Original Investigation

Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis
A Randomized Clinical Trial

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IMPORTANCE High-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation (HSCT) have shown efficacy in systemic sclerosis in phase 1 and small phase 2 trials.

OBJECTIVE To compare efficacy and safety of HSCT vs 12 successive monthly intravenous pulses of cyclophosphamide.

DESIGN, SETTING, AND PARTICIPANTS The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, a phase 3, multicenter, randomized (1:1), open-label, parallel-group, clinical trial conducted in 10 countries at 29 centers with access to a European Group for Blood and Marrow Transplantation–registered transplant facility. From March 2001 to October 2009, 156 patients with early diffuse cutaneous systemic sclerosis were recruited and followed up until October 31, 2013.

INTERVENTIONS HSCT vs intravenous pulse cyclophosphamide.

MAIN OUTCOMES AND MEASURES The primary end point was event-free survival, defined as time from randomization until the occurrence of death or persistent major organ failure.

RESULTS A total of 156 patients were randomly assigned to receive HSCT (n = 79) or cyclophosphamide (n = 77). During a median follow-up of 5.8 years, 53 events occurred: 22 in the HSCT group (19 deaths and 3 irreversible organ failures) and 31 in the control group (23 deaths and 8 irreversible organ failures). During the first year, there were more events in the HSCT group (13 events [16.5%], including 8 treatment-related deaths) than in the control group (8 events [10.4%], with no treatment-related deaths). At 2 years, 14 events (17.7%) had occurred cumulatively in the HSCT group vs 14 events (18.2%) in the control group; at 4 years, 15 events (19%) had occurred cumulatively in the HSCT group vs 20 events (26%) in the control group. Time-varying hazard ratios (modeled with treatment × time interaction) for event-free survival were 0.35 (95% CI, 0.16-0.74) at 2 years and 0.34 (95% CI, 0.16-0.74) at 4 years.

CONCLUSIONS AND RELEVANCE Among patients with early diffuse cutaneous systemic sclerosis, HSCT was associated with increased treatment-related mortality in the first year after treatment. However, HCST conferred a significant long-term event-free survival benefit.

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Systemic sclerosis is a heterogeneous autoimmune connective tissue disease characterized by vasculopathy, autoantibody formation, low-grade inflammation, and fibrosis in skin and internal organs, with varying geographical prevalence (50-300 per million persons per year) and incidence (2.3-22.8 per million persons per year).[1,2] Previous studies have shown that systemic sclerosis is amenable to treatment with autologous hematopoietic stem cell transplantation (HSCT).[3-9] Improvement of skin involvement and functional ability was consistently observed, although some studies showed that HSCT can also ameliorate vasculopathy, improve skin and lung involvement, and correct immune abnormalities.[10-13] The benefits of HSCT must be weighed against the risk of serious toxicities due to organ involvement in systemic sclerosis.[14] It is still unclear whether HSCT prolongs survival in systemic sclerosis. We therefore conducted a randomized clinical trial called ASTIS (Autologous Stem Cell Transplantation International Scleroderma) to compare safety and efficacy of HSCT vs 12 successive monthly intravenous pulses of cyclophosphamide.

