, interstitial lung disease, pulmonary hypertension and cardiac involvement are the major causes of death in patients with SSc.[2,6] Patients with rapidly progressive cutaneous involvement and visceral involvement have poor prognosis, with mortality rates reaching 30% after 5 years of diagnosis, despite conventional treatment.[7,8]

In the mid-1990s, given the lack of effective therapeutic options for refractory autoimmune diseases, and after reports of patients who underwent stem cell transplantation for hematological indications but that presented improvement of coincidental autoimmune conditions, autologous hematopoietic stem cell transplantation (AHSCT) was considered as treatment for patients with severe SSc.[9,10] Since then, several studies with series of patients and phase I/II clinical trials have shown the

Correspondence: Maria Carolina Oliveira
Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo, Avenida dos Bandeirantes, 3900, Ribeirão Preto, SP, 14048-900, Brazil
Email mcarolor@usp.br

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efficacy of AHSCT in SSc.[11–15] More recently, randomized controlled trials have demonstrated the superiority of transplantation over conventional treatment.[16–18]

Experience with AHSCT for SSc has increased over time, and protocols have been refined, in special regarding patient selection. Consensus meetings and discussions within medical specialty societies also established recommendations and guidelines to improve patient outcomes.[9,19–21] Today, almost 25 years after the first transplant, SSc is the most frequently transplanted rheumatic disease in the world. Toxicity associated with the procedure has decreased and long-term disease control has improved. As a consequence, transplanted SSc patients have lived longer lives and it is possible to collect data from long-term follow-up. In this study, we revisit the literature, with special emphasis on the last 10 years, discussing short and long-term clinical outcomes of patients with SSc undergoing AHSCT.

We searched the literature in PubMed and Science Direct databases, within a defined period from 1995 to 2021, using words "stem cell transplantation" and "systemic sclerosis". Only studies in English were included. The articles were initially evaluated by title and abstract and, if necessary, in more detail. Among the available articles, only those with clinical data on autologous hematopoietic stem cell transplantation were selected. Research articles were preferred over case reports, review articles, commentaries, and editorials. Studies were excluded if included less than 5 patients, addressed conditions different than systemic sclerosis or included only pediatric patients. We mostly selected articles from the past 10 years, although older important publications have been referenced. Within the selected articles, the following data were extracted: transplant-related mortality, overall survival, progression-free survival, relapse or progression of SSc, disease progression, changes in modified Rodnan Skin Score (mRSS), changes in lung function, quality of life, fertility and long-term complications such as malignancies and secondary autoimmune diseases.

Transplant Procedure

Autologous stem cell transplantation is a form of intensive immunotherapy that aims to eradicate the autoreactive adaptive immune system. Autologous stem cells are harvested and cryopreserved before beginning of the procedure. These cells, thawed and reinfused intravenously to the patient after administration of an immunoablative conditioning regimen, provide accelerated hematopoietic reconstitution and enables reinstatement of a renewed immune system, with long-lasting tolerance to autoantigens (Figure 1). Autologous hematopoietic stem cell transplantation deeply modifies the immune system, promoting an immunological balance that halts inflammation and tissue destruction, enabling disease control, and, to some degree, tissue repair.[22]

Most transplant centers use a non-myeloablative conditioning regimen consisting of high doses of cyclophosphamide plus anti-thymocyte globulin. Higher intensity regimens including total body irradiation or thiotepa have been preferred by a few centers.[14,18,23,24] Different regimens have been compared and discussed for their advantages and drawbacks, mainly addressing aspects related to safety and efficacy, but so far, there are no specific recommendations.[25] There is also considerable debate about the benefits of graft selection, as numerous transplant centers manipulate the harvested autologous hematopoietic stem cells before cryopreservation, positively selecting the graft for CD34+ cells. Graft selection eliminates most mature lymphocytes and may reduce the risks of reinfusing autoreactive cells within the graft. On the

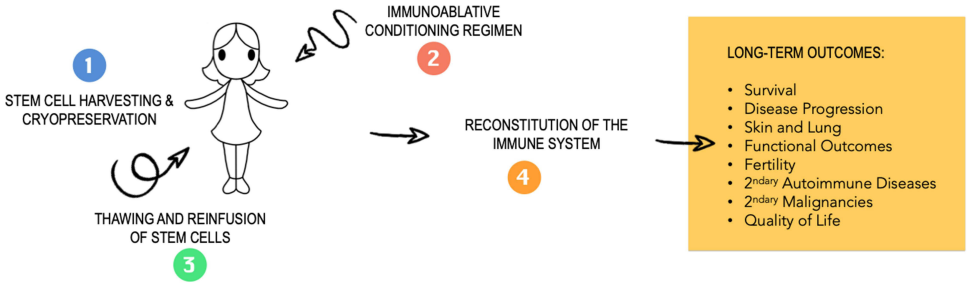

Figure 1 Schematic representation of the transplant procedure. Autologous stem cells are mobilized from the bone marrow to the peripheral blood, from where they are harvested by leukapheresis and cryopreserved (1). The graft can be selected before cryopreservation or remain unmanipulated. The patient then undergoes an immunoablative conditioning regimen (2), followed by intravenous administration of the autologous cells, which are thawed immediately before infusion (3). After a period of aplasia, there is reconstitution of the immune system (4), and the patient is discharged from the hospital. Long-term outcomes are evaluated over time.

