Cardiac involvement and treatment-related mortality after non-myeloablative haemopoietic stem-cell transplantation with unselected autologous peripheral blood for patients with systemic sclerosis: a retrospective analysis

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Summary

Background Autologous haemopoietic stem-cell transplantation (HSCT) benefits patients with systemic sclerosis but has been associated with significant treatment-related mortality and failure to improve diffusion capacity of carbon monoxide (DLCO).We aimed to assess efficacy of HSCT and use of rigorous cardiac screening in this group.

Methods We assessed patients with diffuse systemic sclerosis or limited systemic sclerosis and interstitial lung disease who were treated with HSCT as part of a study or on a compassionate basis at Northwestern University (Chicago, IL, USA) or the University of São Paulo (Ribeirão Preto, Brazil). Unselected peripheral blood stem cells were harvested with cyclophosphamide (2 g/m²) and filgrastim. The transplant regimen was a non-myeloablative regimen of cyclophosphamide (200 mg/kg) and rabbit anti-thymocyte globulin (rATG; 4·5–6·5 mg/kg). We followed patients up to 5 years for overall survival, relapse-free survival, modified Rodnan skin score, and pulmonary function tests.

Findings Five (6%) of 90 patients died from treatment-related causes. Despite standard guidelines that recommend echocardiogram for screening before transplantation, four treatment-related deaths occurred because of cardiovascular complications (one constrictive pericarditis, two right heart failures without underlying infection, and one heart failure during mobilisation), and one death was secondary to sepsis without documented underlying heart disease. Kaplan-Meier analysis showed survival was 78% at 5 years (after eight relapse-related deaths) and relapse-free survival was 70% at 5 years. Compared with baseline, we noted improvements after HSCT in modified Rodnan skin scores at 1 year (58 patients; p<0·0001), 2 years (42 patients; p<0·0001), and 3 years (27 patients; p<0·0001) and forced vital capacity at 1 year (58 patients; p=0·009), 2 years (40 patients; p=0·02), and 3 years (28 patients; p=0·004), but total lung capacity and DLCO were not improved significantly after HSCT. Overall mean DLCO was significantly improved in patients with normal baseline echocardiograms (p=0·005) or electrocardiographs (p=0·05).

Interpretation Autologous HSCT with a non-myeloablative regimen of cyclophosphamide and rATG with a non-selected autograft results in sustained improvement in skin thickness and forced vital capacity. DLCO is affected by baseline cardiac function. Guidelines for cardiac screening of patients with systemic sclerosis to assess treatment-related risk from pulmonary artery hypertension, primary cardiac involvement, or pericardial disease should be reconsidered and updated.

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Introduction

Systemic sclerosis generally affects young women and is a chronic autoimmune disease of unknown cause complicated by a combination of diffuse vasculopathy, immune activation, and tissue fibrosis.[1] Standard therapies are unable to reverse disease progression, although several non-randomised trials involving small numbers of patients suggest that autologous haemopoietic stem-cell transplantation (HSCT) can improve skin and stabilise or improve forced vital capacity.[2–11] In the only randomised trial published to date (the American Scleroderma Stem Cell versus Immune Suppression Trial [ASSIST]),[2] autologous HSCT improved both skin and forced vital capacity, whereas disease progression was noted in patients treated with the standard therapy of monthly intravenous cyclophosphamide.

Several transplantation trials for systemic sclerosis have been complicated by treatment-related mortality.[3,4,6,7,10,12] Such mortality was 10% (eight of 79 patients) in the largest reported trial to date, the European Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial.[12] For cancer[13] and autoimmune diseases including systemic sclerosis,[14,15] published guidelines recommend an echocardiogram to assess cardiac reserve to establish whether a patient can safely tolerate a transplant. However, unlike other diseases for which haemopoietic transplantation is done, the usual disease-related cause of death for systemic sclerosis is cardiac complications arising from pulmonary

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artery hypertension and primary cardiac or pericardial involvement.[16]

Therefore, we analysed results from two centres that used the same mobilisation and non-myeloablative HSCT regimen without selection or manipulation of the graft to assess the causes of treatment-related mortality, whether impaired cardiac function affects outcome, and the appropriate screening method before transplantation to prevent enrolment of patients with insufficient cardiac reserve to safely tolerate the procedure.

Methods

Study design and patients

We undertook a retrospective analysis of all patients treated with HSCT, either as part of a study or on a compassionate basis, at Northwestern University (Chicago, IL, USA) and the University of São Paulo (Ribeirão Preto, Brazil). Patients were enrolled in institutional review board (IRB)-approved studies and retrospective IRB approval was obtained to report off-study patients. We defined duration of disease as duration from time of diagnosis of systemic sclerosis. Patients were followed up for 5 years after HSCT.

