Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial

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Lancet 2011; 378: 498–506

Published Online July 20, 2011 DOI:10.1016/S0140-6736(11)60982-3

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Summary

Background Non-randomised studies of haemopoietic stem-cell transplantation (HSCT) in systemic sclerosis have shown improvements in lung function and skin flexibility but high treatment-related mortality. We aimed to assess safety and efficacy of autologous non-myeloablative HSCT in a phase 2 trial compared with the standard of care, cyclophosphamide.

Methods In our open-label, randomised, controlled phase 2 trial, we consecutively enrolled patients at Northwestern Memorial Hospital (Chicago, IL, USA) who were aged younger than 60 years with diffuse systemic sclerosis, modified Rodnan skin scores (mRSS) of more than 14, and internal organ involvement or restricted skin involvement (mRSS <14) but coexistent pulmonary involvement. We randomly allocated patients 1:1 by use of a computer-generated sequence with a mixed block design (blocks of ten and four) to receive HSCT, 200 mg/kg intravenous cyclophosphamide, and 6·5 mg/kg intravenous rabbit antithymocyte globulin or to receive 1·0 g/m² intravenous cyclophosphamide once per month for 6 months. The primary outcome for all enrolled patients was improvement at 12 months' follow-up, defined as a decrease in mRSS (>25% for those with initial mRSS >14) or an increase in forced vital capacity by more than 10%. Patients in the control group with disease progression (>25% increase in mRSS or decrease of >10% in forced vital capacity) despite treatment with cyclophosphamide could switch to HSCT 12 months after enrolment. This study is registered with ClinicalTrials.gov, number NCT00278525.

Findings Between Jan 18, 2006, and Nov 10, 2009 we enrolled 19 patients. All ten patients randomly allocated to receive HSCT improved at or before 12 months' follow-up, compared with none of nine allocated to cyclophosphamide (odds ratio 110, 95% CI 14·04–∞; p=0·00001). Eight of nine controls had disease progression (without interval improvement) compared with no patients treated by HSCT (p=0·0001), and seven patients switched to HSCT. Compared with baseline, data for 11 patients with follow-up to 2 years after HSCT suggested that improvements in mRSS (p<0·0001) and forced vital capacity (p<0·03) persisted.

Interpretation Non-myeloablative autologous HSCT improves skin and pulmonary function in patients with systemic sclerosis for up to 2 years and is preferable to the current standard of care, but longer follow-up is needed.

Funding None.

Introduction

Systemic sclerosis is a chronic disease that starts as a diffuse vasculopathy, followed by immune activation and subsequent tissue fibrosis.[1] Haemopoietic stem-cell transplantation (HSCT) is a potential treatment for systemic sclerosis[2–8] and relies on early intervention during immune activation. However, there have been no randomised trials published about outcomes of such transplantation for autoimmune diseases in general or systemic sclerosis in particular. Previous studies of HSCT for systemic sclerosis showed significant improvements in skin flexibility, as measured by modified Rodnan skin score (mRSS),[9] and two small non-randomised studies suggested that HSCT improves lung function.[10,11] However, positive efficacy outcomes were tempered by initial reports of high treatment-related mortality, albeit which diminished with increased experience, and absence of a randomised control group.[12] In our phase 2 American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST), we aimed to assess safety and efficacy of autologous non-myeloablative HSCT compared with a control group who received one dose of intravenous cyclophosphamide every month for 6 months.

Methods

Study design and patients

In our randomised phase 2 trial, we screened consecutive patients at Northwestern Memorial Hospital (Chicago, IL, USA). Patients were eligible if they were aged younger than 60 years and had diffuse systemic sclerosis (defined as cutaneous involvement proximal to the elbow or knee

with an mRSS of more than 14), and internal-organ involvement, which was defined as at least one of the following features: diffusing capacity of carbon monoxide (DLCO) of less than 80% or decline in forced vital capacity by 10% or more in the previous 12 months; pulmonary fibrosis or ground-glass appearance on high-resolution chest CT; abnormal electrocardiogram (ECG); or gastrointestinal tract involvement. Patients with restricted skin involvement (mRSS <14) were eligible only if they had coexistent pulmonary involvement.

We excluded patients if they had received more than six previous intravenous injections of cyclophosphamide, a total lung capacity of less than 45% of predicted volume, a left ventricular ejection fraction of less than 40%, symptomatic cardiac disease, duration of systemic sclerosis of more than 4 years from diagnosis, HIV-positive status, positivity for hepatitis B surface antigen, renal insufficiency (creatinine >177 µmol/L), pregnancy, tricuspid annular plane systolic excursion[13] of less than 1·8 cm, pulmonary artery systolic pressure of more than 40 mm Hg, or mean pulmonary artery pressure of more than 25 mm Hg. The trial was approved by Institutional Review Board of Northwestern University (Chicago) and the US Food and Drug Administration under investigational new drug number 11747. All patients provided written informed consent.

Randomisation and masking

One investigator (BJ) randomly allocated patients in a one-to-one ratio to receive HSCT or cyclophosphamide by use of a computer-generated randomisation sequence with a mixed block design, with initial blocks of ten and subsequent block size of four.