Methods

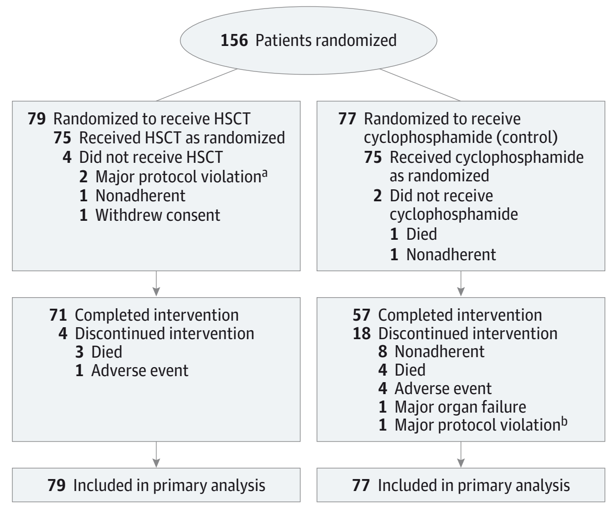
Study Design and Participants

The ASTIS trial was an investigator-initiated, randomized, open-label, parallel-group trial conducted in 10 countries at 29 centers with access to a European Group for Blood and Marrow Transplantation–registered transplant facility.[15] Patients were eligible if they were between 18 and 65 years of age; had diffuse cutaneous systemic sclerosis according to American Rheumatism Association criteria,[16] with maximum disease duration of 4 years; minimum modified Rodnan skin score (mRSS) of 15 (range, 0-51, with higher scores indicating more severe skin thickening); and involvement of heart, lungs, or kidneys (eAppendix in the Supplement). Prior treatment with cyclophosphamide was allowed up to a cumulative dose of 5 g intravenously or up to 2 mg/kg body weight orally for 3 months. Patients with severe major organ involvement including severe pulmonary arterial hypertension (PAH) (mean pulmonary artery pressure >50 mm Hg) or serious comorbidities were excluded. The protocol was amended in 2004 to allow inclusion of patients with disease duration of 2 years or less and no major organ dysfunction as defined above, provided they had an mRSS of at least 20 and an erythrocyte sedimentation rate greater than 25 mm in the first hour and/or hemoglobin less than 11 g/dL not explained by causes other than active scleroderma. The protocol was further amended in 2008 to make it compliant with the European Union Directive for Clinical Trials, to change the power calculation because of a lower than expected accrual and event rate, and to include guidance on monitoring and treatment of Epstein-Barr virus (EBV) reactivation after HSCT.

Ethical Approval

The study protocol was approved by the institutional review board at each site and complied with country-specific regulatory requirements. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Figure 1. Flow of ASTIS (Autologous Stem Cell Transplantation International Scleroderma) Trial



Information on the number of individuals screened and excluded was not available for all centers. Twenty-two patients receiving hematopoietic stem cell transplantation and 31 receiving cyclophosphamide (control group) experienced 1 event (death or persistent major organ failure) throughout follow-up (before October 31, 2013).

[a] Two patients had low diffusion capacity of the lung for carbon monoxide.

[b] One patient received the first cyclophosphamide pulse before randomization.

Randomization

After registration, patients were randomly assigned in a 1:1 ratio by blocked randomization to receive HSCT or 12 intravenous pulses of cyclophosphamide (**Figure 1**). Block randomization was performed centrally by telephone at the study administration office according to a computer-generated randomization program for each site, with random block sizes (2, 4, 6). Treatment was allocated within blocks according to an optimum assignment procedure (minimization) to balance the investigational and standard treatment groups for age (≤40 years, >40 years) and disease duration (<2 years, ≥2 years) but included a 25% chance to be assigned to the nonoptimal group.

Procedures

The protocol for HSCT was designed with the intention to achieve intensive lymphocyte ablation. Peripheral blood hematopoietic stem cells were mobilized with intravenous cyclophosphamide (a total of 4 g/m^2 administered in equal amounts on 2 consecutive days) and filgrastim (10 μg/kg per day), harvested by leukapheresis, and enriched for CD34$^+$ cells using immunomagnetic separation (CliniMACS, Miltenyi Biotec). The conditioning regimen consisted of intravenous cyclophosphamide (a total of 200 mg/kg intravenously over 4 consecutive days) and intravenous rabbit antithymocyte globulin (rbATG, Genzyme) (a total of 7.5 mg/kg administered in equal amounts over 3 consecutive days) administered with intravenous methylprednisolone (1 mg/kg) and hyperhydration, followed by reinfusion of peripheral blood autologous CD34$^+$ stem cells (≥2 × 10^6/kg). Patients in the control group received 12 monthly pulses of intravenous cyclophosphamide (750 mg/m^2). Crossing over was allowed after the second year. Concomitant medications or other treatments deemed necessary for patients' supportive care and safety were allowed at the discretion of the investigators. Adherence to European Group for Blood and Marrow Transplantation guidelines was recommended.[15] After 2008, guidance was provided on the monitoring of EBV load by polymerase chain reaction after HSCT. Investigators were advised to initiate prophylactic treatment with angiotensin-converting enzyme inhibitors in all patients enrolled.

Data Collection and Assessment of Data Quality

Patients were seen every 3 months in the first 2 years, and yearly thereafter, for physical examination, full blood cell count, and urinalysis and for measurement of skin score, toxicity, and the Health Assessment Questionnaire Disability Index (HAQ-DI), for a total follow-up of 7 years. Patients and assessors were not blinded. Options for ethnic origin were predefined in the case record forms and determined by each investigator. Information on quality of life (36-item Short Form General Health Survey [SF-36] and EuroQol [EQ-5D]) was collected at 3 and 6 months and then every 6 months in the first 2 years and annually thereafter. Lung function tests, echocardiography or multiple-gated acquisition scan, and electrocardiography were performed yearly up to 7 years after enrollment. Survival and the absence of major organ failure among patients with follow-up longer than 7 years were ascertained by telephone calls or e-mails with the investigators.

Collected data were transferred to the study administration office, which stored, managed, and analyzed the data. An independent data and safety monitoring committee monitored efficacy and safety data.

Study End Points

The primary end point was event-free survival, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney), defined as left ventricular ejection fraction less than 30% by echocardiography (or multiple-gated acquisition scan), resting arterial oxygen tension less than 8 kPa (60 mm Hg) and/or resting arterial carbon dioxide tension greater than 6.7 kPa (50 mm Hg) without oxygen supply, or the need for renal replacement therapy. Each event (death or major organ failure) was reviewed and adjudicated in a nonblinded manner by the independent data and safety monitoring committee, which determined whether it was deemed treatment-related or attributable to disease progression.

