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Allogeneic Marrow Transplantation in Patients With Severe Systemic Sclerosis:

Resolution of Dermal Fibrosis

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Abstract

Objective—To evaluate the safety and efficacy of allogeneic hematopoietic cell transplantation (HCT) after myeloablative conditioning in patients with severe systemic sclerosis (SSc).

Methods—Eligibility criteria for the study included SSc patients with features indicative of a poor prognosis. The myeloablative conditioning regimen included busulfan, cyclophosphamide, and antithymocyte globulin. Prophylaxis for graft-versus-host disease (GVHD) consisted of cyclosporine and methotrexate. Bone marrow was transplanted from HLA-identical siblings.

Results—Two patients with diffuse cutaneous SSc and lung involvement who were refractory to conventional immunosuppressive treatment were enrolled in the study. In patient 1, there were no complications related to the conditioning regimen, and GVHD did not develop after transplantation. At 5 years after HCT, there was nearly complete resolution of the scleroderma and marked improvement in physical functioning. Internal organ function improved (lung) or remained stable. On examination of serial skin biopsy samples, there was resolution of the dermal fibrosis. Patient 2 experienced skin toxicity from the conditioning regimen and hypertensive crisis that was likely related to high-dose corticosteroids given for treatment of GVHD. Although this patient experienced an improvement in scleroderma and overall functioning, a fatal opportunistic infection developed 17 months after HCT.

Conclusion—Allogeneic HCT may result in sustained remission of SSc. GVHD and opportunistic infections are the major risks associated with allogeneic HCT for SSc, as for allogeneic HCT in general.

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Systemic sclerosis (SSc) is a multisystem auto-immune disease in which the skin, lungs, heart, gastrointestinal (GI) tract, and kidneys are major targets of vasculopathy and progressive fibrosis. There is variability in the clinical manifestations, but patients with diffuse cutaneous SSc and involvement of internal organs often have a markedly reduced lifespan (1).

For this study, it was hypothesized that allogeneic hematopoietic cell transplantation (HCT) could replace host autoreactive immune effector cells with donor-derived nonautoreactive cells and induce sustained remissions of SSc. As the methods for preventing infection and graft-versus-host disease (GVHD) have improved, the risks of transplant-related mortality and morbidity have diminished. Survival after allogeneic HCT for aplastic anemia, thalassemia, sickle cell disease, and chronic myelogenous leukemia in chronic phase have been reported to be between 85% and 95% (2–5). Preclinical studies of allogeneic HCT have been shown to be effective for the prevention or induction of sustained remissions in experimental models of auto-immune disease (6,7). Patients with autoimmune diseases who received transplants for other primary diseases have also experienced sustained remissions of the autoimmune disease (8).

In the present study, 2 patients with poor-prognosis SSc were treated with allogeneic HCT. We describe their outcomes herein.

PATIENTS AND METHODS

In 1999 and 2000, 2 patients with a diagnosis of severe SSc were enrolled in a study of allogeneic HCT. The study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center. The eligibility criteria were comparable with those of a study using autologous cells after high-dose immunosuppression therapies (HDIT) and included patients with a median survival of ~5 years (9). Evaluations included a determination of the modified Rodnan skin thickness score (MRSS) (10), skin biopsy, the Disability Index (DI) of the modified Health Assessment Questionnaire (M-HAQ) (11), and an evaluation of internal organs, as previously reported (9).

Both patients received a myeloablative conditioning regimen consisting of busulfan (targeted to a steady-state concentration of 700 ng/ml), cyclophosphamide (120 mg/kg), and equine antithymocyte globulin (90 mg/kg; Pfizer, New York, NY), and then transplantation of bone marrow from HLA-identical siblings. This conditioning regimen has previously been described in hematopoietic cell transplantation of patients with sickle cell disease (4). Cyclosporine and methotrexate were administered as prophylaxis for GVHD after transplantation (2–4). Patients were hospitalized from the start of the conditioning regimen until neutrophil engraftment and resolution of significant regimen-related toxicities. Infection prophylaxis included trimethoprim/sulfamethoxazole, fluconazole, and acyclovir (2–4).

RESULTS

Patient 1

The patient, a 38-year-old woman, was diagnosed as having SSc in February 1997. She continued to have worsening scleroderma and pulmonary function despite treatment with conventional agents, including penicillamine, cyclophosphamide, and prednisone. She was dyspneic on exertion and had abnormal pulmonary function (diffusing capacity for carbon monoxide corrected for hemoglobin [$DL_{CO_{adj}}$] 43% and forced vital capacity [FVC] 68%). High-resolution computed tomography (HRCT) scan of the chest demonstrated mild-to-moderate interstitial fibrosis of both lower lobes, with a ground-glass appearance. Analysis of bronchoalveolar lavage (BAL) fluid was consistent with alveolitis, with 4% neutrophils and no eosinophils.

The patient had diffuse scleroderma, with an MRSS of 36 (possible score 51). Episodes of Raynaud's phenomenon occurred daily. Multiple digital ulcerations were present over the proximal interphalangeal joints. Renal function was normal, with a serum creatinine level of 0.6 mg/dl and a creatinine clearance of 119 ml/minute. The findings of urinalysis were normal, with no significant proteinuria. The electrocardiogram and echocardiogram findings were normal. Gastrointestinal function was normal except for mild peristaltic esophageal abnormalities. At diagnosis, the patient was positive for antinuclear antibody (ANA), and the Scl-70 antibody level was 5 units/ml (equivocal).