Procedures

We undertook physical examinations, took histories of patients, and assessed mRSS,[9] pulmonary function, high-resolution chest CT, anti-nuclear antibodies, Scl-70

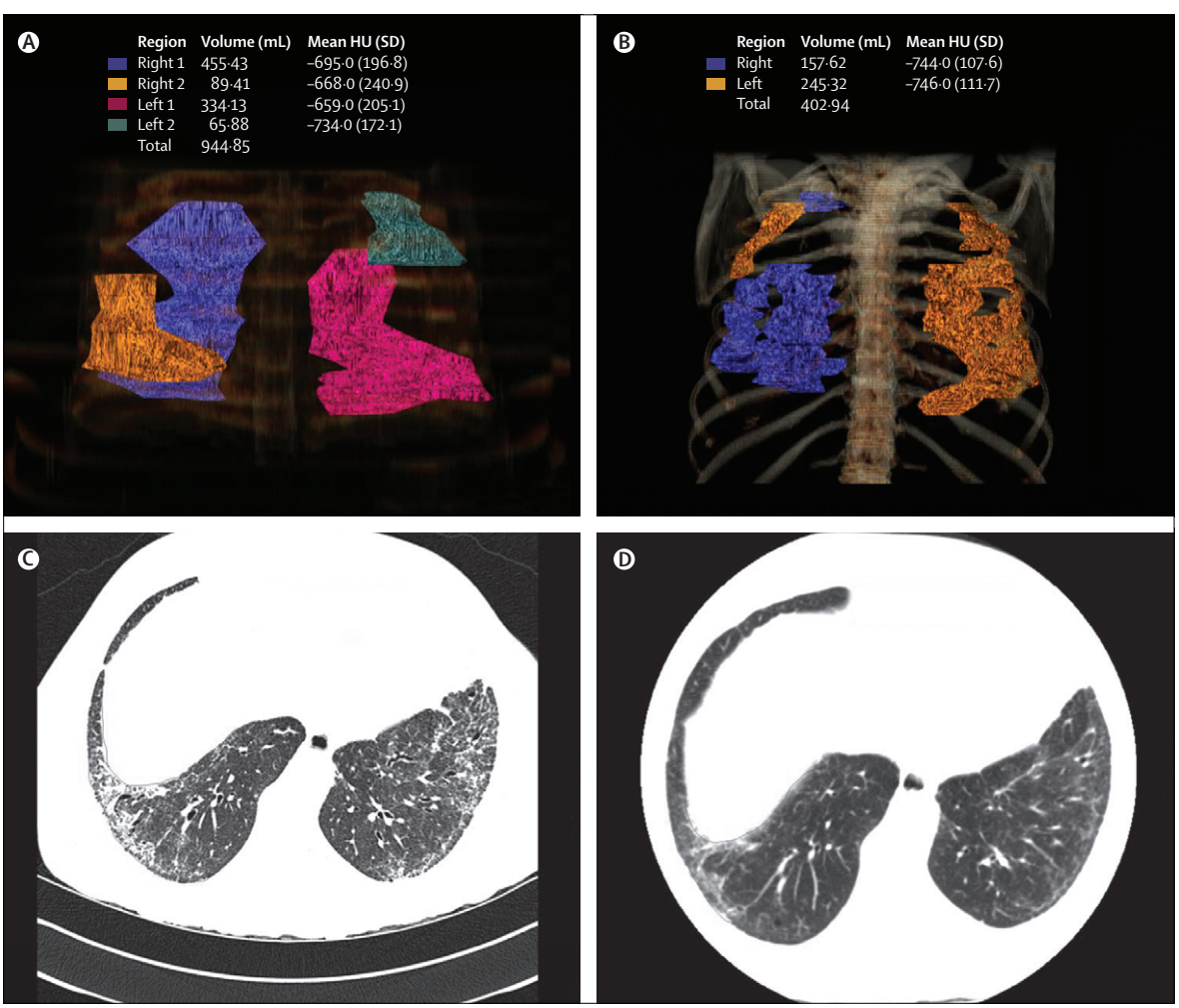

Figure 1: **Computer-generated measurement of diseased lung volumes before haemopoetic stem-cell transplantation and 2 years after transplantation**
Total volume of diseased lung of a patient before transplantation (A) and 2 years after transplantation (B), generated from individual 1 mm thick lung windows (before [C] and after [D]). HU=Hounsfield units.

	Haemopoietic stem-cell transplantation (n=10)	Control (n=9)
Age (years)	45 (32–58)	44 (26–54)
Sex (female)	9	8
Ethnicity		
White	7	8
Hispanic	1	0
Black	2	1
Disease duration from diagnosis (months)	13·6 (2–33)	18 (6–36)
History of Raynaud's	9	9
Modified Rodnan skin score	28 (6–48)	19 (4–45)
Systemic sclerosis		
Diffuse	8	7
Limited (with lung involvement)	2	2
Gastrointestinal		
Gastrointestinal reflux disease	10	9
Patulous (gaping) oesophagus	6	5
Small bowel involvement	1	0
Lung		
Forced vital capacity	62% (53–70)	67% (43–84)
Diffusing capacity of CO_2 corrected	58% (29–82)	75% (29–111)
Involvement on high-resolution chest tomography	7	8
Non-specific interstitial pneumonia	6	8
Usual interstitial pneumonia	1	0
Bronchiectasis	1	0
Honeycombing	1	0
Nodules or micronodules	0	3
Cardiac		
Abnormal electrocardiogram	8	2
Tricuspid annular plane systolic excursion (cm)	2·24 (NA)	2·42 (NA)
Cardiac catheterisation		
Pulmonary artery systolic pressure (mm Hg)	29 (4·5)	28 (6·9)
Mean pulmonary artery pressure (mm Hg)	20 (4·0)	19 (4·8)
Pulmonary capillary wedge pressure (mm Hg)	10 (4·8)	13 (5·2)
Pulmonary vascular resistance (dynes/s per cm^{-5})	137 (44)	97 (37)
Previous renal crisis	0	0
Serology (positive)		
Anti-nuclear antibody positive	10	9
Scl-70 positive	5	7
Previous systemic sclerosis medications*		
Prednisone	6	3
Methotrexate	2	4
D-penicillamine	1	1
Intravenous cyclophosphamide	1	3†
Mycophenolate mofetil	3	3
Other	1 total parenteral nutrition, 1 imatinib, and 2 minocycline	2 hydroxychloroquine, 3 leflunomide, and adalimumab