other hand, it delays immunological recovery and may increase the incidence of viral infections after AHSCT.[26,27] Attempts to compare clinical outcomes from patients transplanted with or without graft selection have conflicting results, and further prospective investigations are needed.[28–30]

Overall Survival and Toxicity

Since the initial reports from the end of the last century, numerous phase I/II studies have shown feasibility and beneficial outcomes of AHSCT (Table 1).[11–15] In the last decade, three randomized controlled studies – ASSIST (Autologous Systemic Sclerosis Immune Suppression Trial, 2011), ASTIS (Autologous Stem Cell Transplantation versus Immunosuppression trial, 2014) and SCOT (Scleroderma: Cyclophosphamide or Transplantation trial, 2018) – have shown that AHSCT is superior in efficacy and safety than monthly intravenous cyclophosphamide (CY) pulses (Table 2).[16–18] A fourth study retrospectively compared the results of AHSCT with those of a historical cohort of SSc patients who shared similar clinical characteristics.[38] This was a single-center study, and updated knowledge on patient selection and intra-transplant management translated into lower transplant-related mortality and higher overall survival. Table 2 describes the main characteristics and patient outcomes from each trial.

ASSIST was a groundbreaking study in 2011, and the first to show benefits of transplantation over conventional therapy, despite the small number of enrolled patients and short follow-up of only 2 years.[16] According to the authors, study enrollment was stopped earlier than originally planned. An interim analysis showed failure of equipoise, since there was significant difference in outcomes between groups after inclusion of only 19 patients, favoring transplant. ASTIS, published in 2014, was a multicenter European trial that had a higher transplant-related mortality and lower overall survival than the other two studies.[17] The higher transplant-related toxicity of ASTIS was ascribed to the lack of a thorough evaluation of patients for cardiac involvement before transplantation.[39] The importance of cardiac screening only became fully known and incorporated into practice around 2010, at the end of patient recruitment in ASTIS.[32,40] As a result, it is possible that patients with severe cardiac involvement were enrolled for transplantation, increasing the death rate. Nevertheless, after 1 year of follow-up, in accordance with the other comparative trials, ASTIS showed superiority of transplantation over conventional cyclophosphamide treatment.

The SCOT trial used a myeloablative and thus high-intensity conditioning regimen, including total body irradiation.[18] Although the described transplant-related mortality was acceptable in this trial, and lower than that of ASTIS, the 85% incidence of major (grade 4) transplant-related adverse effects evidences the potential toxicity of the regimen. In the past, total body irradiation, which included irradiation of the lung tissue, was associated with severe adverse events and high mortality in transplants for SSc patients.[11] Total body irradiation regimens may also be associated with scleroderma renal crises, as patients undergoing AHSCT that include TBI are more likely to develop acute kidney insufficiency.[41] As a result of this experience, lung and renal shielding are adopted in TBI-based regimens for SSc patients.[18,42] The available evidence in the literature is not sufficient to define whether the intensity of the transplant regimen associates with better or worse clinical outcomes. Higher intensity regimens may provide more efficient and long-lasting eradication of the autoreactive immune system, but non-myeloablative regimens may be safer. It is most likely that multiple factors are involved and that other aspects, such as patient selection, have a stronger influence on the process.

Transplant-associated cardiac toxicity is a current concern in AHSCT for SSc patients. Most conditioning regimens include high doses of cyclophosphamide, and this alkylating agent is associated with dose-dependent acute myocardial injury through direct endothelial capillary damage.[43] On the other hand, cardiac involvement is a frequent and underdiagnosed manifestation of SSc, as patients may be asymptomatic, and at early stages, echocardiography may overlook diastolic dysfunction.[44,45] To date, pre-transplant cardiac evaluation has been formally recommended by the European Society for Blood and Marrow (EBMT) and partners, and once incorporated by transplant centers, should contribute to a reduction in transplant-related mortality.[20] In parallel, alternative conditioning regimens, including lower doses of cyclophosphamide or different non-cardiotoxic agents, are also under investigation.[24,46]

Over the 20 past years, transplant-related mortality has declined from over 17% to less than 6%, and some centers have reported zero deaths from the procedure.[16,38,47] Systemic sclerosis is a complex disease and internal organ damage increases the toxicity of the procedure.