Patients who underwent transplantation had diffuse systemic sclerosis, defined as cutaneous involvement proximal to the elbow or knee with a modified Rodnan skin score[17] of 14 or more and internal organ involvement defined as pulmonary fibrosis or ground glass on chest CT, abnormal electrocardiograph, or gastrointestinal track involvement. Patients with little cutaneous involvement (modified Rodnan skin score <14) were eligible if they had coexistent pulmonary involvement. Patients were excluded if they had a total lung capacity of less than 45%, left ventricular ejection fraction of less than 40% or pulmonary artery systolic pressure (PASP) of more than 42 mm Hg, or positive serology for HIV or hepatitis B surface antigen. All patients had an echocardiogram and cardiac assessment. Additional cardiac testing was done on an individual basis until implementation of a standard screening in the last 12 patients enrolled; this screening consisted of echocardiogram with tricuspid annular plane systolic excursion (TAPSE), right heart catheterisation measured before and after a 500 mL intravenous normal saline bolus, and cardiac MRI with gadolinium. Fluid bolus was contraindicated if resting cardiac catheterisation right atrial pressure was more than 12 mm Hg or pulmonary capillary wedge pressure (PCWP) was more than 15 mm Hg. In Chicago, patients were ineligible for study inclusion if they were older than 55 years or had a disease duration of more than 4 years.

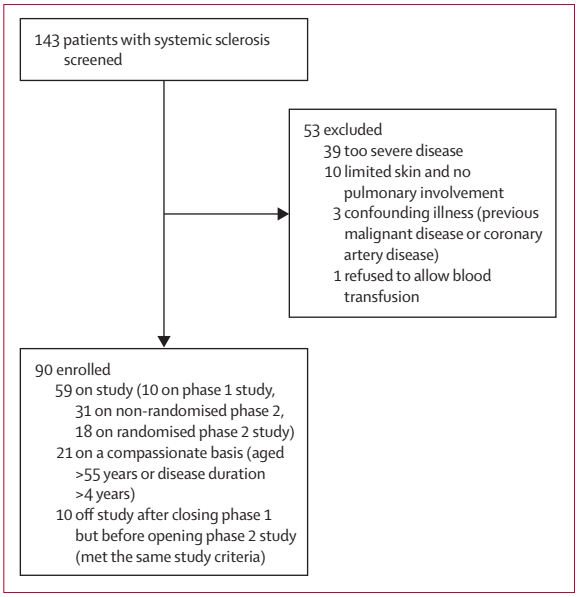

Figure 1: **Trial profile**

Procedures

Peripheral blood stem cells were mobilised with intravenous cyclophosphamide (2 g/m²) and 5–10 µL/kg subcutaneous filgrastim daily started 1 day after cyclophosphamide at the University of São Paulo or 5 days after cyclophosphamide at Northwestern University. Peripheral blood stem cell apheresis was done on day 10 after start of cyclophosphamide and peripheral blood stem cells were cryopreserved without manipulation. The conditioning regimen was 200 mg/kg intravenous cyclophosphamide given in four equal fractions on day –5 to day –2 before stem-cell infusion. rATG (thymoglobulin) was dosed at 0·5 mg/kg intravenously on day –5 and then either 1·0 mg/kg or 1·5 mg/kg intravenously every day on day –4 to day –1.

Blood products were irradiated, cytomegalovirus-safe, and leucocyte depleted. Filgrastim (10 µL/kg per day) was started 5 days after stem-cell infusion and continued until engraftment. Dependent on centre guidelines, intravenous prophylactic cefepime or piperacillin-tazobactam was started prophylactically or withheld until development of neutropenic fever. Oral aciclovir or valaciclovir was started on admission to the transplant centre and continued for 2 months after transplantation at the University of São Paulo or 12 months after transplantation at Northwestern University. Patients received oral daily fluconazole and either oral trimethoprim-sulfamethoxazole 2–3 times per week or aerosolised pentamidine every month for 2–6 months.

Patients started hyperhydration (150–200 mL normal saline per h) with diuretics or normal hydration at 50–75 mL per h with addition of continuous bladder irrigation (125–150 mL normal saline per h) and intravenous mesna at 100% the dose of cyclophosphamide with every dose of cyclophosphamide, continued for 24 h. Patients received methylprednisolone intravenously (250–1000 mg) before rATG (at Northwestern University) or as part of each rATG infusion bag (at University of São Paulo; 125 mg per bag).

	Patients (n=90)
Median age, years	42 (16–71)
Sex, female	73 (81%)
Ethnicity	
White	70 (78%)
Black	11 (12%)
Hispanic	5 (6%)
Biracial	3 (3%)
Native American	1 (1%)
Median disease duration from diagnosis to HSCT, months	25 (2–156)
History of Raynaud's phenomena	83 (92%)
Median modified Rodnan skin score	24 (3–47)
Diffuse systemic sclerosis	72 (80%)
Gastrointestinal track disorders	81 (90%)
Gastro-oesophageal reflux disease	51 (63%)
Patulous esophagous	52 (64%)
Gastrointestinal antral vascular ectasia	5 (6%)
Small bowel involvement	3 (4%)
Total parenteral nutrition	1 (1%)
Pulmonary function tests	
Median forced vital capacity	67% (31–103)
Median DLCO (corrected for haemoglobin)	64% (19–123)
Abnormal lung involvement on imaging	73 (81%)
Interstitial lung disease	73 (100%)
Nodules or micronodules	4 (5%)
Bronchiectasis	7 (10%)
Honeycombing	2 (3%)
Oxygen dependency	2 (3%)
Previous renal crisis	1 (1%)
Abnormal electrocardiography	44 (49%)
Non-specific T-wave abnormalities	17 (39%)
Right bundle branch block	8 (18%)
Left bundle branch block	2 (5%)
Left anterior fasicular block	4 (9%)
Pacemaker	1 (2%)
Intraventricular conduction delay	3 (7%)
First degree atrioventricular block	1 (2%)
Prolonged QT interval	5 (11%)
Ventricular premature contractions	3 (7%)
Atrial fibrillation	1 (2%)
Supraventricular tachycardia	1 (2%)
Atrioventricular nodal re-entry tachycardia	1 (2%)
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Echocardiography	
LVEF >40%*	89 (99%)
Abnormal	25 (28%)
Mild (grade 1) diastolic dysfunction	13 (52%)
Enlarged chambers	7 (28%)
LVEF (40–50%)	3 (12%)
Interventricular septal flattening	3 (12%)
Pericardial effusion >1 cm with diastolic atrial indentation	2 (8%)
Enlarged pulmonary artery	2 (8%)
Septal bounce	1 (4%)
Serology	
ANA positive (>1:40)	87 (97%)
Scl-70 positive (>10 IU)	43 (48%)
Previous immunotherapy†	84 (93%)