Data are n or mean (range or SD). NA=not available. *Not including supportive-care drugs such as proton-pump inhibitors, calcium-channel blockers, angiotension-converting-enzyme inhibitors, pentoxifylline, or aspirin. †One patient received one dose, one patient received two doses, and one patient received three doses.

Table 1: **Characteristics of patients**

antibodies, electrolytes, creatinine, liver-function, SF-36 quality of life, cardiology consultation, right heart catheterisation, ECG, and echocardiogram values with tricuspid annular plane systolic excursion.

Patients were randomly allocated to receive HSCT or six cycles of intravenous cyclophosphamide (1·0 g/m² per month; control group). Disease improvement was defined as at least a 25% decrease in mRSS for patients with an initial score of more than 14 or a greater than 10% increase in forced vital capacity (independent of enrolment score). Disease progression was defined as increase in mRSS of at least 25% in patients with an enrolment score of more than 14 or a decrease in forced vital capacity by 10% in any patient.

Peripheral blood stem cells were mobilised with intravenous cyclophosphamide (2 g/m²) and 10 μg/kg subcutaneous filgrastim from day 5 after cyclophosphamide administration until apheresis and cryopreserved without manipulation. There was an interval of at least 2 weeks between mobilisation of the peripheral blood stem cells and start of the conditioning regimen. The conditioning regimen was 200 mg/kg intravenous cyclophosphamide given in four equal fractions on day –5 to day –2 before stem-cell infusion, along with intravenous mesna, continuous bladder irrigation, and diuresis with mild hydration (50–100 mL/h normal saline). Intravenous rabbit anti-thymocyte globulin (Thymoglobulin, Genzyme, Cambridge, MA, USA) was dosed at 0·5 mg/kg on day –5 before stem-cell infusion and then intravenously injected 1·5 mg/kg from –4 days to –1 day before stem-cell infusion. Methylprednisolone 1000 mg was infused intravenously before every dose of rabbit anti-thymocyte globulin. Supportive care included oral lisinopril (2·5–10·0 mg per day), subcutaneous filgrastim 10 μg/kg per day from 5 days after stem-cell infusion until engraftment, irradiated, leucocyte-depleted, and cytomegalovirus-safe blood products, antimicrobial prophylaxis with intravenous piperacillin-tazobactam or cefepime, and oral or intravenous aciclovir and fluconazole. After engraftment, aciclovir was continued for 12 months and fluconazole was continued for 6 months, and oral trimethoprim-sulfamethoxazole three times a week or nebulised pentamidine inhaled once a month was used for prophylaxis of *Pneumocystis jirovecii* for 6 months. For patients in the control group, intravenous cyclophosphamide was dosed at 1·0 g/m² for 1 h once per month along with normal saline hydration and mesna for 6 months.

The volume of pulmonary disease on high-resolution chest CT was measured with postprocessing computer-aided volumetric software (Vitrea 5.2, Vital Images, Minnetonka, MN, USA) on a peripheral workstation.[14,15] Two experienced observers (KD and KM) manually traced regions of lung (–750 to –650 Hounsfield units [HU]) that showed abnormality and volumes (in mL) of involved lung for every examination (figure 1). Pulmonary function

testing and calculation of rate of change in vital capacity was done as previously described.[16,17] DLCO was corrected for haemoglobin with the Stanford School of Medicine DLCO calculator.

After 1 year, patients who had not responded to cyclophosphamide treatment were allowed, if they chose and had no contraindication, to switch treatment to HSCT.

Statistical analysis

We designed the ASSIST trial to enrol 60 patients on the basis of an assumption of 60% mortality at 5 years with cyclophosphamide, reduced to 25% with transplantation, with a two-sided test and 80% power. Because previous studies showed that disease progression continues with standard care (ie, cyclophosphamide),[18] and because diffuse systemic sclerosis (especially with lung disease) has a disease-related mortality of 5–12% per year,[1] we included stopping rules for significant difference in disease progression between groups with interim analysis at around 25%, 50%, and 75% of patients enrolled.

The Fisher's exact test was used for analysis of improvement and progression. We used a two-tailed unpaired *t* test for comparison between transplantation and control groups and a paired *t* test for comparisons within the transplantation group. Microsoft Excel was used for all analyses.

This study is registered with ClinicalTrials.gov, number NCT00278525.