Table 1 Main Characteristics of Non-Randomized Phase I/II, Retrospective and Observational Studies

	Henes et al. 2012[31]	**Burt et al. 2013**[32]	**Helbig et al. 2018**[33]	**Nakamura et al. 2018**[34]	**Ayano et al. 2019**[29]	**Guillaume-Jugnot et al. 2019**[35]	**Van-Bijnen et al. 2020**[36]	**Henes J et al. 2021**[30]	**Henrique-Neto et al 2021**[37]
Country	Germany	USA/Brazil	Poland	Japan	Japan	France	Netherlands	Europe/Brazil	Brazil
Study design	Prospective Phase I/II 1997–2009	Retrospective 2002–2011	Prospective Phase I/II 2003–2016	Long-term follow-up of phase II 2000–2012	Post-hoc analysis of phase I/II 2002–2009	Retrospective 1997–2013	Retrospective multicenter 1998–2017	Prospective observational multicenter 2012–2016	Retrospective study 2009–2016
Inclusion criteria	Inefficacy of CY pulse therapy or progressive disease with indicators of bad prognosis	mRSS ≥14 plus interstitial lung disease or abnormal EKG or GI tract involvement	≤70 y of age Karnofsky >80 Disease <10 y mRSS ≥15 or mRSS <15 plus progressive pulmonary disease	Diffuse SSc Disease <3y mRSS ≥15 plus refractory digital ulcers or interstitial lung disease	16–65 y of age mRSS ≥15 plus worsening lung or heart or kidney involvement, or mRSS <15 plus pulmonary progression	Not described	Same as in ASTIS trial[17]	18–65 y Progressive disease	18–60 y of age Worsening diffuse skin if mRSS >14 or progressive lung function
Exclusion criteria	Karnofsky <70 PAPsys >50mmHg DLCO<40% predict	PAPsys >40mmHg LVEF <40% FVC<45% predict	PAH Cardiac Insuf. Renal Insuf. DLCO<40% predict	>60 years of age <16 years of age Uncontrolled arrhythmia LVEF <50% DLCO<45% predict	Uncontrolled arrhythmia Severe heart failure PAH Pulmonary or renal failure	Not described	Same as in ASTIS trial[17]		LVEF <40% Diastolic dysfunction PAPsys >40mmHg PAPm >27mmHg FVC <45% predict DLCO<40% predict
N	26	90	18	14	19	56	89	80	70
Median age	39 y	42 y	51.5 y	44.5 y	53.7 y	48 y	46 y	43 y	35.9
Median disease duration	27 y	25 mo	14 mo	22.5 mo	15 mo	25 mo	18 mo	23.8 mo	2y

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Transplant regimen	CY200 + rATG or CY100 + Thiotepa	CY200 + rATG	CY200 + rATG CY 200 + Alemtuz Mel + Alemtuz CY200 alone	CY200	CY 200	Multiple regimens	Cy200 + rATG	CY200 + ATG CY100 +Thiotepa + ATG	CY200 + rATG Flu + Mel + ATG
CD34+ selection	Yes	No	No	Yes in 5 patients	Yes in 11 patients	Yes in most, but not specified for SSc patients	Yes	Yes in 35 patients	No
Follow-up	4.4 y	5 y	42 mo	11 y	8 y	7 y	4.6 y	2 y	8 y
Overall survival	74% at 3 y	78% at 5 y	61% at 42 m	93% at 5 y 93% at 10 y	79% (15/19)	73.7% at 5 y 55.4% at 10 y	77% at 55 mo	91.2% at 1 y 90% at 2y	91.8% at 3 y 85% at 5 y 81% (8y)
Transplant-related mortality	4% (1/26)	6% (5/90)	22% (4/18)	7.1% (1/14)	Zero	8.9% (5/56)	11% (8/89)	6% (5/80)	4% (3/80)
Progression-free survival or Event-free survival	Progression-free survival 53% at 3 y	Event-free survival 70% at 5 years	Progression-free survival 33% at 42 mo	Event-free survival 50% at 5 y 40% at 10 y	Progression-free survival 68.4% at 5 y 51.3% at 8 y	Progression-free survival 44.2% at 5 y 44.1% at 10 y	Event-free survival 78% at 5 y 76% at 10 y 66% at 15 y	Progression-free survival 87.5% at 1 y 81.8 at 2 y	Progression-free survival 71.8% at 3 y 71.8% at 5 y 70.5% at 8 y
Relapse/ progression	30.4% at 3 y	14.4% at 5 y	27.7% at 42 mo	42% at 5 y	Not available	Not available	24% at 5 y	Progression of 6.3% at 1 y and 11.9% at 2 y	24%
mRSS	78.3% improved at 6 mo	Improved up to 5y	No scores available. Improved at 12mo	71% of patients improved at 12 mo	Improved up to 5 y Stable up to 8 y	Not available	Improved up to 5 y	Improved up to 2 y	Improved up to 5 y
FVC and DLCO	FVC improved at 12 mo DLCO unchanged	FVC improved up to 36 mo DLCO stable	No scores available Stable over 12 mo	85% of patients stable at 12 mo	FVC improved until 8 y DLCO stable	Not available	FVC and DLCO improved up to 5 y	FVC improved up to 2 y DLCO stable	FVC and DLCO stable up to 5 y