Data are median (range) or n (%), unless otherwise stated. HSCT=haemopoietic stem-cell transplantation. DLCO=diffusion capacity of carbon monoxide. LVEF=left ventricular ejection fraction. ANA=anti-nuclear antibody. *One echocardiogram was not done; trace mitral regurgitation and left ventricular hypertrophy with no other abnormalities were regarded as normal. †Corticosteroids (60 patients), oral cyclophosphamide (six patients), intravenous cyclophosphamide (28 patients), methotrexate (32 patients), mycophenolate mofetil (17 patients), penicillamine (15 patients), azathioprine (four patients), lidocaine (11 patients), hydroxychloroquine (five patients), minocycline (five patients), protein tyrosine-kinase inhibitor (imatinib or dasatinib; four patients), TNF-inhibitor (infliximab or adalimumab; three patients), or colchicine (two patients).

Table 1: **Patient demographics**

On admission, patients were prescribed an oral calcium-channel blocker to prevent Raynaud's phenomena and an oral angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist to prevent renal crisis. We monitored viral loads of cytomegalovirus after transplantation for 2–3 months and pre-emptively treated patients by switching them from aciclovir to oral valganciclovir (900 mg twice-daily) or intravenous ganciclovir (5 mg/kg twice-daily) until they were cytomegalovirus negative.

The main outcome was treatment-related mortality in patients who underwent HSCT. We also assessed skin thickness by modified Rodnan skin score and pulmonary function by forced vital capacity, total lung capacity, and diffusing capacity of carbon monoxide (DLCO; percentage predicted and corrected for haemoglobin). We administered quality of life questionnaires (short form [SF]-36) for the last 30 consecutive patients from one site (Northwestern University). We defined relapse as any of the following criteria: increase from best improvement of skin score by 25% or decline in forced vital capacity by 10%, renal crisis, start of total parenteral nutrition, or restarting of immune suppressive or modulating medication.

Statistical analysis

We calculated overall survival and relapse-free survival with Kaplan-Meier methods. We used two-tailed paired *t* tests for comparisons within the transplantation group. We analysed the effect of cardiac function and sex on pulmonary function and skin thickness by least-square means and standard deviations adjusted by repeated measures across all visits (averaged over time) via a mixed effects model for outcome. We used the *r* correlation coefficient to determine linear relations between variables. A correlation coefficient of more than 0·8 was regarded as strong, whereas less than 0·5 was regarded

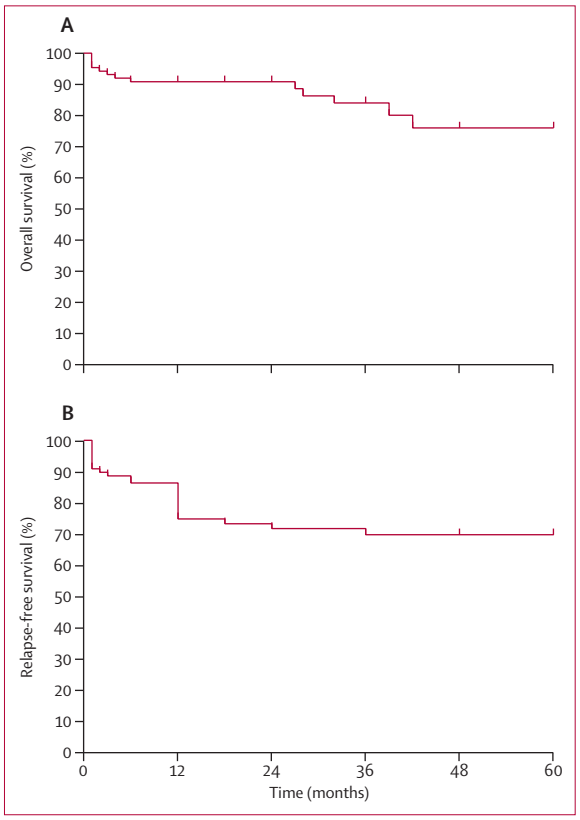

Figure 2: **Overall survival (A) and relapse-free survival (B) after haemopoietic stem-cell transplantation**

as weak. We did all analyses with Graphpad Prism 5 software (Graphpad, CA, USA).

Role of the funding source

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

Results

Between November, 2002, and July, 2011, we included 59 patients at Northwestern University and 31 patients at the University of São Paulo (figure 1). 59 patients were in IRB-approved studies (28 from Northwestern University and 31 from University of São Paulo) and retrospective IRB approval was obtained for 31 patients. Table 1 shows demographic characteristics of 90 patients who were offered autologous HSCT.

