Bone Marrow Transplantation (2003) 32, S65–S67

www.nature.com/bmt

Hematopoietic stem cell transplantation for systemic sclerosis with rapid improvement in skin scores: is neoangiogenesis occurring?

RK Burt, Yu Oyama, A Traynor, K Quigley, M Brush, J Rodriguez and WG Barr

Division of Immunotherapy, Chicago, Department of Medicine, Northwestern University Medical Center, IL, USA

Summary:

Systemic sclerosis (SSc) is presumed to be an immune-mediated vasculopathy of unknown etiology. SSc is unresponsive to most immune-modulating therapies except for intravenous cyclophosphamide, which is reported to demonstrate some benefit. We, therefore, dose-escalated cyclophosphamide to 200 mg/kg and added rabbit ATG 7.5 mg/kg along with infusion of unselected hematopoietic stem cells to minimize the cytopenic interval. Engraftment occurred rapidly (day 8) with minimal unexpected toxicity, no infections, and unexpectedly rapid improvement in the modified Rodnan Skin Score.
Bone Marrow Transplantation (2003) **32,** S65–S67. doi:10.1038/sj.bmt.1704055
Keywords: scleroderma; hematopoietic stem cell transplantation

Systemic sclerosis (SSc) is a disease with prominent vascular pathology associated with vasospasm (Raynaud's phenomenon), impaired vascular relaxation, elevated endothelium von Willebrand factor, telangiecstasias, and vascular obliteration resulting in organ damage.[1] Skin and visceral fibrosis may be the end result of this vasculopathy. An auto- or alloimmune-mediated pathogenesis, although unproven, has been speculated due to association of SSc with other autoimmune disorders, occurrence of autoantibodies (eg antitopoisomerase I, anticentromere antibodies, antipolymerase III antibodies),[2] and occurrence of lymphocytic mixed chimerism.[3] SSc with diffuse skin involvement and/or affected visceral organs has a morbidity of approximately 12% per year or 60% in 5 years.[4] Hematopoietic stem cell transplantation (HSCT) has, therefore, been initiated as a possible new therapy for this difficult patient population.[5,6]

Methods

Patients are eligible if less than 65 years of age with an established diagnosis of diffuse cutaneous scleroderma and a modified Rodnan Skin Score (mRSS)[7] of >14 and any of the following: (1) diffusion limiting capacity of carbon monoxide (DLCO) $<80\%$ of predicted or decrease in DLCO of 10% or more over 12 months, (2) active alveolitis on bronchoalveolar lavage, (3) pulmonary fibrosis or alveolitis on CT scan or chest radiograph, (4) sedimentation rate $\geqslant 25$ mm/h, (5) abnormal electrocardiogram showing nonspecific ST-T-wave abnormalities, low QRS voltage, or ventricular hypertrophy, or (6) scleroderma-related renal disease not explained by infection or other causes manifest as proteinuria ($>$trace on dipstick), hematuria (urine blood on dipstick), or hypertension requiring antihypertensive medications or a diastolic blood pressure >95 mmHg. Candidates are excluded from treatment for a poor performance status (ECOG>2), left ventricular ejection fraction $<40\%$, untreated life-threatening arrhythmia, active ischemic heart disease, heart failure, pulmonary artery pressure >45 mmHg, serum creatinine >2.5 mg/dl, or transaminases $>3\times$ normal.

Hematopoietic stem cells (HSC) were mobilized with 2.0 g/m^2 of cyclophosphamide and beginning 72 h later 10 μg/kg per day G-CSF. HSC were collected with a Cobe Spectra apheresis instrument (Lakewood, CO, USA) upon rebound of the absolute neutrophil count to more than 1000/μl (usually day 10 after cyclophosphamide). The conditioning regimen was cyclophosphamide 200 mg/kg divided into 50 mg/kg per day on days -5, -4, -3, -2 and rabbit ATG (Sangstat) 7.5 mg/kg divided into 1.5 mg/kg per day on days -5, -4, -3, -2, and -1. Methylprednisolone 250 mg/kg was given 30 min prior to each infusion of ATG. Unselected peripheral blood stem cells were infused on day zero. If patients were on an angiotensin enzyme inhibitor (ACEI), it was held 24 h prior to stem collection in order to avoid apheresis-related hypotension. Lisinopril, an angiotensin inhibitor, was given during transplant to prevent steroid-associated renal crises. Antibiotic coverage for the first 6 months after HSCT is diflucan, acyclovir, and bactrim.