Abbreviations: CY, cyclophosphamide; CY200, CY at the dose of 200mg/kg; ATG, anti-thymocyte globulin; rATG, rabbit ATG; Flu, fludarabine; Mel, melphalan; Alemtuz, alemtuzumab; SSc, systemic sclerosis; mRSS, modified Rodnan's skin score; LVEF, left ventricle ejection fraction; FVC, forced vital capacity; DLCO, diffusing lung capacity for carbon monoxide; predict, % of predicted value; y, years; mo, months; GI, gastrointestinal; PAH, pulmonary artery hypertension; PAP, pulmonary artery pressure; PAPsys, systolic PAP; PAPm, mean PAP; EKG, electrocardiography; progression-free survival, proportion of patients who were alive and with no worsening of disease when compared to baseline; event-free survival, proportion of patients who were alive and with no worsening of disease from best improvement after transplant.

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Table 2 Main Characteristics of Comparative Studies, Including Randomized Controlled Trials

	Burt et al 2011 (ASSIST)[16]	van Laar et al 2014 (ASTIS)[17]	Sullivan et al 2018 (SCOT)[18]	Del Papa et al. 2017[38]
Study design	Phase II, randomized 1:1, open-label cross-over to HSCT allowed at 12 mo North American single-center 2006–2009	Phase III, randomized 1:1, open-label European multicenter (EBMT) 2001–2009	Phase II, randomized 1:1, open-label North American multicenter 2005–2011	Phase II, retrospective historical SSc control group Italian, single-center 2003–2011
Comparisons	HSCT vs 6-mo intravenous CY	HSCT vs 12-mo intravenous CY	HSCT vs 12-mo intravenous CY	HSCT vs historical cohort
Inclusion criteria	<60 y of age Disease duration ≤4 y Diffuse SSc mRSS ≥15 Internal organ involvement	18–65 y of age Disease duration ≤2–4 y[a] Diffuse SSc mRSS ≥15 Internal organ involvement	18–69 y of age Disease duration ≤4 y Diffuse SSc mRSS ≥16 Internal organ involvement	Diffuse SSc Disease duration ≤4 y mRSS ≥14 Clinical activity score (ESSG) ≥3
Exclusion criteria	PAPm >25mmHg or PAPsys >40mmHg LVEF <40% Creatinine >177μmol/L >6 Intravenous CY courses	PAPm>50mmHg LVEF <45% Creatinine >40mL/min Cumulative IV CY dose >5g or Cumulative oral CY dose >3g	Mean PAP >30mmHg LVEF<50% FVC <45% predicted DLCO <40% predicted Creatinine clearance <40mL/min Cumulative IV CY dose >3g/m^2 or Oral CY dose >4 months, or >6 Intravenous CY courses	PAH LVEF <45% DLCO <50% predicted, Prior renal crisis
Number of participants	19 (10 HSCT + 9 CY arm)	156 (79 HSCT + 77 CY arm)	75 (33 HSCT + 32 CY arm)	18 HSCT + 36 SSc controls
Median age	45 y	43.8 y	45.9 y	41 y
Disease duration	13.6 mo	16.8 mo	27 mo	24 mo
Transplant regimen	CY200 + rabbit ATG	CY200 + rabbit ATG	TBI + CY120 + equine ATG	CY200 + rabbit ATG
Total body irradiation	No	No	Yes	No
CD34+ selection	No	Yes	Yes	Yes
Follow-up after AHSCT	2.6 y (median)	5.8 y (median)	4.5 y (minimum)	5 y (minimum)
Overall survival	100% at median 2.6 y for both groups	80% in HSCT vs 65% in CY at 4 y 75% in HSCT vs 60% in CY at 8 y	86% in HSCT vs 51% in CY at 6 y	89% in HSCT vs 39% in SSc controls at 5 y
Transplant-related mortality	0%	10.6% (8/79 HSCT)	3% (1/33 HSCT)	5.6% (1/18 HSCT)

(*Continued*)

Table 2 (Continued).