The main secondary end points of the study were treatment-related mortality, toxicity, and changes in mRSS (minimally important difference, 3.2-5.3),[17] organ function (heart, lung, kidney), HAQ-DI (minimally important difference, 0.10-0.14)[17], body weight, SF-36 score, and EQ-5D score within 24 months following randomization. The need for immunosuppressive therapy between 12 and 24 months served as an additional end point.

Power Analyses

We calculated that 75 patients were needed in each group, with a total study and follow-up period of 11 years, including at least 1-year follow-up of the last patient with an annual event rate of 9.5% (50 events in total), to detect a hazard ratio of 0.5, indicating that half as many patients in the intervention group had experienced an event as compared with the control group, assuming a 5% loss to follow-up after 8 years in both groups (α = .05 [2-sided]; power = .67 [1-sided]).

Statistical Analysis

Data collected by October 31, 2013, were included in the analysis, consistent with a 4-year follow-up after the last participant was enrolled. Data for patients who survived and for those surviving event-free were censored at the date of the last follow-up visit. We analyzed all data by intention-to-treat (ITT) and report raw estimates without adjustment for baseline characteristics. In addition, per-protocol sensitivity analyses of secondary outcomes were performed.

Primary analyses compared event-free survival between the study groups by constructing Kaplan-Meier survival curves based on the time to the first event, ignoring additional failures, and by using the log-rank test and a Cox regression model. Because the survival curves crossed, the treatment × time interaction was modeled allowing a gradual change of the hazard of the transplant group crossing the hazard of the control group at 0.5 years and ending up as a constant after 2 years of follow-up. We analyzed, by ITT, the treatment responses in clinical outcome variables such as the mRSS, HAQ-DI, visceral involvement, body weight, SF-36 score, and EQ-5D score in patients still alive at 2 years using area under the time-response curve (AUC). We tested whether data were missing at random by comparing baseline characteristics between patients with missing values (cases with missings) and without missing values (complete cases) during the first 2 years in 2 scenarios: (1) inclusion of patients who died in the first 2 years of follow-up and (2) exclusion of nonsurvivors. Some baseline characteristics were statistically significantly different between complete cases and cases with missings when nonsurvivors were included in the analysis. Although there were no statistically significant differences between complete cases and cases with missings when nonsurvivors were excluded, for some parameters the *P* value was slightly greater than .05. We concluded that data were not missing at random. We therefore used the nearest observation in time for patients who survived the first 2 years or the poorest possible values when data were missing because of death. Areas under the curve were compared between the treatment groups by *t* test.

In a post hoc analysis, we used the Breslow-Day test for homogeneity of odds ratios to determine differences in the treatment effect across categories for subgroups of age (≤45 years, >45 years), sex, disease duration (<2 years, ≥2 years), smoking status (never smoked, ever smoked), pretrial use of cyclophosphamide, and baseline body weight (≤66.5 kg, >66.5 kg) at 2 years' follow-up.

Ninety-five percent confidence intervals were computed where appropriate, with *P* values less than .05 (2-sided) considered statistically significant. Binary variables were analyzed by the Fisher exact test. Statistical analyses were performed using STATA version 12.0 (StataCorp).

Results

Patients and Treatment

From March 2001 to October 2009, 156 patients underwent randomization in 29 centers (28 in Europe and 1 in Canada). Sev-