Disease activity is monitored by the mRSS, Health Assessment Questionnaure (HAQ), pulmonary function tests, high-resolution chest CT, echocardiogram, serum creatinine, and proteinuria. Assessments are performed prior to enrollment and then 6 and 12 months and yearly after HSCT.

Correspondence: Dr RK Burt, Division of Immunotherapy, Northwestern University Medical Center, 320 East Superior, Searle 3-489, Chicago, IL 60611, USA

Table 1 Rapid improvement in skin score following hematopoietic stem cell transplantation in patients with systemic sclerosis

Patient	*mRSS pre-transplant*	*mRSS within 4 weeks after stem cell infusion*
1	26	21 (4 weeks)
2	31	24 (2 weeks)
3	31	25 (25 days)

mRSS = modified Rodnan Skin Score.

Results

Four patients have been enrolled and three have completed HSCT. All patients had sufficient stem cells collected after a single apheresis. In the 2-week interval between mobilization and admission for HSCT, the patient's skin scores did not change. All patients had disease-related EKG abnormalities (inverted T waves) prior to HSCT and during HSCT mild pulmonary compromise requiring nasal prong oxygen for normal saturation was transiently required for two patients. There were no other non-hematologic toxicities. Engraftment, defined as an ANC over 1000/μl occurred on days 7, 8, and 9 for the three patients. The second patient never required a platelet transfusion. The other two patients received three single donor units/nine random donor units and three single donor units of platelets, respectively. The patients reported subjective improvement in skin elasticity beginning prior to hospital discharge. Notably, but of unknown significance, for the first time since disease onset, mRSS improved in all three patients (see Table 1).

Discussion

HSCT for scleroderma has been pursued in America by the Seattle consortium using a cyclophosphamide, total body irradiation (TBI), and ATG regimen.[6] Cyclophosphamide has some documented but limited efficacy in patients with scleroderma.[8] Therefore, escalation of cyclophosphamide in the conditioning regimen seems appropriate. On the other hand, radiation, whether localized or total nodal irradiation, has a troublesome history in scleroderma that includes multiple reports of worsening or accelerating scleroderma-related complications. O'Dell *et al*[9] terminated a trial of nonmyeloablative total nodal irradiation when the first three patients, despite profound immune suppression, clinically deteriorated. One patient died of gastrointestinal complications and the other two had permanent pulmonary deterioration despite the absence of direct radiation to the lung parenchyma.[9] In patients with SSC and a solid malignancy, irradiation of the tumor has been associated with lethal fibrotic complications that extend beyond the radiation portals.[10] In fact, scleroderma is considered a relative contraindication to breast irradiation in patients with breast cancer.[11] In contrast to the experience of using radiation in patients with cancer and scleroderma, a chemotherapy regimen of vincristine, melphalan, and cyclophosphamide used to treat a malignancy caused an incidental marked improvement of the patient's scleroderma.[12] Radiation (TBI) was, therefore, excluded from our conditioning regimen and instead cyclophosphamide was increased from 120 mg/kg as used in the Seattle regimen to 200 mg/kg as used in several other autoimmune disease HSCT regimens and as employed by most Europeans. For additional safety, because scleroderma affects the heart and lungs[13] and because cyclophosphamide-related cardiovascular stress can occur, patients with evidence of pulmonary artery hypertension ($>$45 mmHg) are excluded and volume overload is carefully avoided during HSCT.