	Burt et al 2011 (ASSIST)[16]	van Laar et al 2014 (ASTIS)[17]	Sullivan et al 2018 (SCOT)[18]	Del Papa et al. 2017[38]
Event-free survival	80% in the HSCT group at 2 y 11% in the CY group at 2 y	81% in HSCT vs 74% in CY at 4 y	79% in HSCT vs 50% in CY at 4.5 y 74% in HSCT vs 47% in CY at 6 y	Not described
Progression-free survival	100% in HSCT vs 11% CY at 1 y 88% in HSCT at 2.6 y	77% in HSCT vs 65% in CY at 5.8 y	Not described	Not available. Higher survival in HSCT than in the SSc control group
Disease progression	0 in HSCT vs 89% (8/9) in CY at 1 y	11% in HSCT vs 35% in CYC at 5.8 y	18% in HSCT vs 41% in CY at 6 years	Not available. Lower disease progression in HSCT than in controls
mRSS	Improvement up to 2 y in HSCT Worsening in CY group	Improvement at 2 y in HSCT HSCT better than CY at 2 y	Not described	Improvement from baseline to 12 mo after HSCT and stabilization thereafter
FVC/DLCO	FVC improved more in HSCT than in CY DLCO remained stable and not different between groups	FVC improved more in HSCT than CY DLCO remained stable and not different between groups	FVC improved/stabilized in more patients from HSCT than from CY group	Stabilization of FVC and DLCO No difference between HSCT and controls

Notes: [a]The protocol was amended in 2004 to shorten maximum duration of disease for enrolment to 2 years, instead of the previous 4 years. Progression-free survival (PFS): proportion of patients who were alive and with no worsening of disease when compared to baseline; event-free survival: proportion of patients who were alive and with no worsening of disease from best improvement after transplant.

Abbreviations: SSc, systemic sclerosis; HSCT, hematopoietic stem cell transplantation; mRSS, modified Rodnan's skin score; ESSG, European Scleroderma Study Group scoring system; LVEF, left ventricle ejection fraction; PAP, pulmonary artery pressure; PAPsys, systolic PAP; PAPm, mean PAP; CY, cyclophosphamide; CY200, CY at a dose of 200mg/kg; ATG, anti-thymocyte globulin; TBI, total body irradiation; PAH, pulmonary artery hypertension; FVC, forced vital capacity; DLCO, diffusing lung capacity for carbon monoxide; y, years; mo, months.

Therefore, the expertise of the transplant team in selecting the appropriate patients, and thereby excluding those with too advanced organ damage, and in managing intra-transplant events and complications, is essential for good patient outcomes. An EBMT study from 2010 retrospectively analyzed data from multiple autoimmune disease transplants, showing that less experienced transplant centers, ie, those with lower number of transplanted patients, had higher transplant-related deaths. These results indicate that there is an important learning curve associated with outcomes, especially considering that SSc is a disease difficult to manage during AHSCT.[48]

Tissue damage is accumulated over time in SSc.[49] Patients earlier in disease course have less internal organ impairment and should thus present less transplant-related toxicity and perhaps better disease control after AHSCT. In line with this, recent prospective studies have included patients with disease duration limited to 2 to 4 years.[16–18,38] Indeed, a very recent prospective study conducted by the EBMT showed, by multivariate analysis, that mRSS above 24 at baseline and older age at transplantation were significantly associated with lower progression-free survival, corroborating that patients should be enrolled earlier in disease course.[30] The contribution of this selection strategy to the final patient outcome is unknown, but an ongoing study that aims to enroll patients for AHSCT as upfront treatment and, therefore, shortly after diagnosis, should answer some of the pending questions.[50]

Disease Progression

Studies are heterogeneous on reports of disease control after AHSCT. Nevertheless, most studies demonstrate positive effects of AHSCT on patient outcomes. Disease progression, defined as worsening manifestations from baseline, varied between the phase I/II non-randomized studies, even between those with similar duration of follow-up. Disease progression rates varied from 11.9% at 2 years to 30.4% at 4.4 years after ASHCT.[30,31] For studies

with longer follow-up, the 8-year progression rate ranged from 10.5% to 24%,[29,37] reaching 42% at 11 years.[34] These different rates are probably secondary to differences in patient selection, different criteria for progression and duration of follow-up.

