Bone Marrow Transplantation (2007) 39, 435–437

www.nature.com/bmt

LETTER TO THE EDITOR

Non-myeloablative allogeneic hematopoietic stem cell transplantation for severe systemic sclerosis: graft-versus-autoimmunity without graft-versus-host disease?

Bone Marrow Transplantation (2007) **39,** 435–437. doi:10.1038/sj.bmt.1705611; published online 19 February 2007

No treatment for systemic sclerosis (SSc) has been shown to be curative to date. In an attempt to escalate immunosuppressive therapy, autologous hematopoietic stem cell transplantation (HSCT) has been employed with mixed results[1,2] whereas data on allogeneic HSCT in SSc has been sparse.[3,4] Herein, we report a patient with diffuse cutaneous SSc who successfully underwent non-myeloablative allogeneic HSCT from her HLA-identical sibling.

The patient is a 38-year-old female with SSc diagnosed 18 months before referral for transplant, and previously treated with prednisone without improvement. At referral, she had diffuse involvement of the face, and upper and lower extremities, with fixed contractures of the elbows and inter-phalangeal joints. The baseline Rodnan skin score was 25 (fingers/hands inevaluable owing to overly taut skin). Anti-Scl 70 and other auto-antibodies were negative. Two-dimensional echocardiogram revealed normal left ventricular function and an elevated pulmonary artery systolic pressure (PASP) of 31 mm Hg.

The patient and donor were histocompatible at HLA-A, HLA-B and HLA-DR loci with minor ABO mismatch (donor O+; recipient A+). Filgrastim-primed peripheral blood stem cells (cell dose 10.35×10^6/kg CD34) were harvested from the donor via apheresis and infused uneventfully following a conditioning regimen consisting of intravenous cyclophosphamide 200 mg/kg and alemtuzumab 100 mg. Graft-versus-host disease (GVHD) prophylaxis, as well as host-versus-graft prophylaxis to prevent allograft rejection, was with cyclosporine for 4 months and mycophenolate mofetil for 1 year. The patient's chimerism was studied serially via polymerase chain reaction for variable number of tandem repeats.

Neutrophil engraftment was achieved on day +9; platelet counts never dropped below 20×10^9/l. Clinical course post-HSCT was stable with no documented infections despite profound suppression of T-cell numbers for up to 12 months post-HSCT. By 4 weeks, joint mobility and skin thickness had improved. By 12 months, oral stricture had resolved and both elbows fully straighten without difficulty; although inter-phalangeal joint contractures remain. Her clinical parameters are summarized in Table 1. The quasi *t*-statistic (QTS) was computed to determine the significance of observed differences. This is defined as the ratio of the difference between the final and baseline observations to the average difference between adjacent observations; the bigger the value of the QTS above 1, the more statistically significant the change in final observation relative to baseline. Of the variables analyzed, the improvement in PASP was found to be significant (QTS = −3.75, that is, the overall improvement was 3.75 times greater than the average change between adjacent PASP readings). Rodnan skin scores also improved significantly (QTS = −2.75), despite initial skin scores being underestimated owing to inevaluable overly-taut areas. The patient achieved stable mixed chimerism that has persisted on follow-up (Figure 1). All immunosuppressants were discontinued by 12 months and the patient has never developed GVHD.

Currently available therapy for SSc is limited, with no studies demonstrating consistent benefit. Patients with diffuse cutaneous SSc have been shown to have a higher risk of premature death (adjusted hazard ratio 1.2; 95% CI 1.0–1.4). This justifies continued research into new modalities of treatment: such as either autologous or allogeneic HSCT.

