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Statement

Systemic Sclerosis as an Indication for Autologous Hematopoietic Cell Transplantation: Position Statement from the American Society for Blood and Marrow Transplantation

Keith M. Sullivan[1,*], Navneet S. Majhail[2], Christopher Bredeson[3], Paul A. Carpenter[4], Soumya Chatterjee[5], Leslie J. Crofford[6], George E. Georges[4], Richard A. Nash[7], Marcelo C. Pasquini[8,9], Stefanie Sarantopoulos[1], Jan Storek[10], Bipin Savani[11], E. William St. Clair[12]

[1] *Department of Hematologic Malignancies and Cellular Therapy, Duke University Medical Center, Durham, North Carolina*
[2] *Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland, Ohio*
[3] *Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*
[4] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[5] *Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, Ohio*
[6] *Division of Rheumatology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee*
[7] *Blood and Marrow Transplant Program, Colorado Blood Cancer Institute, Denver, Colorado*
[8] *Department of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin*
[9] *Center for International Blood and Marrow Transplant Research, Milwaukee, Wisconsin*
[10] *Blood and Marrow Transplant Program, University of Calgary, Calgary, Alberta, Canada*
[11] *Division of Hematology and Oncology, Vanderbilt University Medical Center, Nashville, Tennessee*
[12] *Department of Rheumatology and Immunology, Duke University School of Medicine, Durham, North Carolina*

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A B S T R A C T

Systemic sclerosis is a progressive inflammatory disease that is frequently fatal and has limited treatment options. High-dose chemotherapy with autologous hematopoietic cell transplantation (AHCT) has been evaluated as treatment for this disease in observational studies, multicenter randomized controlled clinical trials, and meta-analyses. On behalf of the American Society for Blood and Marrow Transplantation (ASBMT), a panel of experts in transplantation and rheumatology was convened to review available evidence and make a recommendation on AHCT as an indication for systemic sclerosis. Three randomized trials have compared the efficacy of AHCT with cyclophosphamide only, and all demonstrated benefit for the AHCT arm for their primary endpoint (improvement in the American Scleroderma Stem Cell versus Immune Suppression Trial, event-free survival in Autologous Stem Cell Transplantation International Scleroderma trial, and change in global rank composite score in Scleroderma: Cyclophosphamide or Transplantation trial). AHCT recipients also had better overall survival and a lower rate of disease progression. These findings have been confirmed in subsequent meta-analyses. Based on this high-quality evidence, the ASBMT recommends systemic sclerosis should be considered as a "standard of care" indication for AHCT. Close collaboration between rheumatologists and transplant clinicians is critical for optimizing patient selection and patient outcomes. Transplant centers in the United States are strongly encouraged to report patient and outcomes data to the Center for International Blood and Marrow Transplant Research on their patients receiving AHCT for this indication.

INTRODUCTION

Systemic sclerosis, or scleroderma with internal organ involvement, is a chronic progressive inflammatory disorder characterized by diffuse vasculopathy, immune activation, and tissue fibrosis that typically manifests as skin thickening and involvement of lungs, heart, gastrointestinal tract, kidneys, and other organs [1]. Immunosuppressive drugs and other biologic agents are commonly used to treat patients with diffuse skin or severe organ involvement. These treatment strategies offer only modest benefit in delaying disease progression or improving lung function and do not reverse the natural course of this disease, which is frequently fatal [2-7].

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* Correspondence and reprint requests: Keith Sullivan, MD, Division of Cellular Therapy, Duke University Medical Center, Box 3961, Durham, NC 27710.
E-mail address: keith.sullivan@duke.edu (K.M. Sullivan).

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Table 1
Summary of ASSIST, ASTIS, and SCOT Trials