The three randomized studies – ASSIST, ASTIS and SCOT – showed better disease control in transplanted versus conventionally treated (control) patients.[16–18] This difference in event-free survival between transplanted and control groups is more pronounced in the SCOT (74% in transplanted vs 47% in controls), than in the ASTIS trial (77% in transplanted vs 65% in controls), probably owing to the higher transplant-related mortality of ASTIS and to slightly different criteria for disease progression between studies. In the SCOT trial, the progression rate was not described in traditional terms, as patient outcomes were measured by a specific global rank composite score (GRCS). This score included a hierarchy of events reflecting disease improvement or worsening, resulting in a final score that enabled comparisons between participants of the study. Unfortunately, the evaluating method does not allow outcomes to be directly compared to those from other studies. Nevertheless, a recent study retrospectively evaluated the French cohort of the ASTIS trial, consisting of 49 patients, for GRCS results, showing superiority of transplanted versus conventionally treated patients.[51] In this study, GRCS was 9 for transplanted versus −19 for conventionally treated patients at 60 months (p=0.018), while in SCOT, respective results were 20 and −8 at 48 months (p=0.008).

Skin Outcomes

Clinical trials on AHSCT for SSc show a significant reduction in skin thickening, assessed by the modified Rodnan skin score (mRSS).[52] Improvement in skin involvement is considered when mRSS decreases by more than 25%.[16,18,30] Collectively, phase I/II studies show improvement of mRSS early after AHSCT, usually more pronounced within the first year after transplantation, and tending to stabilize thereafter.[16,30,32,37] Longer follow-up studies show sustained mRSS improvement for at least 60 and 96 months, respectively.[29,37] In a post-hoc analysis of a phase I/II non-randomized study, patients who underwent AHSCT with and without graft selection were compared. CD34+ graft selection had an overall positive influence on patient outcomes but was specifically associated with improvements in mRSS.[29]

In the randomized controlled studies, the differences in mRSS between patients undergoing AHSCT and those treated with cyclophosphamide (control) are significant, usually with improving curves in transplanted and progressively worsening in control patients. In ASSIST, mRSS improved from 30 at baseline, to 16 at 12 months, and 9 at 24 months after AHSCT, while scores worsened in the control group. Patients from the control group were allowed to cross over to the transplantation group after 1 year of follow-up, and these also had improvements in mRSS.[16] The ASTIS and SCOT trials also show superior efficacy of transplanted over control patients regarding skin involvement, with sustained outcomes at 24 and 54 months, respectivelly.[17,18]

In a non-randomized, but comparative study, both mRSS and European Scleroderma Study Group (ESSG) scores showed a strongly significant reduction since 12 months after AHSCT. When groups were compared at 3-years, the probability that mRSS could decline to below 14 was above 90% in the AHSCT group, while only 60% in the control group.[38]

Improvement of the skin involvement may be also indirectly assessed by functional evaluations, such as joint range-of-motion measurements, hand grip strenght, finger-to-palm distance, mouth opening, and functional questionnaires for hand (Cochin) and upper limbs (DASH, Disabilities of the arm, shoulder and hand). A recent study showed improvements of these functional parameters at 6 and 12 months after AHSCT, when compared to baseline.[53]

Although the mRSS is the universally used method to quantify skin thickening in SSc, it bears intrinsic limitations and depends on evaluator expertise and opinion that affect reproducibility and consistency of the method.[54] Therefore, the reliability of mRSS to evaluate skin outcomes after AHSCT has been questioned. Nevertheless, skin biopsies, the gold-standard method to quantify cutaneous involvement in SSc, correlate well with mRSS, as the degree of fibrosis decreases while mRSS scores decline after AHSCT.[14,55]

Pulmonary Outcomes

Most phase I/II studies showed stabilization or slight improvement in FVC after transplantation, and DLCO stabilization.[30–33] One study showed significant improvement for both FVC and DLCO over 5 years and another study showed that FVC and DLCO improved only in the subgroup of patients with progressive lung disease as an

indication for AHSCT.[36,37] The ASSIST and ASTIS randomized trials showed that lung function outcomes in transplanted patients were superior to those from the control group treated with cyclophosphamide.[16,17] In ASSIST, in addition to the favorable difference between groups, CVF and computed tomography volumes increased in transplanted patients at 24 months of follow-up.[16] The SCOT study does not describe pulmonary function data in a format that enables comparisons, but there is a higher absolute number of patients having improved FVC after AHSCT than after cyclophosphamide pulses.[18]

A retrospective study from the EBMT did not associate graft selection with clinical outcomes, including pulmonary function test results.[28] A more recent study, however, prospectively compared two groups of SSc patients, randomized for AHSCT with manipulated or non-manipulated graft.[29] The authors showed that although overall survival was similar between the two groups, patients who received CD34+ selected grafts had better progression-free survival over an 8-year follow-up. Forced vital capacity also progressively increased over the years in the CD34+ selected patients, while remained mostly stable in the non-selected group, with a tendency to better outcomes in the selected versus non-selected group.