Median day of engraftment (absolute neutrophil count >1000 cells per μL) was day 9 (range 8–11). 63 patients (70%) developed fever of more than 38°C, which was blood-culture negative in 59 patients (two patients had *Klebsiella pneumoniae* infections, one had *Pseudomonas aeruginosa* infection, and one had *Acinetobacter baumannii* infection). On admission, five patients had positive rectal or nasal surveillance cultures for colonisation with vancomycin-resistant enterococcus. Five patients developed *Clostridium difficile* toxin-positive diarrhoea during hospitalisation.

14 patients had a volume overload of more than 5 kg because of hyperhydration (200 mL per h of normal saline) during the conditioning regimen. After the first 20 patients were treated, hydration during conditioning was decreased to 50–100 mL/h, supplemented with intravenous mesna infusion and intravesicle bladder irrigation (150 mL/h of normal saline) with no further episodes of volume overload. One patient developed transient acute tubular necrosis (confirmed by renal biopsy) from the combination of diuretics and angiotensin-converting enzyme inhibitor. Another patient developed transient renal crisis during transplantation mandating temporary dialysis. One further patient had paradoxical emboli from a patent foramen ovale and needed distal amputation of three toes.

No patients developed fungal or cytomegalovirus infections. Two months after discharge home, one patient developed West Nile virus encephalomyelitis with prolonged but continuing recovery. No patients developed leukaemia, myelodysplasia, or cancer.

One enrolled patient declined treatment and one patient received treatment but did not return for follow-up. Five patients (6%) had treatment-related deaths. Four treatment-related deaths were from cardiac events, with one sudden cardiac arrest during mobilisation and three sudden cardiac arrests during transplantation (one because of constrictive pericarditis and two secondary to heart failure). One death was secondary to septic neutropenia in a patient not on pre-emptive broad-spectrum antibiotics.

For 88 patients with follow-up, 5 year overall survival was 78% and relapse-free survival was 70% (figure 2). Eight (62%) of 13 patients who relapsed subsequently died of their disease despite reinstitution of immunotherapy. Deaths related to relapse were related to cardiopulmonary causes for six patients (three deaths ~2 years after transplantation and three deaths 3–4 years after transplantation) and were related to renal crisis for two patients (3 months and 4 months after transplantation). The initial presentation of relapse was renal crisis in four patients (3, 4, 12, and 18 months after transplantation).

Modified Rodnan skin scores improved after transplantation (figure 3). Compared with the mean score before transplantation (24·1), mean scores had improved by 6 months (16·5; $p<0·0001$), 12 months (12·9; $p<0·0001$), 24 months (12·2; $p<0·0001$), 36 months (11·1; $p<0·0001$), 48 months (10·3; $p=0·0001$), and 60 months (8·9; $p=0·0003$).

Forced vital capacity also improved after transplantation (figure 3). Compared with a mean forced vital capacity before transplantation of 66·2%, patients had improvements at 6 months (70·8%; $p=0·0009$), 12 months (71·1%;