Role of funding source

There was no funding source for this study. The statistician (BJ), corresponding author (RKB), and research fellow (SJ) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 19 patients between Jan 18, 2006, and Nov 10, 2009 (table 1, figure 2). No deaths occurred in either treatment group during follow-up. For patients treated with HSCT, engraftment of white blood cells (absolute neutrophil count >500 cells per μL) occurred at a mean of 10 days (SD 1·4) and platelets (transfusion independent >20 000 cells per μL) occurred at a mean of 11 days (2·4). Patients received a mean of 5·3 units (5·5) of single donor platelet transfusion and 4·4 units (2·3) of packed red blood cells, and mean time to hospital discharge was 13 days (3·8). During hospitalisation for transplantation, one patient had a positive stool culture for *Clostridium difficile*, one patient had a positive blood culture for micrococcus, two patients developed arrhythmias (supraventricular tachycardia and atrial fibrillation) that were controlled with oral medications, and two patients developed volume overload that was controlled with diuretics. The only late infectious event was a cytomegalovirus reactivation on surveillance blood test in one patient, which was treated with oral vanganciclovir. 3 months after HSCT, one patient who had a pretransplantation history of supraventricular tachycardia underwent an atrial tachycardia ablation procedure with an uneventful recovery. One patient in the control group developed cellulitis that was treated with oral antibiotics, and two needed protracted outpatient treatment for nausea, vomiting, and diarrhoea.

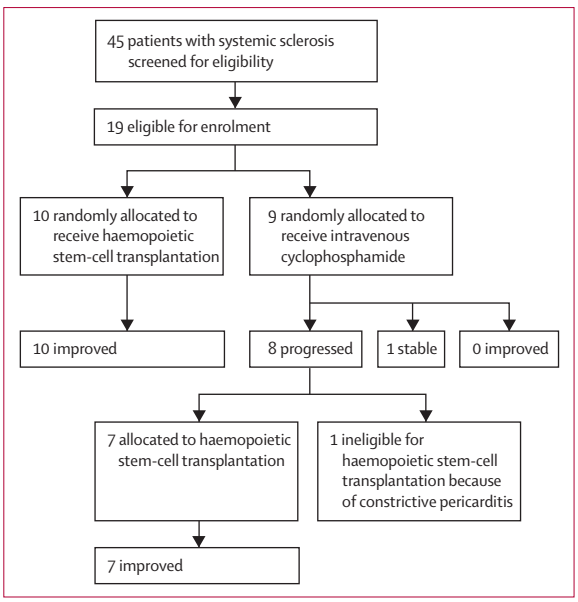

Figure 2: **Trial profile**

All ten patients who were randomly allocated to receive HSCT improved within the first 12 months compared with none of nine controls (odds ratio 110, 95% CI 14·04–∞; p=0·00001). Treatment failure (ie, disease progression without interval improvement), occurred in eight of nine controls compared with none of ten patients treated by HSCT (p=0·0001).

After long-term follow-up (mean 2·6 years) of patients who underwent transplantation, all but two patients randomly allocated to receive HSCT had sustained improvement in mRSS and forced vital capacity with a longest follow-up of 60 months. After an initial post-transplantation improvement, one patient developed hypertensive renal crisis accompanied by disease progression in skin and lung after treatment with erythropoietin administered by a community doctor for iron-deficient anaemia. A second patient who received a transplant subsequently developed a dichotomous response with ongoing improvement in mRSS but deterioration in forced vital capacity.

Seven patients randomly allocated to receive cyclophosphamide switched treatment groups at a mean of 14 months after enrolment and underwent HSCT without complications. One patient progressed but was declined a transplant after development of a medical contraindication (constrictive pericarditis). One patient