Physical capacity, assessed by the 6-minute walk test (6MWT), improved after AHSCT, as an indirect evidence of better pulmonary function, although the cardiovascular and musculoskeletal systems may have participated.[53] Another method to evaluate how AHSCT affects interstitial lung disease is high-resolution quantitative computed tomography. Studies have shown improvement of lung volumes and/or pulmonary tissue quality (evaluated by density), after transplantation, associated with pulmonary function outcomes.[16,56–58]

Quality of Life

Quality of life is an important indicator of transplant outcomes, as it reflects the patient's perspective and evaluates how patients are affected by the procedure in the context of their daily lives and environment. Quality of life assessments have been included in several clinical trials, but only one study has specifically addressed this aspect of evaluation in SSc patients undergoing AHSCT.[59] This retrospective study compared Short-Form 36 (SF36) questionnaire results from 41 SSc patients who underwent AHSCT and 65 conventionally treated (control) SSc patients, over a 7-year follow-up. Patient groups were different for physical components of quality of life, favoring transplant, but no difference was detected between groups regarding the mental components of quality of life. In addition, Health Assessment Questionnaire (HAQ) scores were considerably lower (indicating better function) at all times in patients treated with AHSCT compared to the control group.[59]

Recently, a prospective, open and multicenter study assessed Scleroderma HAQ (sHAQ) scores in 15 patients who underwent AHSCT, showing significant improvement at 1 year and and 2 years of follow-up.[30] Another single-center study also prospectively evaluated quality of life in 28 SSc patients treated with AHSCT, showing improvement of the physical components of SF36 at 6 and 12 months, and of the mental components of SF36 at 12 months.[53] Finally, a systematic review from 2020 analyzed three randomized and five uncontrolled clinical trials that contained information about quality of life in transplanted SSc patients, showing that SF36 results were heterogeneous across studies, but with overall improvements in the physical components of quality of life. For the mental components, however, data were inconsistent.[60]

Fertility After AHSCT

Fertility is usually preserved in SSc patients, as there are no differences in rates of conception between SSc women and the general healthy population.[61,62] In the subset of cyclophosphamide-treated patients, however, fertility rates may be compromised, due to gonadal toxicity of the treatment, especially in women.[63] Pregnancies, on the other hand, may have worse outcomes in SSc women than in the non-SSc patients.[61] An Italian study has retrospectively evaluated 109 pregnancies in SSc women, showing a higher rate of preterm deliveries, intrauterine growth restriction and very low-weight babies than in the general obstetric population.[62] Male fertility is much less investigated and few studies have specifically addressed male impotency in SSc.[64,65]

In the setting of AHSCT, reduced fertility is a frequently reported complication, both in men and women, although SSc data are reported combined with other autoimmune diseases. Multicenter data from the EBMT that were retrospectively analyzed showed that among 324 adult female patients with autoimmune diseases that underwent AHSCT, 15 of them had 22 pregnancies along post-transplantation follow-up. Five of these patients had SSc as baseline disease, and all had received high-dose cyclophosphamide as part of the transplant-conditioning regimen. One of the SSc patients had three

pregnancies, including one miscarriage. There were no deaths during pregnancy, but one patient died shortly after delivery due to worsening of skin and pulmonary fibrosis.[66]

A single center from Germany described 15 patients (11 female), who had been previously treated with autologous AHSCT for severe autoimmune diseases, out of which 3 had SSc. All but one patient had received cyclophosphamide as conventional treatment prior to AHSCT and all received high-dose cyclophosphamide as part of transplant conditioning regimen. One female patient with SSc was considered to have impaired fertility since before AHSCT, remaining amenorrheic and not becoming pregnant after AHSCT. Another female SSc patient became temporarily amenorrheic shortly after AHSCT, recovering regular menses a few months later. This woman became spontaneously pregnant twice after AHSCT, with successful preterm deliveries at 34 and 35 weeks due to premature labour and breech presentation, respectively.[67]

Secondary Autoimmune Diseases After AHSCT

A debated concern in the field of AHSCT for autoimmune diseases is whether the profound manipulation of the immune system in genetically predisposed patients may lead to development of secondary autoimmune diseases.[68] Therefore, continuous long-term surveillance of post-transplant immune status is recommended for patients who undergo AHSCT.