Autologous HSCT for SSc has been performed with mixed results. Thirty-three patients, treated with a myeloablative total body radiation (TBI)-based regimen, had a mortality of 30% and disease progression of 30% (five of whom died from progressive disease).[2] The French, using a lympho-depleting regimen, reported five of eight initially responding patients relapsing after autologous HSCT.[2] The EBMT/EULAR registry reported a partial and complete response rate of 92% at 22.9 months among 50 cases, but a relapse rate of 35% among initially responding patients at 10 months.[1] Oyama *et al*., also using a lympho-depleting regimen, have reported no deaths in 10 patients with two relapses (American Society of Hematology 46th Annual Meeting, abstract 5195). Three randomized trials are currently underway: the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (www.astis-trial.com) in Europe, the American Scleroderma Stem Cell vs Immune Suppression Trial (ASSIST, www.clinicaltrials.gov, NCT00278525) and Scleroderma: cyclophosphamide or transplantation (SCOT, www.clinicaltrials.gov, NCT00114530). The former two utilize a lympho-depleting but non-myeloablative approach whereas the SCOT trial uses a TBI-based myeloablative approach.

Although the role of autologous HSCT in patients with SSc is still being assessed, the recurrence/progression of disease reported thus far raises concerns about the ability of this strategy to cure SSc. In contrast, following allogeneic HSCT, immune cells are regenerated from genetically different stem cells that will alter genetic susceptibility to

Table 1 Clinical outcomes and parameters

Baseline	*6 months*	*12 months*	*24 months*	*36 months*	*QTS*
(a) Serial Rodnan skin scores					
25	27	12	18	9	−2.75
Both hands/fingers not assessed as too taut	Right hand/fingers not assessed	Right hand/fingers not assessed	All areas assessed	All areas assessed	

	Baseline	*6 months*	*12 months*	*24 months*	*36 months*	*QTS*
(b) Serial cardiac and pulmonary function						
PASP (mm Hg)	31	30	27	24	22	−3.75
DLCO Hgb-Adj (% predicted)	76	56	81	80	82	0.37
DLCO/VA (% predicted)	87	75	97	101	101	1.1
LVEF (%)	55	60	70	55	55	0

Abbreviations: DLCO Hgb-Adj = diffusion capacity of lungs for carbon monoxide adjusted for hemoglobin; DLCO/VA = DLCO adjusted for volume averaging; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; QTS = quasi-*t* statistic.

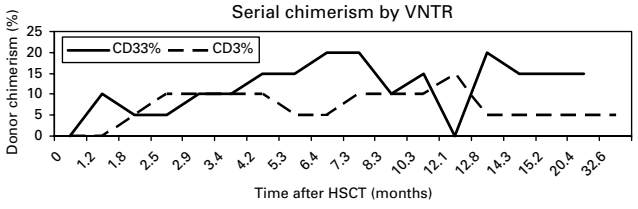

Figure 1 Serial chimerism studies.

disease. The pathogenesis of SSc has been postulated to involve decreased numbers of circulating endothelial progenitor cells (EPC),[5] which arise from the bone marrow HSC compartment; an allogeneic HSCT may thus provide a genetically distinct population of circulating EPC.

The major drawback of allogeneic HSCT is GVHD. In particular, severe cutaneous chronic GVHD may manifest as a scleroderma-like illness with significant morbidity. We chose to use alemtuzumab as it has been shown to significantly decrease occurrence of GVHD,[6] although its use has been associated with an increased incidence of opportunistic infections.

Our patient achieved a state of stable mixed chimerism, which may explain the absence of GVHD. Although mixed chimerism is usually an unfavorable state in hematological malignancies, the complete 'replacement' of host immune system may not be necessary for induction of tolerance. In animal models of lupus and autoimmune diabetes, mixed chimerism has been shown to induce remission of disease without GVHD.[7]

The concept of a 'graft-versus-autoimmunity' (GVA) effect (first hypothesized by Shimon Slavin and Alberto Marmont) has also been postulated to induce remission by donor-derived T lymphocytes eradicating host self-reacting lymphocytes, resulting in long-term remission.[8,9] Whether mixed chimerism is sufficient for control of autoimmunity, and to what degree donor-derived hemopoiesis is required, is uncertain: some reports have shown near complete chimerism being required; others not.[10] Existing clinical evidence is limited and controversial and the limitation of case reports and anecdotal evidence is recognized. In a recent report of two patients with SSc who underwent myeloablative allogeneic HSCT, one patient with full chimerism developed acute GVHD with skin desquamation and significant morbidity; then chronic GVHD necessitating multiple immunosuppressants and eventually succumbed to infection at 18 months.[4] In our patient, the persistence of 10–15% donor T cells appears to have been sufficient for disease control sustained at 36 months, possibly through GVA, and without the occurrence of a detrimental GVHD despite no immunosuppressants for 24 months. This was similar to the case of successful nonmyeloablative HSCT performed for a patient with both SSc and lupus in whom stable mixed chimerism resulted in remission from both diseases.[3]