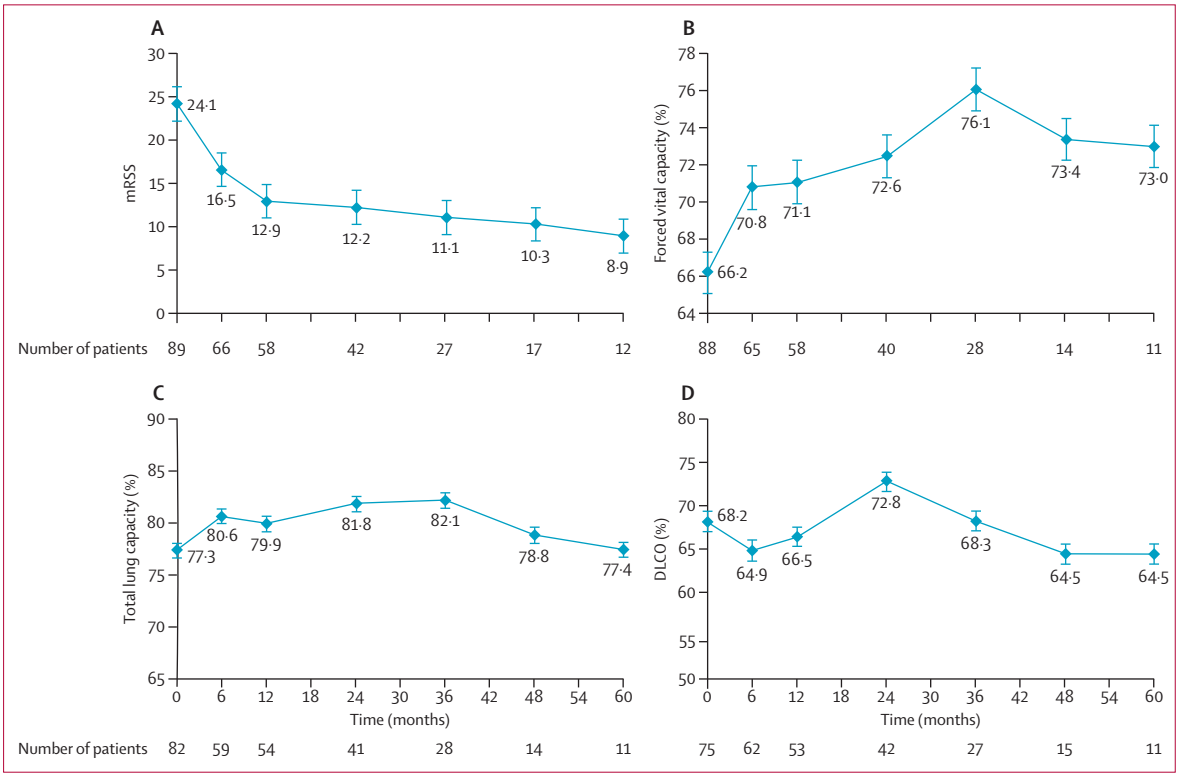

Figure 3: **Modified Rodnan skin score and pulmonary function tests before (0 months) and after haemopoietic stem-cell transplantation**
Vertical lines show standard error at each time point. mRSS=modified Rodnan skin score. DLCO=diffusion capacity of carbon monoxide.

p=0·009); 24 months (72·6%; p=0·02), and 36 months (76·1%; p=0·004), but these improvements were not significant at 48 months (73·4%; p=0·11) or 60 months (73·0%; p=0·26). Total lung capacity and percentage DLCO corrected for haemoglobin did not change for the entire group (figure 3). Compared with mean DLCO values before transplantation (68·2%), values after transplantation did not differ at 6 months (64·9%; p=0·41), 12 months (66·5%; p=0·56), 24 months (72·8%; p=0·82), 36 months (68·3%; p=0·27), 48 months (64·5%; p=0·48), and 60 months (64·5%; p=0·67).

We noted at best a weak correlation (r<0·5) between DLCO values after transplantation and modified Rodnan skin score, age, and duration of disease before transplantation (table 2). We identified an intermediate correlation (r=0·5–0·8) between baseline DLCO values and DLCO values after transplantation, but baseline DLCO, forced vital capacity, and modified Rodnan skin scores had weak correlation with change in DLCO after transplantation (table 2). The only baseline factors that correlated significantly with DLCO outcome after transplantation were baseline echocardiogram or electrocardiograph abnormalities (table 3, figure 4). DLCO values after transplantation were improved if the baseline electrocardiograph or echocardiogram was normal (p=0·05 for electrocardiograph and p=0·005 for echocardiogram).

	Before HSCT	1 year after HSCT
Duration of disease since diagnosis *vs* DLCO	–0·34	–0·47
Patients age *vs* DLCO	–0·25	–0·08
mRSS *vs* DLCO before transplantation	0·26	0·43
FVC *vs* DLCO before transplantation	0·58	0·63
DLCO before transplantation *vs* DLCO after transplantation	NA	0·65
mRSS before transplantation *vs* change from baseline in DLCO after transplantation	NA	–0·003
FVC before transplantation *vs* change from baseline in DLCO after transplantation	NA	–0·04
DLCO before transplantation *vs* change from baseline in DLCO after transplantation	NA	–0·36
Duration of disease *vs* change from baseline in DLCO after transplantation	NA	–0·08
Age *vs* change from baseline in DLCO after transplantation	NA	0·14

Data are linear correlation coefficients (r>0·8 is strong correlation, r<0·5 is weak correlation). HSCT=haemopoietic stem-cell transplantation. mRSS=modified Rodnan skin score. DLCO=diffusing capacity of carbon monoxide (% predicted, corrected for haemoglobin). FVC=forced vital capacity (% predicted). NA=not applicable.

Table 2: **Correlation coefficient (r) between pretransplantation parameters and DLCO before or after transplantation**

Cardiac assessments before transplantation evolved during the study from echocardiogram and cardiac assessment (for 90 patients) to include echocardiogram with TAPSE and right heart catheterisation (for 23 patients and 39 patients, respectively), and finally a consistent approach of echocardiogram with TAPSE, right heart catheterisation without and with fluid

	Normal echocardiogram or electrocardiograph or female sex	Abnormal echocardiogram or electrocardiograph or male sex	p value*
DLCO			
Group: echocardiogram	Normal 71·3% (3·1)	Abnormal 56·7% (3·8)†	0·0045
Group: electrocardiograph	Normal 73·3% (4·6)	Abnormal 62·0% (3·0)‡	0·045
Group: sex	Female 66·3% (2·8)	Male 64·5% (4·9)	0·75
FVC			
Group: echocardiogram	Normal 70·8% (3·2)	Abnormal 68·4% (2·4)	0·58
Group: electrocardiograph	Normal 73·6% (4·6)	Abnormal 68·2% (2·1)	0·28
Group: sex	Female 66·1% (2·5)	Male 66·3% (3·1)	0·95
Total lung capacity			
Group: echocardiogram	Normal 80·3% (3·4)	Abnormal 78·8% (2·3)	0·70
Group: electrocardiogram	Normal 81·9% (4·4)	Abnormal 78·7% (2·1)	0·51
Group: sex	Female 75·8% (2·4)	Male 75·2% (3·0)	0·80
mRSS			
Group: echocardiogram	Normal 16·1 (1·7)	Abnormal 18·2 (1·3)	0·33
Group: electrocardiograph	Normal 16·1 (2·4)	Abnormal 17·8 (1·1)	0·51
Group: sex	Female 17·0 (1·4)	Male 16·4 (2·1)	0·77

DLCO=diffusion capacity for carbon monoxide (% predicted, corrected for haemoglobin). FVC=forced vital capacity (% predicted). mRSS=modified Rodman skin score. *Least-square means (SDs) adjusted by repeated measurements across all visits (before and after transplantation) averaged over time via a mixed effects model. †Abnormal echocardiogram was diastolic or systolic dysfunction, enlarged chambers, left ventricular ejection fraction <50%, interventricular diastolic flattening, pericardial effusion >1 cm with diastolic atrial indentation, enlarged pulmonary artery, or septal bounce. ‡Abnormal electrocardiogram was non-specific T-wave abnormalities, bundle branch or fasicular block, conduction delay, pacemaker, prolonged QT interval, ventricular premature contractions, or arrhythmias.