	ASSIST (Burt et al. [23])		ASTIS (van Laar et al. [24])		SCOT (Sullivan et al. [25])	
Trial design	Randomized phase II		Randomized phase III		Randomized phase III	
No. of centers	1 (USA)		29 (Europe)		26 (USA)	
Recruitment period	2006-2009		2001-2009		2006-2011	
No. of patients randomized	19		156		75	
Age range, yr	<60		18-65		18-69	
Primary endpoint	Improvement at 12 mo		Event failure-free survival at 24 mo		Global rank composite score at 54 mo*	
Crossover allowed	Yes		No		No	
Inclusion criteria						
SSc duration, yr	≤4		<2 or ≤4		≤5	
mRSS†	≥15		≥20 or ≥15		≥16	
SSc internal disease	Yes		Yes or no		Yes	
FVC, % predicted	<80 or 10% decrease		<80		70-45	
DLco, % predicted	<80		80-40		70-40	
Interstitial lung disease	Yes		Yes or no		Yes	
Exclusion criteria						
TLC, % predicted	<45		—		—	
LVEF, %	<40		<45		<50	
PAP, mean mm Hg	>25		>50		>30	
Prior CY therapy, mo	>6		>5		>6	
	CY Arm	AHCT Arm	CY Arm	AHCT Arm	CY Arm	AHCT Arm
Stem cell mobilization	—	CY 2 g/m^2 and G-CSF	—	CY 4 g/m^2 and G-CSF	—	G-CSF and prednisone
CD34 selection	—	No	—	Yes	—	Yes
Treatment	CY 1000 mg/m^2/mo × 6 doses	CY 200 mg/kg + rabbit ATG 6.5 mg/kg + MP 5000 mg	CY 750 mg/m^2/month × 12 doses	CY 200 mg/kg + rabbit ATG 7.5 mg/kg	CY 750 mg/m^2/mo × 12 doses	CY 120 mg/kg + horse ATG 90 mg/kg + TBI 800 cGy
Patients randomized	9	10	77	79	39	36
Patient characteristics						
Mean age, yr	44	45	43	44	47	45
Mean duration of SSc, yr	1.5	1.2	1.5	1.4	2.4	2.1
Previous use of CYC, %	33	20	22	22	44	22
Lung involvement, %	89	70	87	80	95	100
Mean FVC, % predicted	67	62	81.7	81.1	73.8	74.5
Mean DLco, % predicted	75	58	59.3	57.7	52.7	53.9
Mean mRSS	19	28	25.8	24.8	30.8	28.5
Mean HAQ-DI score‡	—	—	1.44	1.25	1.4	1.2
Outcomes						
Primary endpoint (intention-to-treat)	Clinical improvement in 0/9 patients on CY arm vs. 10/10 patients on AHCT arm (odds ratio, 110; $P = .0001$)		Hazard ratio for death or major organ failure at 2-year follow-up, .35 (95% CI, .16-.74; $P = .006$) favoring AHCT arm		At 54 mo, median global rank composite score −6.0 in CY arm vs. 17.0 in AHCT arm ($P = .01$)	
Overall survival (treated population)	100% at 12 mo for both arms§		Hazard ratio at 10-year follow-up, .29 (95% CI, .13-.64; $P = .002$) favoring AHCT arm‖		At 72 mo, 51% in CY arm vs. 86% in AHCT arm ($P = .02$)§	
Treatment-related mortality	0% at 12 mo for both arms		0% in CY arm vs. 10.1% in AHCT arm ($P = .007$)		At 54 mo, 0% in CY arm vs. 3% in AHCT arm ($P = .48$)	
Recurrent disease	Disease progression in 8/9 patients in CY arm vs. 0/10 patients on AHCT arm ($P = .0001$)		Between 12 and 24 mo, 43.8% in CY arm received immunosuppressive drugs vs. 22.4% in AHCT arm ($P = .02$)		At 54 mo, 44% in CY arm restarted DMARDs vs. 9% in AHCT arm ($P = .001$)	

Table provides an overview of the trials; details of patient selection, treatment regimens, and supportive care for AHCT are publically available through the journal websites where trial results have been published (full protocol for SCOT trial is available at http://www.nejm.org/doi/10.1056/NEJMoa1703327). SSc indicates systemic sclerosis; mRSS, modified Rodnan skin score; FVC, forced vital capacity; DLco, diffusion capacity of carbon monoxide; TLC, total lung capacity; LVEF, left ventricular ejection fraction; PAP, pulmonary arterial pressure; CY, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; MP, methylprednisolone; ATG, antithymocyte globulin; TBI, total body irradiation; HAQ-DI, Health Assessment Questionnaire-Disability Index; DMARDs, disease-modifying antirheumatic drugs.

* Primary endpoint was a global rank composite score based on hierarchy of following disease outcomes: death, event-free survival (survival without respiratory, renal, or cardiac failure), FVC, Disability Index of Health Assessment Questionnaire score, and mRSS.

† mRSS ranges from 0 (normal skin) to 51 (severe skin thickening).

‡ HAQ-DI scores can range from 1 to 3, with higher scores indicating more disability.

§ Per-protocol analysis.

‖ Intention to treat analysis.

The use of high-dose chemotherapy and autologous hematopoietic cell transplantation (AHCT) as a treatment for selected patients with severe manifestations of systemic sclerosis has been investigated in several observational and clinical studies. Based on these studies, the European League Against Rheumatism issued evidence-based guidelines for the treatment of systemic sclerosis that recommend AHCT for the treatment of selected patients with rapidly progressive disease at risk of organ failure [2]. In an effort to forge interdisciplinary collaboration and best practices in severe systemic sclerosis, the American Society for Blood and Marrow Transplantation's (ASBMT) Practice Guidelines Committee, in collaboration with the Center for International Blood and Marrow Transplant Research (CIBMTR), established a Task Force of experts in transplantation and rheumatology to review available evidence and provide a recommendation on systemic sclerosis as a potential indication for AHCT.