In this case a non-myeloablative allogeneic HSCT was safely performed without GVHD and resulted in significant improvements in skin scores and PASP. In addition, mixed chimerism is stable for 3-years post-HSCT without immunosuppression, and is associated with disease amelioration. More patients will have to be treated to determine accurately safety, efficacy, and optimal level and durability of donor chimerism.

Y Loh[1], Y Oyama[1], L Statkute[1], L Verda[1], K Quigley[1], K Yaung[1], W Barr[2], B Jovanovic[3] and RK Burt[1]
[1]*Division of Immunotherapy, Northwestern University Feinberg Medical Center, Chicago, IL, USA;*
[2]*Division of Rheumatology, Northwestern University Feinberg Medical Center, Chicago, IL, USA and*
[3]*Department of Preventive Medicine, Northwestern University Feinberg Medical Center, Chicago, IL, USA*
E-mail: rburt@northwestern.edu

References

1 Farge D, Passweg J, van Laar JM, Marjanovic Z, Besenthal C, Finke J *et al.* Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. *Rheum Dis* 2004; **63**: 974–981.
2 Burt RK, Marmont A, Oyama Y, Slavin S, Arnold R, Hiepe F *et al.* Randomized controlled trials of autologous hemato-

poietic stem cell transplantation for autoimmune diseases: the evolution from myeloablative to lymphoablative transplant regimens. *Arthritis Rheum* 2006; **54**: 3750–3760.
3 Khorshid O, Hosing C, Bibawi S, Ueno N, Reveille J, Mayes MD *et al*. Nonmyeloablative stem cell transplant in a patient with advanced systemic sclerosis and systemic lupus erythematosus. *J Rheumatol* 2004; **31**: 2513–2516.
4 Nash RA, McSweeney PA, Nelson JL, Wener M, Georges GE, Langston AA *et al*. Allogeneic marrow transplantation in patients with severe systemic sclerosis. Resolution in dermal fibrosis. *Arthritis Rheum* 2006; **54**: 1982–1986.
5 Kuwana M, Okazaki Y, Yasuoka H, Kawakami Y, Ikeda Y. Defective vasculogenesis in systemic sclerosis. *Lancet* 2004; **364**: 603–610.
6 Kottaridis PD, Milligan DW, Chopra R, Chakraverty RK, Chakrabarti S, Robinson S *et al*. *In vivo* CAMPATH-1H prevents GvHD following nonmyeloablative stem-cell transplantation. *Blood* 2000; **96**: 2419–2425.
7 Wang B, Yamamoto Y, El-Badri NS, Good RA. Effective treatment of autoimmune disease and progressive renal disease by mixed bone-marrow transplantation that establishes a stable mixed chimerism in BXSB recipient mice. *Proc Nat Acad Sci USA* 1999; **96**: 3012–3016.
8 Slavin S, Nagler A, Varadi G, Or R. Graft vs autoimmunity following allogeneic non-myeloablative blood stem cell transplantation in a patient with chronic myelogenous leukemia and severe systemic psoriasis and psoriatic polyarthritis. *Exp Hematol* 2000; **28**: 853–857.
9 Marmont AM, Gualandi F, van Lint MT, Bacigalupo A. Refractory Evans' syndrome treated with allogeneic SCT followed by DLI. Demonstration of a graft-versus-autoimmunity effect. *Bone Marrow Transplant* 2003; **31**: 399–402.
10 Burt RK, Oyama Y, Verda L, Quigley K, Brush M, Yaung K *et al*. Induction of remission of severe and refractory rheumatoid arthritis by allogeneic mixed chimerism. *Arthritis Rheum* 2004; **50**: 2466–2470.