Table 1. Baseline Characteristics of Study Patients

Characteristic	All Patients (N = 156)	HSCT Group (n = 79)	Control Group (n = 77)
	No. (%)		
Age, mean (SD), y	43.8 (11.3)	44.2 (11.1)	43.3 (11.5)
Women	92 (59.0)	43 (54.4)	49 (63.6)
Ethnic origin			
White	125 (80.8)	63 (79.7)	62 (80.5)
North African	9 (5.1)	5 (6.3)	4 (5.2)
Asian	6 (3.8)	2 (2.5)	4 (5.2)
Middle Eastern	2 (1.3)	0	2 (2.6)
Other[a]	14 (9.0)	9 (11.4)	5 (6.5)
Time since diagnosis, mean (SD), y	1.4 (1.3)	1.4 (1.2)	1.5 (1.4)
Duration of skin involvement, mean (SD), y	1.7 (1.3)	1.7 (1.2)	1.7 (1.3)
Major organ involvement			
Lung	135 (86.5)	68 (86.1)	67 (87.0)
Kidney	5 (3.2)	3 (3.8)	2 (2.6)
Heart	13 (8.3)	6 (7.6)	7 (9.1)
None	16 (10.3)	8 (10.1)	8 (10.4)
Smoking status			
Current	23 (14.7)	10 (12.7)	13 (16.9)
Former	61 (39.1)	31 (39.2)	30 (39.0)
Never	72 (46.2)	38 (48.1)	34 (44.2)
Pretrial use of cyclophosphamide	34 (21.8)	17 (21.5)	17 (22.1)
Weight, mean (SD), kg[b]	68.6 (14.4)	71.5 (15.2)	65.6 (12.9)
Body mass index, mean (SD)[c]	23.8 (4.1)	24.7 (4.1)	22.9 (4.0)
Modified Rodnan skin score, mean (SD)[d]	25.3 (8.0)	24.8 (8.1)	25.8 (7.9)
Creatinine clearance, mean (SD), mL/min[e]	76.7 (25.9)	76.8 (26.1)	76.5 (26.0)
Cardiac			
Abnormal electrocardiogram[f]	24 (16.0)	10 (13.2) [n = 76]	14 (18.9) [n = 74]
Pericardial effusion	12 (7.8)[g]	4 (5.1) [n = 78]	8 (10.5) [n = 76]
LVEF (%) by cardiac echocardiography, mean (SD)	65.6 (7.6)	65.6 (7.5) [n = 70]	65.7 (7.8) [n = 67]
Lung			
Abnormal thoracic computed tomography[h]	125 (83.3)	66 (86.8) [n = 76]	59 (79.7) [n = 74]
Forced vital capacity, mean (SD), % predicted	81.4 (18.4)	81.7 (19.3)	81.1 (17.6)
Total lung capacity, mean (SD). % predicted	80.7 (16.6)	81.0 (17.1) [n = 75]	80.5 (16.2) [n = 75]
Residual volume, mean (SD), % predicted	90.1 (30.3)	90.4 (30.1) [n = 71]	89.9 (30.6) [n = 71]
DLCO mean (SD), % predicted	58.5 (14.1)	59.3 (14.3) [n = 79]	57.7 (14.0) [n = 76]
Pulmonary arterial hypertension[i]	10 (6.6)	4 (5.2) [n = 77]	6 (8.1) [n = 74]
HAQ-DI, mean (SD)[j]	1.35 (0.80)	1.25 (0.74) [n = 68]	1.44 (0.84) [n = 73]
SF-36, mean (SD)[k]		[n = 59]	[n = 66]
Physical component	32.2 (10.0)	32.2 (10.4)	32.2 (9.6)
Mental component	42.0 (11.4)	41.2 (10.7)	42.6 (12.0)
EQ-5D, mean (SD)[l]		[n = 65]	[n = 73]
Index-based utility score	0.47 (0.32)	0.46 (0.32)	0.47 (0.32)
VAS score	51.9 (21.5)	53.4 (22.1)	50.7 (21.1)
Antinuclear antibody positive	150 (95.1)	75 (94.9)	75 (97.4)
Antitopoisomerase antibody positive[m]	114 (73.5)	52 (66.7)	62 (80.5)

Abbreviations: DLCO, diffusion capacity of the lung for carbon monoxide; HAQ-DI, health assessment questionnaire disability index; HSCT, hematopoietic stem cell transplantation; LVEF, left ventricular ejection fraction; SF-36, 36-Item Short Form General Health Survey; VAS, visual analog scale.

[a] Included the West Indies (8 patients), South America (4 patients), and mixed (2 patients).

[b] Weight differed significantly between groups ($P = .01$).

[c] Calculated as weight in kilograms divided by height in meters squared. Index differed significantly between groups ($P = .007$).

[d] Scores can range from 0-51, with higher scores indicating more severe skin thickening.

[e] Estimated using the Cockcroft-Gault formula.

[f] Defined as presence of atrial or ventricular rhythm disturbances such as recurrent episodes of atrial fibrillation or flutter, recurrent atrial paroxysmal tachycardia or ventricular tachycardia, second- or third-degree AV block, or diffuse microvoltage or repolarisation abnormalities related to pericardial effusion, whereas non–scleroderma-related causes were excluded.

[g] All 12 patients had moderate pericardial effusion as assessed by echocardiography.

[h] Defined as interstitial lung disease on HR-CT scan, whereas other causes of clinically relevant obstructive disease and emphysema were excluded

[i] Defined as a mean pulmonary artery pressure greater than 25 mm Hg and less than 50 mm Hg, measured by cardiac echocardiography or catheterization of the right side of the heart.

[j] Scores can range from 1 to 3, with lower scores indicating less disability.

[k] Scores can range from 0-100, with higher scores indicating better health status.