Table 3: **Effect of cardiac function and sex on lung and skin disease in patients with systemic sclerosis**

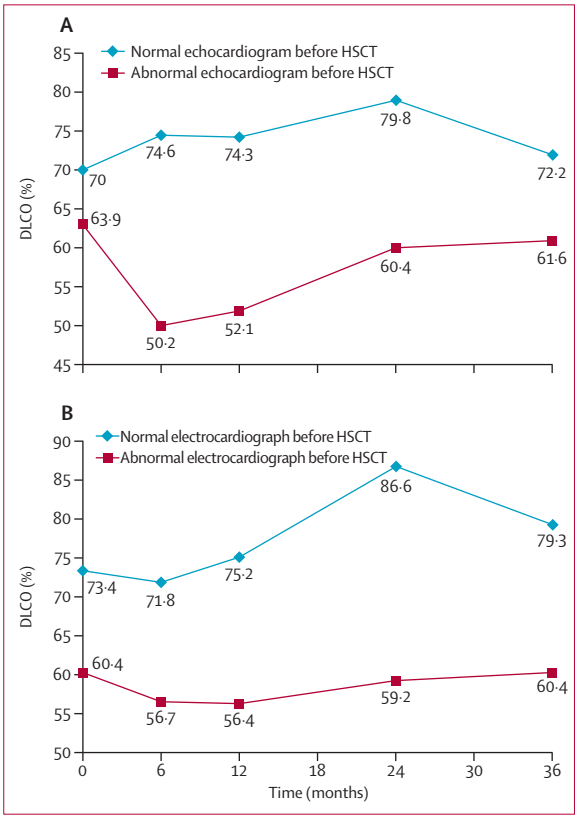

Figure 4: **DLCO corrected for haemoglobin before and after HSCT, by normal or abnormal echocardiogram or electrocardiograph before transplantation**
Abnormal echocardiogram was diastolic or systolic dysfunction, enlarged chambers, left ventricular ejection fraction <50%, interventricular diastolic flattening, pericardial effusion >1 cm with diastolic atrial indentation, enlarged pulmonary artery, or septal bounce. Abnormal electrocardiograph was non-specific T-wave abnormalities, bundle branch or fasicular block, conduction delay, pacemaker, prolonged QT interval, ventricular premature contractions, or arrhythmias. HSCT=haemopoietic stem-cell transplantation.

challenge, and cardiac MRI with gadolinium for the last 12 patients assessed (table 3).

Table 4 shows the information for the last 12 patients enrolled provided by echocardiogram, cardiac catheterisation without and with fluid challenge, and cardiac MRI. Patients without significant pulmonary artery hypertension tolerated fluids without significant increase in PASP. By comparison, after infusion of 500 mL normal saline, patients with underlying pulmonary artery hypertension had a striking increase in PASP, mean pulmonary pressure, and pulmonary vascular resistance. In these patients, cardiac MRI showed significant indentation of the right ventricle into the left ventricle via the common interventricular septum—ie, diastolic septal flattening or D-sign.

In patients without pulmonary artery hypertension, fluid challenge with 500 mL normal saline could also provoke left ventricle compromise, shown by increase of PASP, mean pulmonary pressure, and PCWP without an increase in pulmonary vascular resistance (table 4). These patients also usually show diffuse gadolinium enhancement on cardiac MRI and a history of palpitations, recurrent atrial, ventricular premature contractions, or recurrent, multifocal, non-sustained ventricular tachycardia.

Quality of life before transplantation and at last follow-up improved significantly in total score and in all scales and dimensions apart from emotional role limitation and mental health score (table 5).

Discussion

HSCT was associated with treatment-related mortality in five (6%) of 90 patients in our study, which is about half the rate (eight [10%] of 79 patients) in the European multicentre ASTIS trial.[12] Treatment-related mortality in our study was predominantly related to cardiac events (four of five deaths). We attribute the reduced mortality in our study compared with ASTIS to recognition that echocardiogram and resting right heart catheterisation might be insufficient to assess cardiac risk in patients with systemic sclerosis (panel). The ASTIS trial[12] mandated echocardiogram whereas cardiac catheterisation was only required for patients with pulmonary artery hypertension suggested by an echocardiogram. However, pulmonary artery hypertension determined by echocardiographic calculation of PASP can significantly overestimate or underestimate invasive PASP because of image problems, Doppler alignment, or violation of viscosity assumptions in the modified Bernoulli equation used to calculate echocardiographic PASP.[18,19]