A study from the EBMT has reported a cumulative incidence of secondary autoimmune diseases of 9.8% over a 5-year follow-up after AHSCT, among 347 patients who underwent AHSCT with an autoimmune disease as primary indication.[69] Most secondary autoimmune diseases were organ or tissue-specific, with variable severity. Two, out of the 29 patients who developed secondary autoimmune diseases after AHSCT, died as direct consequence of antiphospholipid syndrome (cerebral ischemia) and hemorrhage (acquired hemophylia), respectively. Multivariate analysis identified systemic lupus erythematosus as primary indication for AHSCT and use of anti-thymocyte globulin associated with graft selection in the conditioning regimen as risk factors for development of secondary autoimmune disease.[69]

Additional secondary autoimmune diseases have been reported in smaller case series. One, out of 26 transplanted SSc patients, presented morphea as a secondary autoimmune manifestation after AHSCT.[31] In a cohort of 14 Japanese SSc patients treated with AHSCT, one patient developed multiple overlapped autoimmune disorders including Grave's disease, immune thrombocytopenia, systemic lupus erythematosus and antiphospholipid syndrome, and a second patient developed Sjogren's syndrome.[34] In a case series of 6 SSc patients who underwent AHSCT with thiotepa as part of the conditioning regimen, two female patients developed symptomatic Grave's disease with detectable autoantibodies against thyroid stimulating hormone (TSH) receptor, at 13 and 19 months after AHSCT. A third male patient developed antibodies against SSA and polyclonal hypergammaglobulinaemia 6 months after transplantation.[24] Finally, a French long-term outcome study reported secondary autoimmune diseases in 5 (8.9%) out of 56 transplanted SSc patients; thyroiditis, autoimmune hemolytic anemia, myasthenia gravis, sarcoidosis and anti-phospholipid syndrome.[35]

Secondary Malignancies After AHSCT

Systemic sclerosis is associated with increased relative risk of cancer, mainly lung, liver, hematologic and bladder, although with a low absolute risk.[70] Multiple mechanisms may contribute to such outcomes, including genetic background, defective immunological surveillance, pro-inflammatory status, epithelial hyperplasia and prior exposure to carcinogens, including those associated with cytotoxic treatment.[71]

Data on secondary malignancies in SSc after AHSCT are limited and variable. In addition, it is difficult to establish how much is influenced by the transplant procedure itself or by previous immunosuppressive and cytotoxic treatment, as well as prior viral infections. The ASTIS trial reported only one patient developed Epstein–Barr virus-related post-transplant lymphoproliferative disease shortly after AHSCT. Other five non-transplanted SSc patients from the cyclophosphamide (control) group also developed malignancies.[17] In the SCOT study, 3 of 33 SSc patients from the transplant group, and one from the conventional-treatment control group developed cancer. The authors believe that the regimen including total body irradiation may have contributed to the increased incidence of malignancy in the transplanted patients.[18] In a retrospective evaluation, the French Society for Bone Marrow Transplantation and Cellular Therapy reported 4 (7%) of 56 SSc patients who underwent AHSCT and developed cancer (oesophagus epidermoid carcinoma,

unspecified carcinoma, lung epidermoid carcinoma, spinocellular carcinoma) over a median follow-up of 83 months.[35] Collectively, these results indicate that these patients may require longer follow-up and more detailed inspection for possible malignancies. Further studies should define if other factors, such as smoking or previous treatments, impose additional risks.

Future Developments

Although the field of AHSCT for SSc has grown over the years, translating into benefits for the patient, further improvements are still warranted. Strategies to discriminate subjects that may achieve best results after AHSCT may contribute to better outcomes and to consolidate the procedure as a therapeutic alternative for SSc. In this context, a study analyzing biological samples from participants of the SCOT trial clustered patients into groups, according to different gene expression profiles associated with different pathogenic mechanisms of disease. When each of these groups were analysed for clinical outcomes after AHSCT, patients with a more fibroproliferative profile showed the most significant long-term benefit, indicating a potential biomarker for patient selection before AHSCT.[72] More recently, this same research group was able to associate histological findings of fibroblast polarization with the previously defined fibroproliferative gene profile, and to further correlate them with severity of skin involvement assessed by mRSS.[73] In addition, ongoing prospective clinical trials aim to evaluate the role of post-transplant maintenance therapy with immunosuppressors in decreasing disease reactivation and progression after AHSCT.[74,75] Furthermore, more specific approaches to lessen transplant-related toxicity have been investigated. A recent strategy, still mostly limited to oncology and hematology fields, describes the use of antibody-targeted destruction of specific cell types.[76,77] Conjugation of toxins to anti-CD45 antibody, for instance, may concentrate depletion in hematopoietic cells and, thus, spare non-hematopoietic cells. This may be a future strategy for AHSCT in SSc patients, aiming to reduce transplant-related toxicity. Combined, clinical and translational activities are essential to develop the field, and to have patient welfare as the most important goal.

Disclosure

The authors report no conflicts of interest for this work.

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