For the **DLCO calculator** see http://bmt.stanford.edu/calculators/dlco.html

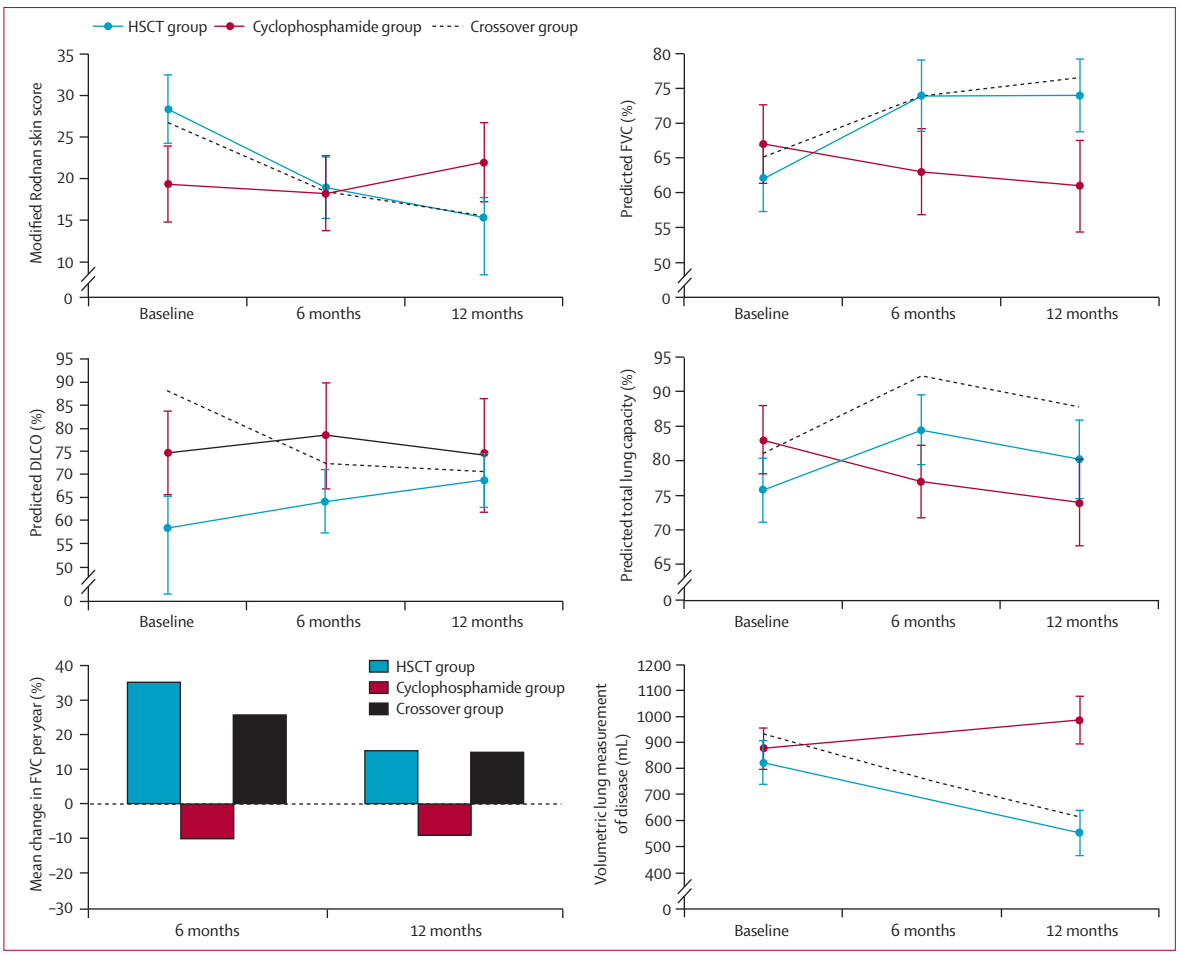

Figure 3: **1-year follow-up for patients receiving haemopoetic stem-cell transplantations, monthly cyclophosphamide, or transplantation after failure of cyclophosphamide**

HSCT=haemopoietic stem-cell transplantation. FVC=forced vital capacity. DLCO=diffusing capacity of carbon monoxide.

did not improve or decline after 2 years of follow-up and has not been offered the option to switch treatment groups. All seven patients who progressed on cyclophosphamide and then switched to HSCT subsequently improved (figure 3).

By 1 year after start of treatment, the mean mRSS increased in controls and decreased in patients receiving a transplant (table 2, figure 3). Mean predicted forced vital capacity and total lung capacity declined for controls, whereas both increased for patients receiving HSCT (table 2). DLCO did not differ between groups (table 2). In patients undergoing HSCT compared with controls, the rate of change from pretreatment forced vital capacity was 34% compared with –10% at 6 months (p=0·002) and 15% compared with –9% at 12 months (p=0·006). 1 year after start of treatment, high-resolution chest CT volumetric measurement of lung disease decreased after HSCT but increased in controls (table 2).

Patients in the control group whose disease progressed and were at least 1 year after start of treatment were allowed to switch to transplantation. Seven patients who did not respond to cyclophosphamide switched to HSCT; four have been followed-up for at least 1 year. In these patients, the mean mRSS decreased from 27 (SD 15·5) to 15 (7·4) points, forced vital capacity increased from 65% (20·6) to 76% (26·5), total lung capacity increased from 81% (14·0) to 88% (13·9), and measurements of disease-involved lung decreased from 934 mL (223·7) to 614 mL (296·8). The rate of improvement in forced vital capacity was 26% at 6 months and 14% at 12 months.

At 2-year follow-up, one patient treated with cyclophosphamide did not progress and had no significant change in mRSS or forced vital capacity. Overall, of 17 patients treated with HSCT, 14 have at least 1 year of follow-up after transplantation (11 for ≥24 months, four for ≥36 months, and two for 48–60 months). At 24 months after transplantation there was significant improvement in modified Rodnan skin, predicted forced vital capacity, and high-resolution chest CT volumetric measurement of involved lung (table 2, figure 4). Total lung capacity and DLCO did not differ between baseline and 2 years