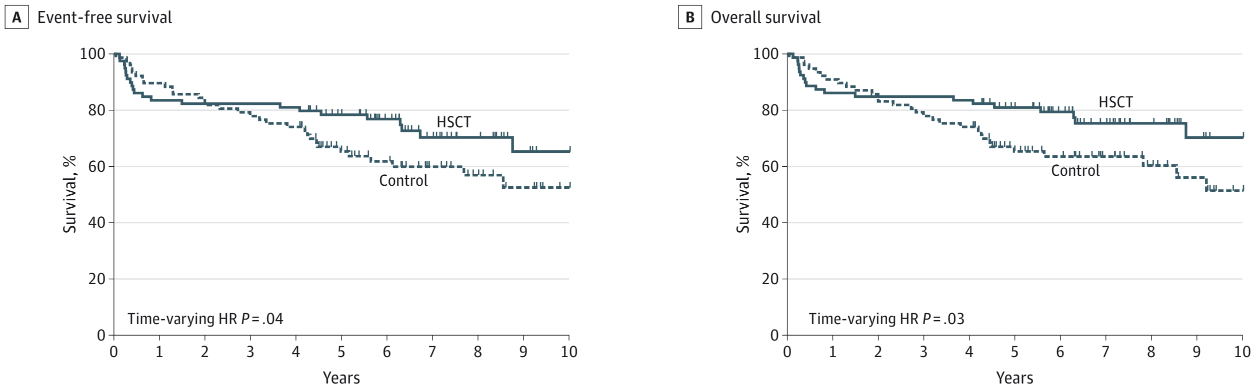
[l] Typically interpreted along a continuum in which 1 represents best possible health and 0 represents dead. VAS scores range from 0 (worst imaginable health state) to 100 (best imaginable health state).

[m] Data were available for 155 patients.

enty-nine patients were randomized to HSCT and 77 were randomized to cyclophosphamide (Figure 1). The number of individuals screened and excluded was not available for all centers. Baseline characteristics of the patients were similar between the 2 groups (**Table 1**).

Seventy-five patients in each group started treatment. Six patients did not receive the allocated treatment, whereas 71 (89.8%) and 57 (74.0%) completed treatment in the HSCT and cyclophosphamide groups, respectively (Figure 1). All 156 patients were included in the ITT population. The median

Figure 2. Event-Free and Overall Survival During 10-Year Follow-up



A

No. at risk	0	1	2	3	4	5	6	7	8	9	10
HSCT	79	66	65	65	64	53	41	29	21	13	10
Control	77	69	63	60	57	40	33	23	17	11	6

B

No. at risk	0	1	2	3	4	5	6	7	8	9	10
HSCT	79	68	67	67	66	55	43	32	23	14	11
Control	77	70	64	60	57	40	34	25	18	12	6

Hazard ratios (HRs) and 95% CIs were calculated by Cox regression. Hazard ratios were time-varying. The hazard (slope of the survival curve) in the hematopoietic stem cell transplantation (HSCT) group is initially high because of treatment-related mortality but gradually improves. At 1-year follow-up, the HR already favors the HSCT group, which leads to the crossing of the survival curves at 2 years' follow-up. A, Three-month follow-up: HR, 2.01 (95% CI, 0.74-5.49); *P* = .17; 6-month follow-up: HR, 1.35 (95% CI, 0.62-2.96); *P* = .45; 1-year follow-up: HR, 0.52 (95% CI, 0.28-0.96); *P* = .04; 2-year follow-up: HR, 0.35 (95% CI, 0.16-0.74); *P* = .006; 3- through 10-year follow-up: HR, 0.34 (95% CI, 0.16-0.74); *P* = .006. B, Three-month follow-up: HR, 2.40 (95% CI, 0.75-7.67); *P* = .14; 6-month follow-up: HR, 1.50 (95% CI, 0.61-3.68); *P* = .38; 1-year follow-up: HR, 0.48 (95% CI, 0.25-0.91; *P* = .02; 2-year follow-up: HR, 0.29 (95% CI, 0.13-0.65); *P* = .002; 3- through 10-year follow-up: HR, 0.29 (95% CI, 0.13-0.64); *P* = .002.

follow-up of event-free survival of the ITT populations was 5.8 years (interquartile range, 4.1-7.8). Treatment-specific details are provided in eTable 1A and eTable 1B in the Supplement.

Primary End Point

A total of 53 events occurred during the study: 22 in the HSCT group (19 deaths and 3 irreversible organ failures; 8 patients died of treatment-related causes in the first year, 9 of disease progression, 1 of cerebrovascular disease, 1 of malignancy) and 31 in the control group (23 deaths and 8 irreversible organ failures [7 of these patients died later]; 19 patients died of disease progression, 4 of cardiovascular disease, 5 of malignancy, 2 of other causes) (eTable 2A and eTable 2B in the Supplement).