These patients demonstrated rapid subjective and objective improvement in skin flexibility. Similar observations have been made in patients treated with the Seattle protocol. There is no nontransplant therapy that has been reported to rapidly diminish skin tightness. Other important parameters such as survival and internal organ function will require longer follow-up and more patients. The reason for rapid skin improvement is surprising and unknown. The high doses of methylprednisolone that accompany the ATG infusions may influence the immediate post-transplant period. Besides the intense immune suppression that may terminate the cascade of inflammatory cytokines, the mobilization and infusion of stem cells and use of growth factors that mobilize stem cells into the blood may also contribute to neoangiogenesis.[14–16] Unselected marrow cells as well as AC133$^+$ hematopoietic progenitor cells have been reported to differentiate into endothelial cells and improve ischemic peripheral vascular and coronary artery disease by neovascularization.[14–16] If as the current research suggests, hematopoietic stem cells contribute to the genesis of new capillaries,[17] conditioning agents should be designed to avoid further damage to marrow stem cells. TBI is cidal to marrow stem cells and only the limited number of infused hematopoietic stem cells given after TBI could contribute to both marrow repopulation and neoangiogenesis. In contrast, HSCs are resistant to cyclophosphamide-related toxicity and both the marrow stem cell pool as well as the infused HSCs could contribute to neoangiogenesis following a cyclophosphamide-conditioning regimen. Further research into HSC therapy for scleroderma, a notoriously treatment refractory disease, should continue to explore safe and effective immunesuppressive conditioning regimens as well as the role of stem-cell-induced neoangiogenesis as an independent mechanism of therapeutic benefit.

References

1 Herrick AL. Vascular function in systemic sclerosis. *Curr Opin Rheumatol* 2000; **12**: 527–533.
2 Harvey GR, McHugh NJ. Serologic abnormalities in systemic sclerosis. *Curr Opin Rheumatol* 1999; **11**: 495–502.
3 Artlett CM, Smith JB, Jimenez SA. Identification of fetal DNA and cells in skin lesions from women with systemic sclerosis. *N Engl J Med* 1998; **338**: 1186–1191.
4 Medsger Jr TA, Masi AT, Rodnan GP *et al*. Survival with systemic sclerosis (scleroderma). A life-table analysis of clinical and demographic factors in 309 patients. *Ann Intern Med* 1971; **75**: 369–376.
5 Binks M, Passweg JR, Furst D *et al*. Phase I/II trial of autologous stem cell transplantation in systemic sclerosis:

procedure related mortality and impact on skin disease. *Ann Rheum Dis* 2000; **60**: 577–584.
6 McSweeney PA, Nash RA, Sullivan KM *et al*. High-dose immunosuppressive therapy for severe systemic sclerosis: initial outcomes. *Blood* 2002; **100**: 1602–1610.
7 Clements PJ, Lachenbruch PA, Seibold JR *et al*. Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. *J Rheumatol* 1993; **20**: 1892–1896.
8 White B, Moore WC, Wigley FM *et al*. Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. *Ann Intern Med* 2000; **132**: 947–954.
9 O'Dell JR, Steigerwald JC, Kennaugh RC *et al*. Lack of clinical benefit after treatment of systemic sclerosis with total lymphoid irradiation. *J Rheumatol* 1989; **16**: 1050–1054.
10 Varga J, Haustein UF, Creech RH *et al*. Exaggerated radiation-induced fibrosis in patients with systemic sclerosis. *JAMA* 1991; **265**: 3292–3295.
11 Canadian Association of Radiation Oncologists. Breast radiotherapy after breast-conserving surgery. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. *Can Med Assoc J* 1998; **158** (Suppl. 3): S35–S42.
12 Bachleitner-Hofmann T, Machold K, Knobler R *et al*. Marked and sustained improvement of systemic sclerosis following polychemotherapy for coexistent multiple myeloma. *Clin Exp Rheumatol* 2002; **20**: 85–88.
13 Coghlan JG, Mukerjee D. The heart and pulmonary vasculature in scleroderma: clinical features and pathobiology. *Curr Opin Rheumatol* 2001; **13**: 495–499.
14 Tateishi-Yuyama E, Matsubara H, Murohora T *et al*. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone marrow cells: a pilot study and a randomised controlled trial. *Lancet* 2002; **360**: 427–435.
15 Inaba S, Egashira K, Komori K. Peripheral-blood or bone-marrow mononuclear cells for therapeutic angiogenesis. *Lancet* 2002; **360**: 2083–2084.
16 Stamm C, Westphal B, Kleine HD *et al*. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. *Lancet* 2003; **361**: 45–46.
17 Reyes M, Dudek A, Jahagirdar B *et al*. Origin of endothelial progenitors in human postnatal bone marrow. *J Clin Invest* 2002; **109**: 337–346.