	Before switch to transplantation					After switch to transplantation			
	Cyclophosphamide group (n=9)		Transplant group (n=10)		p value	All transplants			p value at 24 months
	Baseline	1 year	Baseline	1 year		Baseline (n=15)*	12 months (n=14)	24 months (n=11)	
Predicted forced vital capacity (%)									
Mean (SD)	67% (17·0)	61% (19·8)	62% (15·0)	74% (15·7)	0·004	62% (16·4)	75% (18·5)	74% (19·8)	0·029
Median (range)	78% (43–84)	69% (35–83)	62% (36–85)	82% (52–96)	..	63% (35–85)	82% (43–107)	72% (43–103)	..
Rate of change (%)†	..	–9%	..	15%	0·006	..	15%	10%	NA
Predicted total lung capacity (%)									
Mean (SD)	83% (14·8)	74% (18·7)	76% (14·6)	80% (17·9)	0·005	77% (14·1)	83% (16·6)	82% (17·9)	0·14
Median (range)	89% (59–99)	69% (45–95)	73% (57–102)	72% (62–104)	..	76% (57–102)	80% (62–104)	78% (56–108)	..
Predicted DLCO corrected for haemoglobin (%)									
Mean (SD)	75% (27·5)	74% (37·0)	58% (21·8)	69% (18·6)	0·36	68% (31·0)	68% (19·1)	64% (19·8)	0·82
Median (range)	80% (29–111)	73% (28–120)	58% (29–94)	67% (33–90)	..	67% (29–136)	68% (33–90)	65% (33–90)	..
Volume diseased lung (mL)‡									
Mean (SD)	877 (240·6)	985 (277·1)	823 (268·9)	551 (277·1)	0·001	840 (250·9)	567 (271·0)	499 (293·9)	0·003
Median (range)	961 (462–1195)	858 (808–1189)	850 (359–1095)	546 (240–1118)	..	854 (359–1189)	510 (240–1118)	469 (208–924)	..
Modified Rodnan skin score									
Mean (SD)	19 (13·7)	22 (14·2)	28 (13·6)	15 (7·9)	0·0004	29 (13·7)	15 (7·4)	12 (8·4)	0·0001
Median (range)	16 (6–45)	22 (3–44)	30 (6–47)	16 (2–29)	..	30 (3–47)	15 (2–26)	9 (2–23)	..

DLCO=diffusion capacity for carbon monoxide.*17 patients underwent haemopoietic stem-cell transplantation, two patients were awaiting first post-transplantation assessment, one patient was 6 months after transplantation, 14 were at least 12 months after transplantation, and 11 were at least 24 months after transplantation. †Rate of change in vital capacity = (forced vital capacity time 2 – forced vital capacity time 1) / forced vital capacity time 1 / (time 2 – time 1) × 100. ‡Volume of diseased lung parenchyma by high-resolution chest CT tomography.

Table 2: **Skin and pulmonary function results**

for all transplant recipients (p=0·82). The rate of change of forced vital capacity in these patients was 10% at 2 years.

Patients perceived their general health status to be significantly improved 1 year after HSCT and significantly worse 1 year after start of monthly cyclophosphamide (table 3). The total SF-36 score at 1 year after transplantation improved from 39 to 56 (p=0·004). By contrast, 1 year after the start of monthly cyclophosphamide therapy, the total SF-36 score declined from 50 to 40 (p=0·04). After failure of cyclophosphamide and switch to HSCT, after 1 year of follow-up, the total SF-36 score improved from 42 to 78 (p=0·04). For all patients who underwent transplantation, whether initially randomised to transplantation or cyclophosphamide, the long-term (mean 2·6 years) follow-up total SF-36 scores improved from 39 to 56 (p=0·009; table 3).

Discussion

In our study, non-myeloablative HSCT significantly improved forced vital capacity, decreased diseased-lung volume, and showed that systemic sclerosis interstitial lung disease might be at least partially reversed with continued improvement in lung function for at least 2 years after transplantation. The improvement that we noted in lung function after HSCT was associated with improved high-resolution chest CT, skin score, and quality of life. Non-myeloablative autologous HSCT is the first treatment shown to improve lung function in systemic sclerosis in a randomised trial. However, to minimise risk of treatment, HSCT needs to be offered early in the course of disease before onset of cardiac dysfunction and use a regimen that reduces risk of further lung injury. By comparison, intravenous cyclophosphamide given once per month to patients with systemic sclerosis for 6 months was associated with a continued decline in pulmonary function, an increase in disease-involved lung volume and skin scores, and decline in quality of life.

The standard of treatment for interstitial lung disease in scleroderma is cyclophosphamide. However, two randomised trials[19–21] did not show improvement in lung function with this treatment, and two meta-analyses[18,22] concluded that cyclophosphamide does not improve lung function. Several non-randomised trials[2–8] of HSCT have reported improvements in skin scores, and two small non-randomised studies[10,11] suggested that HSCT might improve lung function. To better establish the effect of HSCT on scleroderma, three randomised controlled investigations were undertaken: SCOT, ASTIS, and ASSIST (panel).

Toxic effects of HSCT (myeloablative or non-myeloablative), arise from selection of patients and the conditioning drugs used, rather than the infused autologous stem cells themselves. As we reported,[23,24] non-myeloablative autologous HSCTs are safer than are more toxic myeloablative regimens. Moreover, although stem-cell transplantation for leukaemia has been