The hazard ratios for event-free survival and overall survival were time-varying (*P* = .04 and *P* = .03, respectively) (**Figure 2**). Patients treated with HSCT experienced more events in the first year but had better long-term event-free survival than those treated with cyclophosphamide. During the first year, there were 13 events (16.5%) in the HSCT group vs 8 (10.4%) in the control group (relative risk [RR], 1.59 [95% CI, 0.7-4.4]). After 2 years of follow-up there were 14 events (17.7%) in the HSCT group vs 14 (18.2%) in the control group (RR, 0.97 [95% CI, 0.5-2.0]). After 4 years of follow-up there were 15 events (19.0%) in HSCT group vs 20 (26.0%) in the control group (RR, 0.73 [95% CI, 0.4-1.3]). Corresponding time-varying hazard ratios for the primary outcome of death or major organ failure were 0.52 (95% CI, 0.28-0.96; *P* = .04) at 1-year follow-up; 0.35 (95% CI, 0.16-0.74; *P* = .006) at 2-year follow-up; and 0.34 (95% CI, 0.16-0.74; *P* = .006) at 4-year follow-up. Patients in the HCST group experienced higher mortality in the first year but had better long-term overall survival than those treated with cyclophosphamide. During year 1 there were 11 deaths (13.9%, including 8 treatment-related deaths) in the HSCT group vs 7 (9.1%, none treatment-related) in the control group (RR, 1.53 [95% CI, 0.4-5.4]). After year 2 of follow-up there were 12 deaths (15.2%) in the HSCT group vs 13 (16.9%) in the control group (RR, 0.90 [95% CI, 0.4-1.8]). After 4 years of follow-up there were 13 deaths (16.5%) in the HSCT group vs 20 (26.0%) in the control group (RR, 0.64 [95% CI, 0.3-1.1]). Corresponding time-varying HRs for mortality were 0.48 (95% CI, 0.25-0.91; *P* = .02) at 1-year follow-up, 0.29 (95% CI, 0.13-0.65; *P* = .002) at 2-year follow-up, and 0.29 (95% CI, 0.13 to 0.64; *P* = .002) at 4-year follow-up. The lower hazard ratios vs higher relative risks for event-free survival and overall survival at 1 year for the HSCT vs control group reflect a change in event rate in the HSCT group, because the majority of events are being observed in the first 6 months but the event rate in the HSCT group is already favorable at 1 year as compared with the relatively constant event rate in the control group.

No center effect was found, with 5 of 8 treatment-related deaths observed in 3 of the 4 most active autoimmune disease transplant centers in Europe.

Secondary End Points

The analysis of the AUC showed significant differences in the secondary outcome measures. Mean change from baseline until 2 years' follow-up in mRSS was significantly better in the HSCT group (−19.9) than in the control group (−8.8) (difference, 11.1 [95% CI, 7.3 to 15.0]; *P* < .001), as were mean changes in forced vital capacity (6.3% predicted vs −2.8% predicted; difference, −9.1 [95% CI, −14.7 to −2.5]; *P* = .004), total lung capacity (5.1% predicted vs −1.3% predicted; difference, −6.4 [95% CI, −11.9 to −0.9]; *P* = .02), HAQ-DI (−0.58 vs −0.19; difference, 0.39 [95% CI, 0. 0.51 to 0.73]; *P* = .02), the physical component score of the SF-36 (10.1 vs 4.0; difference, −6.1 [95% CI, −10.9 to −1.4]; *P* = .03), and the EQ-5D index-based utility score (0.31 vs 0.03; difference, −0.29 [95% CI, −0.45 to −0.12]; *P* < .001) whereas mean change in creatinine clear-

Table 2. Treatment Responses in Clinical Outcome Variables, Change in the Area Under the Time Response Curve From Baseline to 2 Years' Follow-up

Variable	AUC, Mean (SD) HSCT Group (n = 67)[a]	AUC, Mean (SD) Control Group (n = 64)[a]	Difference (95% CI)	*P* Value
Weight, kg	-0.7 (9.5)	-0.8 (9.6)	-0.2 (-3.5 to 3.1)	.91
Modified Rodnan skin score	-19.9 (10.2)	-8.8 (12.0)	11.1 (7.3 to 15.0)	<.001
Creatinine clearance, mL/min[b]	-12.1 (29.7)	-1.2 (24.1)	10.9 (1.5 to 20.3)	.02
LVEF, % by cardiac echocardiography	-2.2 (14.7)	-1.9 (13.8)	0.3 (-4.7 to 5.2)	.91
Forced vital capacity, % predicted	6.3 (18.3)	-2.8 (17.2)	-9.1 (-14.7 to -2.5)	.004
Total lung capacity, % predicted	5.1 (17.5)	-1.3 (13.9)	-6.4 (-11.9 to -0.9)	.02
Residual volume, % predicted	-4.8 (33.7)	-2.1 (26.9)	2.7 (-7.9 to 13.2)	.62
DLCO, % predicted	-4.7 (13.7)	-4.1 (17.6)	0.6 (-4.9 to 6.0)	.84
HAQ-DI	-0.58 (1.14)	-0.19 (0.79)	0.39 (0.51 to 0.73)	.02
SF-36 score				
Physical component	10.1 (15.8)	4.0 (11.2)	-6.1 (-10.9 to -1.4)	.01
Mental component	3.1 (16.0)	3.4 (17.1)	0.3 (-5.41 to 6.07)	.91
EQ-5D				
Index-based utility score	0.31 (0.50)	0.03 (0.44)	-0.29 (-0.45 to -0.12)	<.001
VAS score	16.9 (44.5)	10.2 (39.7)	-6.7 (-21.33 to 7.87)	.36