ASBMT DEFINITIONS FOR HCT INDICATIONS

The guiding principles and processes that ASBMT follows when considering a disease or condition as an indication for transplantation have been described previously [8,9]. Briefly, ASBMT criteria for classifying HCT indications include (1) "standard of care," where indication for HCT is well defined and supported by evidence; (2) "standard of care, clinical evidence available," where large clinical trials and observational studies are not available but HCT has been shown to be effective therapy; (3) "standard of care, rare indication" for rare diseases, where HCT has demonstrated effectiveness but large clinical trials and observational studies are not feasible; (4) "developmental" for diseases, where preclinical and/or early-phase clinical studies show HCT to be a promising treatment option; and (5) "not generally recommended," where available evidence does not support the routine use of HCT.

SUMMARY OF EVIDENCE

Observational Studies and Early-Phase Clinical Trials

Many observational single-center, multicenter, and registry-based studies as well as single-arm phase I/II trials have suggested the efficacy of AHCT in treating patients with severe systemic sclerosis [10-22]. One retrospective study compared outcomes between 18 AHCT recipients with rapidly progressive diffuse cutaneous systemic sclerosis and a demographically and clinically matched cohort of 36 patients receiving conventional therapies [17]. Compared with the transplantation cohort, control patients had significantly lower overall survival (hazard ratio, 6.94; $P < .002$), including the subset of control patients who had received cyclophosphamide-based regimens (hazard ratio, 5.98; $P < .006$). AHCT recipients had a significantly higher likelihood of improving skin sclerosis and disease activity and preserving lung function.

Randomized Clinical Trials

To address the efficacy of transplantation, 3 randomized clinical trials have compared AHCT and standard care (cyclophosphamide only) for severe systemic sclerosis: the American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST) [23], the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial [24], and the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial [25]. Eligibility criteria and characteristics of patients enrolled were notably similar among the 3 trials (Table 1). All 3 trials demonstrated a benefit in the AHCT arm with respect to their primary endpoints (clinical improvement in ASSIST, event-free survival in the ASTIS trial, and change in global rank composite score in the SCOT trial). Also, patients on the AHCT arm had better overall survival and a lower rate of disease progression.

Systematic Reviews and Meta-Analyses

A systematic review conducted before the publication of the SCOT trial collated results of 2 randomized clinical trials (ASSIST and ASTIS trial) and 7 single-arm observational studies [26]. This review concluded that AHCT is beneficial in some patients with systemic sclerosis. A subsequent systematic review and meta-analysis included 3 randomized trials (including the SCOT trial) and 1 comparative observational study [17,23-25,27]. The control arm was monthly cyclophosphamide in all 3 trials and with most patients in the observational study. Compared with control subjects, patients receiving AHCT experienced lower all-cause mortality (risk ratio, .50; 95% confidence intervals .33 to .75; $P = .0007$) and improved skin thickness, forced vital capacity, total lung capacity, and quality of life. The improvement in overall mortality was maintained in sensitivity analyses that only included patients treated on randomized trials (risk ratio, .61; $P = .02$).

POSITION STATEMENT

Based on the supporting evidence from high-quality randomized controlled trials and meta-analyses summarized above, the ASBMT Task Force recommends AHCT as "standard of care" for patients with severe systemic sclerosis.

PATIENT SELECTION AND TRANSPLANTATION REGIMEN

Close collaboration between rheumatologists with expertise in treating systemic sclerosis and transplant physicians is critical to identify patients who are candidates for AHCT and to ensure optimal outcomes [28]. This position paper does not provide specific recommendations on patient selection criteria for AHCT or preferred methods for mobilization and stem cell collection, conditioning regimen, or post-transplant supportive care. Instead, clinicians offering AHCT are advised to refer to published guidelines [29] and to eligibility criteria and treatment regimens detailed in the publicly available reports of 2 large phase III multicenter randomized clinical trials [24,25]. Of note, both the ASTIS and SCOT trials used CD34 selected grafts, which if available should be considered. The procedures used in the SCOT trial for CD34 selection of hematopoietic progenitor cells have been published [30]. For more information, the SCOT trial protocol with details of eligibility and AHCT procedure is available at http://www.nejm.org/doi/10.1056/NEJMoa1703327.

DATA REPORTING TO CIBMTR

As AHCT is applied to the treatment of patients with severe systemic sclerosis, additional data and research will be critical to understand its utilization, plan future research, and improve patient outcomes. Thus, transplant centers in the United States and Canada and international centers affiliated with the CIBMTR are strongly encouraged to report data to the CIBMTR on their patients who receive an AHCT for this indication.

CONCLUSION

In summary, the ASBMT endorses AHCT as a "standard of care" for severe systemic sclerosis. This document provides guidance to physicians, patients, payers, policymakers, and other stakeholders on coverage decisions and the appropriate utilization of this procedure for systemic sclerosis.

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