For the **SCOT study** see http://www.sclerodermatrial.org

For the **ASTIS study** see http://www.astistrial.com

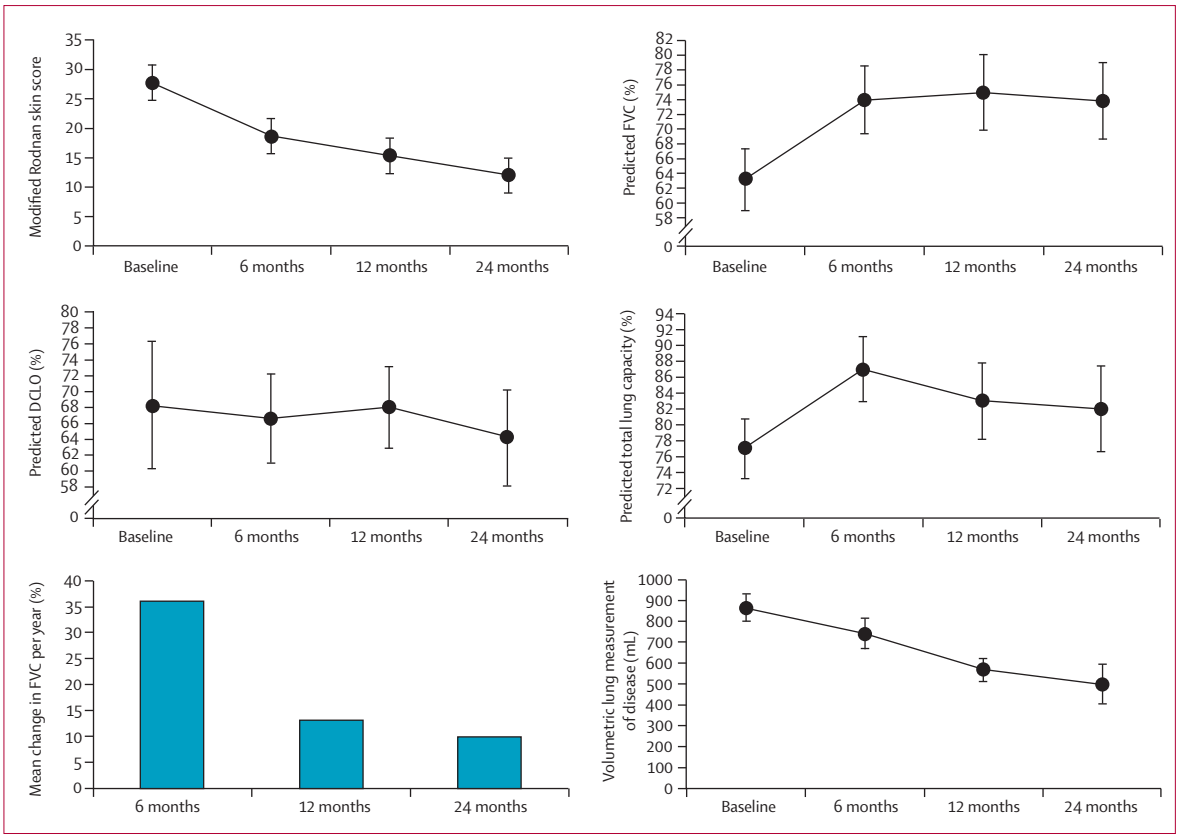

Figure 4: **2-year follow-up for all patients undergoing haemopoetic stem-cell transplantation**
Data are for all patients who underwent transplantation and had at least 1 year of follow-up. FVC=forced vital capacity. DLCO=diffusing capacity of carbon monoxide.

	Scale								Dimension		Total
	Physical function	Physical role limitation	Body pain	General heath perception	Vitality energy fatigue	Social function	Emotional role limitation	Mental health	Physical health	Mental health	SF-36 score
Before HSCT	28	17	34	38	33	38	59	64	30	46	39
1-year after HSCT	60	44	55	44	46	60	67	73	50	58	56
Difference (SD)	32 (29·62)	27 (38·88)	21 (23·00)	6 (27·38)	13 (21·48)	22 (31·46)	8 (45·57)	9 (15·72)	20 (22·10)	12 (21·01)	17 (20·59)
p value	0·002	0·095	0·023	0·662	0·079	0·078	0·707	0·118	0·007	0·076	0·003
Before cyclophosphamide	44	15	59	35	34	53	87	70	38	56	50
1-year after cyclophosphamide	37	22	53	12	36	41	46	75	32	42	40
Difference (SD)	7 (31·45)	7 (34·76)	−6 (21·77)	−23 (27·18)	2 (26·48)	−12 (28·32)	−41 (43·88)	5 (13·76)	−6 (22·01)	−14 (17·24)	−10 (18·03)
p value	0·347	0·451	0·570	0·182	0·853	0·387	0·028	0·305	0·317	0·043	0·042
Cyclophosphamide group before switch to HSCT	31	30	56	8	46	35	53	75	34	43	42
Cyclophosphamide group after switch to HSCT	67	80	85	67	72	85	87	85	74	79	78
Difference (SD)	36 (35·73)	50 (49·72)	29 (25·33)	59 (41·80)	26 (25·90)	50 (45·94)	34 (42·88)	10 (13·85)	40 (28·95)	36 (28·42)	36 (27·84)
p value	0·085	0·089	0·189	0·062	0·212	0·071	0·141	0·080	0·046	0·040	0·035
All patients before HSCT	28	17	34	38	33	37	59	64	30	46	39
Longest follow-up after HSCT	58	44	61	46	48	61	67	66	51	58	56
Difference (SD)	30 (29·66)	27 (38·87)	27 (24·50)	8 (23·97)	15 (22·11)	24 (29·85)	8 (42·60)	2 (16·03)	21 (22·05)	12 (20·11)	17 (20·45)
p value	0·008	0·095	0·002	0·510	0·038	0·036	0·664	0·650	0·007	0·086	0·009

Data are mean scores. HSCT=haemopoietic stem-cell transplantation.