Abbreviations: AUC, area under the curve; DLCO, diffusion capacity of the lung for carbon monoxide; HAQ-DI, Health Assessment Questionnaire Disability Index; HSCT, hematopoietic stem cell transplantation; LVEF, left ventricular ejection fraction; SF-36, 36-item Short Form General Health Survey; VAS, visual analog scale.

[a] Sixty-seven patients in the HSCT group and 64 patients in the control group were still alive at 2 years after randomization and were included in the analysis per the intention-to-treat principle. If a clinical outcome value was missing, the nearest available observation (in time, previous or next observation) was used to impute the missing value. Increase in the modified Rodnan skin score and HAQ-DI indicates worsening. Increase in all other variables indicates improvement.

[b] Two patients in the HSCT group and 1 patient in the control group, all with renal failure, were excluded from the analysis. Creatinine clearance was estimated by using the Cockroft-Gault formula.

ance (mL/min) was significantly worse in the HSCT group (−12.1) than in the control group (−1.2) (difference, 10.9 [95% CI, 1.5-20.3]; *P* = .02) (**Table 2**). No statistically significant differences in left ventricular ejection fraction, residual volume, and the diffusion capacity of the lung for carbon monoxide were observed between the 2 groups.

These results were also confirmed by the sensitivity analysis, which showed similar point estimates of the effect size (differences in mean AUC) for all of the secondary end points; however, losing statistical significance for some end points because of the smaller number of patients in the analysis or using the poorest possible values (based on observed data in the whole trial population) when data were missing because of death (forced vital capacity, total lung capacity, HAQ-DI, and the physical component score of the SF-36) (eTable 3 in the Supplement). In the post hoc subgroup analysis, there were no statistically significant differences in the odds ratios of the treatment effect on the primary end point across categories of age, sex, disease duration, pretrial cyclophosphamide use, and baseline weight at 2 years' follow-up (*P* ≥ .26). However, there was significant heterogeneity in the treatment effect across categories of smoking status (*P* = .02) (eFigure 1 in the Supplement). Eight patients in the control group received rescue HSCT after 2 years, 1 of whom died from treatment-related acute myeloid leukemia despite allogeneic HSCT. Two patients in the HSCT group received rescue intravenous cyclophosphamide therapy after 2 years. A smaller number of patients in the HSCT group as compared with the control group received immunosuppressive medication between 12 and 24 months (15 [22.4%] vs 28 [43.8%], *P* = .02) (eTable 4 in the Supplement).

Eight deaths (10.1% of ITT population), including 1 during mobilization and 1 during conditioning in the HSCT group, were deemed treatment-related by the independent data monitoring committee vs none in the control group (*P* = .007). Causes of treatment-related deaths included EBV, lymphoma, heart failure, myocardial infarction, and acute respiratory distress syndrome (eTable 5 in the Supplement). Seven of 8 patients who died from treatment-related causes were current or former smokers. Five (2 in the HSCT group and 3 in the control group) of 10 patients with PAH died before the cutoff date. Grade 3 or 4 adverse events occurred in 51 patients (62.9%) in the HSCT group and 30 (37.0%) in the control group (*P* = .002) (**Table 3**). Viral infections were detected in 22 patients (27.8%) in the HSCT group vs 1 (1.3%) in the control group (*P* < .001). Except for 1 patient in the control group with a primary herpes simplex virus infection, all infections with cytomegalovirus (9), EBV (6), herpes simplex virus (11), varicella zoster virus (3), and hepatitis B virus (1) occurred in the HSCT group (eTable 6 in the Supplement). Three patients in the HSCT group had cytomegalovirus/herpes simplex virus co-infection. Two of the patients with EBV developed EBV-positive lymphoproliferative disorder: 1 was successfully treated with rituximab, the other presented with fulminant disease with fatal outcome. Five patients with CMV infection received oral or intravenous antiviral treatment.