	Echocardiogram			Right heart catheterisation						Cardiac MRI/arrhythmias
	Summary	LVEF	PASP	PASP (mPAP)	PASP (mPAP) after 500 mL normal saline	PCW	PCW after 500 mL normal saline	PVR	PVR after 500 mL normal saline	
Eligible for HSCT										
Patient 1	Normal	65%	35	26 (18)	35 (25)	7	13	148	143	Normal
Patient 2	Normal	65%	30	23 (18)	25 (21)	10	15	89	65	Normal
Patient 3	Normal	55%	NR	27 (20)	34 (29)	11	18	93	85	Normal
Patient 4	LVH	65%	22	19 (14)	25 (21)	3	5	95	179	Patchy myocardial enhancement, LVH, LADB
Patient 5	Normal	60%	24	16 (11)	22 (18)	5	11	69	86	Normal
Patient 6	Grade 1 diastolic dysfunction	55%	23	27 (19)	36 (30)	10	19	105	NR	Normal
Patient 7	Normal	60%	34	30 (22)	46 (38)	12	25	119	198	Patchy left ventricular myocardial enhancement
Denied HSCT because of PAH										
Patient 8	Septal flattening	65%	27	42 (27)	51 (34)	14	7	110	225	D-sign, interventricular septal diastolic flattening, atrial premature beats
Patient 9	Grade 1 diastolic dysfunction	55%	NR	38 (28)	51 (39)	14	19	175	240	D-sign, interventricular septal diastolic flattening, enlarged right ventricle, inferior infarct
Denied HSCT because of right or left ventricle dysfunction										
Patient 10	Grade 1 diastolic dysfunction	46%	40	31 (23)	42 (31)	9	16	174	158	LVEF 40%; systolic hypokinesis and diastolic dysfunction
Patient 11	Septal flattening	55%	26	31 (24)	NP	NP	NP	119	NR	LVEF 39%; D-sign, notably enlarged right ventricle; diffuse left and right ventricular enhancement; frequent PVCs, low QRS voltage
Patient 12	Normal*	55%	23	13 (8)	21 (14)	3	7	61	81	LVEF 45%; right ventricular ejection fraction 30%; diffuse left and right ventricular myocardial enhancement; right ventricular dilatation, non-sustained multifocal ventricular tachycardia

LVEF=left ventricular ejection fraction. PASP=pulmonary artery systolic pressure (mm Hg). mPAP=mean pulmonary artery pressure (mm Hg). PCW=pulmonary capillary wedge (mm Hg). PVR=pulmonary vascular resistance (dynes·s·cm^{-5}). HSCT=haemopoietic stem-cell transplantation. NR=not reported. LVH=left ventricular hypertrophy. LADB=left anterior divisional block. PAH=pulmonary artery hypertension. NP=not performed. PVCs=premature ventricular contractions. *Echocardiogram reported as normal but after obtaining results of cardiac MRI, reassessment of echocardiogram reported as inferior hypokinesis.

Table 4: **Echocardiogram, right heart cardiac catheter parameters before and after fluid challenge, and cardiac MRI in 12 consecutive patients with systemic sclerosis referred for HSCT**

	Scale								Dimension		Total SF-36 score
	Physical function	Physical role limitation	Body pain	General health perception	Vital energy fatigue	Social functioning	Emotional role limitation	Mental health	Physical health	Mental health	
Before HSCT	28	23	45	38	39	47	58	74	35	51	44
Last follow-up after HSCT	58	53	62	52	52	69	71	76	55	64	62
Difference (SD)	30 (31·47)	30 (47·20)	17 (26·47)	14 (46·98)	13 (27·84)	22 (35·12)	13 (46·84)	2 (11·70)	20 (27·69)	13 (23·36)	18 (20·25)
p value	<0·0001	0·001	0·001	0·105	0·024	0·002	0·129	0·308	<0·0001	0·005	<0·0001

SF-36=short form 36. HSCT=haemopoietic stem-cell transplantation.

Table 5: **Quality of life by SF-36 before and after HSCT**

Right heart catheterisation is regarded as the gold standard to rule out pulmonary artery hypertension[20,21] and is recommended for early detection of pulmonary artery hypertension in patients with systemic sclerosis.[21–23] Nevertheless, PASP obtained via resting right heart catheterisation can be falsely reassuring for patients with systemic sclerosis. As shown in table 4, pulmonary artery pressure can be volume dependent in patients who have systemic sclerosis because of abnormal stiffening of pulmonary arteries or myocardium. At the time of measurement, patients are relatively volume depleted because they have had no oral hydration since the previous night in preparation for the procedure. In our study, fluid challenge unmasked patients with volume dependent pulmonary artery hypertension manifest by increase in PASP, mean pulmonary pressure, and pulmonary vascular resistance and patients with pulmonary venous hypertension because of left ventricle compromise in which pulmonary artery and PCWP increased without an increase in pulmonary vascular resistance.

Because patients with systemic sclerosis might not notice cardiopulmonary symptoms at rest but have symptoms only with exertion or volume loading, volume confrontational testing might be required to diagnose

***Panel:* Research in context**

Systemic review

We searched PubMed without language restriction for original research articles published between June 25, 1997, and May 1, 2012, with the terms "stem cell transplantation" and "systemic sclerosis". We identified no distinct large phase 2 non-randomised studies or phase 3 trials with long-term follow-up that used the same regimen as our study. The only completed randomised trial reported to date[2] was strongly in favour of transplantation and was stopped early after 19 patients. We identified no distinct phase 2 or phase 3 studies that identified risk factors for transplantation, focused on extensive cardiac assessment before transplantation, or documented improvement in diffusing capacity of carbon monoxide (DLCO) after transplantation. Two randomised trials have yet to be concluded, the European Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial[12] and Scleroderma Cyclophosphamide versus Transplant (SCOT) trial; ASTIS has reported a treatment-related mortality of 10% (eight of 79 patients).