Table 3: **Quality of life**

undertaken for more than 50 years, survival is still better in some centres than it is in others.[25] This centre effect is to be expected in the application of a new technology to a complex disease such as systemic sclerosis. Effects caused by different centres or doctors can affect survival of HSCT for autoimmune diseases.[26] Although our previous results should not be viewed as a deterrent to expansion of this therapy, they do suggest a cautious approach should be used, which is initially restricted to experienced centres that have an equivalent conditioning regimen to the one that we used in this trial.

Protocol-specific factors that were unique to this study might have contributed to our outcomes. In our study, the rate of improvement in forced vital capacity was most rapid within the first 6 months after transplantation. We did not use total body irradiation (as in the ongoing SCOT trial) because, apart from risk of leukaemia and late solid tumours, radiation might cause acute pneumonitis that could blunt the early post-transplantation rate of improvement in forced vital capacity. We also used a lower initial dose of intravenous rabbit anti-thymocyte globulin (0·5 mg/kg) and premedication with high-dose intravenous methylprednisolone (1·0 g) compared with the ongoing ASTIS trial to reduce first-infusion syndrome caused by cytokine release to a minimum, which could otherwise initiate further lung injury and pulmonary oedema.[27] Finally, to reduce transplantation risk in patients with systemic sclerosis, we advocate a careful and complete pretransplantation cardiac assessment beyond the usual assessment of left ventricular ejection fraction that is normally recommended before HSCT.[28,29]

In our study, the patients who were treated initially with cyclophosphamide but improved after transplantation might have improved as a result of the natural disease course of steady improvement without transplantation intervention. However, the Scleroderma Lung Study Group reported lung function declined after 1 and 2 years in patients receiving cyclophosphamide.[20,21] In our study, pulmonary function declined for 12 months in patients receiving cyclophosphamide, but unlike the Scleroderma Lung Study Group, reversed and improved after the switch to HSCT.

Patients with highest baseline skin scores might have had the best chance of improvement. In our study, patients with low skin scores and limited systemic sclerosis who were randomly allocated to receive HSCT had improved scores on pulmonary function tests, disease-free lung volumes, and quality of life whereas patients with limited systemic sclerosis who were randomly allocated to receive cyclophosphamide had steady deterioration in pulmonary function, disease-free lung volumes, and quality of life. Patients treated with cyclophosphamide might, despite randomisation, have been differently or less responsive to medical treatments. However, all patients were treated early after diagnosis (mean 14 months for HSCT and 18 months for controls) and cardiac involvement, the strongest risk factor for mortality,[30] was prescreened and excluded before enrolment. Patients from both groups responded alike to HSCT. Systemic sclerosis is most common in women (female-to-male ratio of 4:1–14:1),[1] which is consistent with our study in which about 10% of patients were men.

Because patients who did not respond to cyclophosphamide responded to HSCT, there is an argument that such transplantation ought to be reserved for patients who do not respond to cyclophosphamide. However, there are no data to support the expense, inconvenience, and potential toxic effects of a treatment that does not reverse disease progression. Furthermore, delaying of transplantation might allow progression of vital organ injury that would contraindicate or substantially increase the risk of transplantation, as was the case for one control in our study who developed occult constrictive pericarditis.[31]

We built stopping rules into the protocol for significant differences in disease progression for the two groups at interim analyses. The study was stopped early because of failure of equipoise. Equipoise is based on the Hippocratic responsibility of doctors to provide optimal care to every patient.[32] Individual equipoise advocates cessation of a study if interim analyses show significant differences. Community equipoise allows for the study to continue if there is uncertainty within the expert medical community and generally applies to non-substantial differences in outcomes. In a scenario in which the treatment difference

***Panel:* Research in context**

Systematic review

We searched the PubMed database for original research articles without language restrictions published between Jan 25, 1997, and May 24, 2011, related to haemopoietic stem-cell transplantation (HSCT) for systemic sclerosis with the search terms "systemic sclerosis" and "stem cell transplant". We identified no distinct phase 2 studies, meta-analyses, or randomised trials that assessed efficacy and safety of HSCT in systemic sclerosis. There are two ongoing unpublished phase 3 trials: ASTIS and SCOT.

Interpretation

Previous studies showed improvements in patients' skin scores after HSCT but high initial mortality, enrolled heterogeneous groups of patients in terms of disease duration, did not undertake extended pretransplantation cardiac assessments, reported no improvement in pulmonary function tests, and did not have control groups. Our study had a randomised controlled design and showed that, if undertaken early in disease course with careful precardiac assessment, HSCT has little morbidity and improves lung function, whereas delaying of transplantation through treatment with standard of care (cyclophosphamide) allows disease progression, increases transplantation risk, and might contraindicate HSCT.

is large and the disease is potentially fatal, the ethical question is whether an ineffective control group can even be allowed as occurred in trials on antiretroviral therapy for vertical transmission of HIV-infected women.[33,34] The WHO Declaration of Helsinki[35] states that "The interests of science and society should never take precedence over considerations related to the wellbeing of the subject".

Contributors

All authors contributed to review and proof of our report. RKB and WB designed the protocol and RKB wrote the report. SJS and MG did the cardiac assessments. KD, TG, and KM did the high-resolution chest CT analyses. ER, WB, and JS did the rheumatological assessments. JC and KD did the cardiac radiological assessments. SJ, AM, and RKB did the inpatient and outpatient care. SJ and FM reviewed charts and data. RC and IH did the gastrointestinal assessments. BJ did the statistical randomisation.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

We dedicate our report to the memory of our colleague, Walter Barr.

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