Discussion

This phase 3 study demonstrated that autologous HSCT using high-dose cyclophosphamide, rbATG, and reinfusion of CD34-selected cells was associated with early treatment-related deaths but better long-term event-free survival (the primary outcome measure) and better overall survival at a median of 5.8 (interquar-

Table 3. Grade 3 and 4 Adverse Events in the First 2 Years of Follow-up

Adverse Event[a]	Patients, No. (%) HSCT Group (n = 79)	Patients, No. (%) Control Group (n = 77)	P Value[b]
Grade 3 or 4 adverse event, severe or life-threatening	51 (62.9)	30 (37.0)	.002
Any grade 3 adverse event	38 (48.1)	20 (26.0)	.005
Any grade 4 adverse event	29 (36.7)	21 (27.3)	.23
Adverse event with a fatal outcome	12 (15.2)	13 (16.9)	.83
Adverse event of grade 3-4			
Respiratory	15 (19.0)	6 (7.8)	.06
Cardiovascular	13 (16.5)	8 (10.4)	.35
Gastrointestinal	10 (12.7)	11 (14.3)	.82
Hematologic	10 (12.7)	1 (1.3)	.009
Renal	8 (10.1)	4 (5.2)	.37
Infection	8 (10.1)	4 (5.2)	.37
Neurologic	5 (6.3)	1 (1.3)	.21
Fever	5 (6.3)	0	.06
Musculoskeletal	3 (3.8)	2 (2.6)	>.99
Cancer	0	3 (3.9)	.12
Allergy/hypersensitivity	3 (3.8)	0	.24
Urogenital	0	2 (2.6)	.24
Sarcoidosis	1 (1.3)	0	>.99
Flushing	0	1 (1.3)	.49
Psychiatric	0	1 (1.3)	.49

Abbreviation: HSCT, hematopoietic stem cell transplantation.

[a] All grade 3 and 4 (severe and life-threatening) adverse event data are included. Severity for each adverse event, including any laboratory abnormality, was determined by using the World Health Organization Common Toxicity Parameters, wherever possible. In those cases in which these criteria did not apply, a severe adverse event was defined as one causing inability to perform normal daily activities, and a life-threatening event as one posing immediate risk of death from the reaction as it occurred.

[b] *P* values were calculated by Fisher exact test.

tile range, 4.1-7.8) years' follow-up compared with intravenous pulse cyclophosphamide for patients with diffuse cutaneous systemic sclerosis. The long-term survival benefit of HSCT was particularly striking in those who had never smoked. Smoking has been shown to be associated with more severe systemic sclerosis and has been shown to influence the outcome after allogeneic HSCT in malignant diseases, in part through effects on pretransplant lung function.[18-20]

HSCT was also more effective than intravenous pulse cyclophosphamide for the outcomes of skin score, functional ability, quality of life, and lung function, consistent with previous studies.[4-11] HSCT was associated with more grade 3 and 4 adverse events including respiratory distress, possibly due to rbATG and 10.1% treatment-related mortality, viral infections, and a modest decrease in creatinine clearance. The latter may be attributable to the nephrotoxic effects of medication used during conditioning (glucocorticoids, cyclophosphamide, rbATG). Of note, treatment-related mortality decreased from 17% in the first phase 1-2 multicenter study to 6% to 8.7% in 2 registry analyses of HSCT in autoimmune diseases that also reported evidence of a center effect.[4,9,21,22] We did not find a center effect, but 7 of 8 treatment-related deaths occurred in current or former smokers. A recent retrospective study suggested that catheterization of the right side of the heart with fluid challenge and cardiac magnetic resonance imaging may identify patients at risk of treatment-related mortality.[9] Another recent study demonstrated the clinical utility of left heart catheterization in addition to catheterization of the right side of the heart with fluid challenge by showing a high prevalence of left ventricular dysfunction in patients suspected of having PAH.[23] Three of 8 treatment-related deaths in our study were attributed to a primary cardiac cause. To balance the potential risks of HSCT, our trial deliberately targeted patients with severe systemic sclerosis, including 10 patients with PAH, 5 of whom died. A key problem in the management of systemic sclerosis is to identify patients at risk of disease progression and strike the right balance between the long-term benefits and upfront risks, including treatment-related mortality of an intensive treatment modality such as HSCT as opposed to standard immunosuppression currently recommended.[24] Disease characteristics recently associated with premature mortality may be used to identify patients suitable for HSCT.[25,26]

Our study has limitations. First, wide confidence intervals for some secondary outcome measures are indicative of less certainty about results for these outcomes. Second, the unblinded assessments may have influenced our results. Third, the drop-out rate in the cyclophosphamide group was greater than 20% because of death, major organ failure, adverse events, or nonadherence.

Conclusions

Among patients with early diffuse cutaneous systemic sclerosis, HSCT was more effective than monthly intravenous pulse cyclophosphamide and, despite an early treatment-related mortality rate of 10.1% and an increase in serious adverse events, conferred a long-term survival benefit.

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