Interpretation

Previous studies showed improvement in patients' skin scores and forced vital capacity after haemopoietic stem-cell transplantation (HSCT) but transplantation based on published guidelines for baseline cardiac screening have shown no improvement in DLCO and a number of deaths. To our knowledge, our study is the first to show a benefit of extensive cardiac screening at baseline and that pretransplantation cardiac structure, function, and electrophysiology affect DLCO after transplantation. These findings argue for early referral of patients for transplantation before onset of cardiac or pericardial-related compromise in heart function and for reassessment of present cardiac screening guidelines for systemic sclerosis.

and assess the severity of pulmonary artery hypertension[23] as has been reported in assessment of portopulmonary hypertension in recipients of liver transplants.[24] Our data for cardiac catheterisation with and without fluid confrontation argue for reconsideration of the presently published cardiac guidelines about assessment of cardiac risk in patients with systemic sclerosis.[14,15] However, a confrontational fluid challenge might, itself, be dangerous in patients with little cardiac reserve.[25] Thus, we excluded fluid challenge in patients with resting cardiac catheterisation right atrial pressure of more than 12 mm Hg or PCWP of more than 15 mm Hg.

Cardiac MRI is helpful for assessment of ventricular volumes, function, wall motion, and myocardial fibrosis or inflammation in patients with systemic sclerosis.[26,27] Pulmonary artery hypertension-induced displacement of the common interventricular wall into the left ventricle (diastolic septal flattening or D-sign) decreases left ventricular compliance and impairs left ventricular filling, thereby potentially increasing left atrial pressure and causing pulmonary oedema in the setting of hyperhydration. Myocardium scar detected by late gadolinium enhancement of myocardium on cardiac MRI is an indication of poor myocardial reserve, increased risk of arrhythmias,[28] and left ventricle dysfunction as uncovered by fluid challenge during cardiac catheterisation. Patients with systemic sclerosis complicated by either pulmonary artery hypertension or myocardial fibrosis are volume sensitive and fluids might precipitate cardiac failure. One death in our study was due to constrictive pericarditis, which is another complication that is exacerbated by fluids and that, in retrospect, might have been identified by pericardial enhancement or septal bounce on cardiac MRI or cardiac catheterisation with rapid fluid challenge.[29]

In three patients, the first manifestation of relapse was renal crisis after the transplantation. None of the patients who developed renal crisis had been maintained on angiotensin blockade. We currently recommend that patients start an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker on admission and indefinite continuation after discharge from the transplant centre.[30]

Factors that reduce DLCO include: anaemia, lung disease that impairs alveolar gas exchange or results in uneven distribution of air, intrapulmonary or intracardiac shunts, and cardiac insufficiency.[31] Because heart failure can diminish DLCO[32–34] and systemic sclerosis involves the heart, in retrospect, our findings that abnormal baseline echocardiograms correlate with a decline in DLCO after transplantation that does not return to baseline for at least 2 years is not surprising (figure 3). By comparison, normal baseline echocardiograms correlate with improved DLCO after transplantation.

Because our study was non-randomised, our patients might have been at a later stage of disease where skin thickness and quality of life can improve without intervention. However, our results are consistent with those from our previous randomised trial in a smaller subset of patients in which skin score, forced vital capacity, and quality of life improved equally in the transplantation group but declined in the control group.[2] Moreover, no other type of therapy or natural history study has reported improvement in pulmonary function—ie, in forced vital capacity or DLCO. Furthermore, we noted no correlation between duration of disease before transplantation and improvement in DLCO after transplantation. Conversely, DLCO values after transplantation correlated with cardiac structure and function before HSCT.

In conclusion, previous reports of high treatment-related mortality might suggest to physicians that HSCT should be reserved as salvage therapy. However, this bias would result in a self-fulfilling prophecy of high transplant-related mortality, especially without appropriate cardiac assessment before HSCT. Our findings suggest that cardiac screening guidelines for systemic sclerosis should incorporate not only echocardiogram but also confrontational right heart catheterisation, including a fluid challenge test and cardiac MRI to appropriately assess procedure risk. We also showed that DLCO can improve after transplantation if baseline cardiac function and electrocardiograph findings are normal. Systemic sclerosis-related cardiac involvement before an HSCT is an important variable in determining both treatment-related mortality and DLCO after transplantation. HSCT can be considered as upfront therapy if baseline cardiac assessment is favourable.

Contributors

All authors contributed to review and proof of this report. RKB designed the protocol, wrote the report, and was responsible for the conduct of the trial in Chicago, IL, USA. RKB, SJ, and AM were responsible for treatment and care of patients in Chicago. SJS and MG were responsible for baseline cardiac consultation. JS and ER were responsible for baseline rheumatology consultation. JV, MCO, DAM, and BS were responsible for conduct of the trial and care of patients in São Paulo, Brazil. SJS and ZJC assessed all echocardiograms. XH and SJ collected data and reviewed records. IBH and BJ did statistical analysis.

Conflicts of interest

We declare that we have no conflicts of interest.

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We dedicate this manuscript to the memory of our colleague and friend, Professor Julio Voltarelli MD, PhD (Dec 17, 1948–March 21, 2012).

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