In March 1999, after myeloablative conditioning, the patient received a transplant of bone marrow from an HLA-identical brother. The posttransplant course was complicated on day 30 with BK virus–associated hemorrhagic cystitis and on day 51 with bacterial pneumonia, which resolved with treatment. No GVHD developed, and cyclosporine was discontinued 7 months after transplantation. The patient experienced mild hypertension, which resolved after discontinuation of cyclosporine. The peak serum creatinine level of 1.1 mg/dl occurred at 3 months after HCT. The serum creatinine level was 0.8 mg/dl at 1 and 5 years after HCT.

After an initial decrease typically seen after myeloablative conditioning, the $DL_{CO_{adj}}$ was stable at 42% at 5 years after transplantation (Figure 1A). The FVC substantially improved, from 68% at baseline to 96% at 5 years. A BAL fluid analysis at both 2 and 3 years showed normal results, consistent with resolution of the alveolitis. At the 5-year followup, the ground-glass opacities had largely resolved on HRCT of the chest. No significant cardiac complications developed, and the left ventricular ejection fraction (LVEF) was 72% at 5 years. The MRSS gradually decreased to 2–4, with residual sclerodactyly at 5 years (Figure 1B).

Skin biopsies performed at baseline and 5 years after HCT showed resolution of the collagenous deposits in the dermis, stable thickness of the epidermis, and normal microvascular content (Figure 2). The patient's overall function, as assessed by the M-HAQ DI, improved, with a decrease in the score from 1.35 to 0 (Figure 1B). The frequency and severity of the Raynaud's phenomenon improved, and at 5 years, the episodes were infrequent and only occurred in the winter. Digital ulcerations had resolved by 1–2 months after HCT and did not recur.

Hematopoietic chimerism was assessed by fluorescent in situ hybridization studies of the X and Y chromosomes. At 1 and 3 months after HCT, the bone marrow was 99% and 99.4% donor-derived, respectively, and T cells from the peripheral blood were 100% and 98.8% donor-derived, respectively. At 2 years, both CD3+ and CD33+ cells from the peripheral blood were 100% donor-derived.

Patient 2

The patient, a 31-year-old woman, was diagnosed as having SSc in October 1998. She had continually worsening scleroderma and pulmonary function despite treatment with penicillamine, hydroxychloroquine, and methotrexate. At baseline, before HCT, she had weekly episodes of Raynaud's phenomenon, no digital ulcerations, and an MRSS of 40/51, with significant contractures. She had arthralgias in multiple joints. Pulmonary function was abnormal ($DL_{CO_{adj}}$ 63% and FVC 64%). An HRCT scan of the chest yielded normal results. Results of BAL fluid analysis showed marked abnormalities, with 48% lymphocytes and 3% neutrophils. Renal (serum creatinine level 0.6 mg/dl), cardiac (LVEF 65%), and gastrointestinal function were normal. ANA were positive (titer 1:320), and Scl-70 antibodies were negative.

In August 2000, the patient received a transplant of bone marrow from her HLA-identical sister. On day 4 after transplantation, she started to develop "patchy" desquamation of the skin on her legs and arms. This was attributed to skin toxicity from the conditioning. Over the next

several weeks, her skin improved, but she later developed acute GVHD, with recurrence of desquamation. She was treated for GVHD with prednisone (2 mg/kg) on day 37 after HCT. She developed a hypertensive crisis on day 39, with seizures and renal dysfunction, and her serum creatinine level increased to 4.4 mg/dl, but dialysis was not required. Antihypertensive agents were started, including sodium nitroprusside and an angiotensin-converting enzyme inhibitor, which were effective in resolving the hypertensive crisis. The dosage of prednisone was decreased to 1 mg/kg/day, cyclosporine was continued, and mycophenolate mofetil (MMF) was started. The patient experienced complete remission of the GVHD, so the prednisone and MMF were discontinued on day 80. The serum creatinine level at that time was 1.1 mg/dl, and her blood pressure was controlled with enalapril and amlodipine.

The patient developed chronic GVHD on day 100, and prednisone and MMF treatment were restarted. At 3 months after HCT, the CD3+ and CD33+ cells from the peripheral blood were 100% donor-derived. The skin score had improved to 28. Pulmonary function was considered to be stable during the early period posttransplantation ($DL_{CO_{adj}}$ 44% and FVC 65%) (Figure 1A). The percentage of lymphocytes in the BAL fluid had decreased to 9%, with 0% neutrophils.

During the first year after transplantation, there were flares of chronic GVHD manifesting as skin rash and oral ulcerations. Cyclosporine therapy was changed to tacrolimus. Other treatments initiated for the management of chronic GVHD were infliximab and topical therapy with clobetasol and tacrolimus. Pulmonary aspergillosis and nocardia developed, but HRCT scans of the chest showed resolution after treatment with posaconazole and sulfisoxazole.

At 16 months after HCT, the MRSS had decreased to 11, and the M-HAQ DI had decreased to 0.75 (Figure 1B). The patient reported no episodes of Raynaud's phenomenon or arthralgias since the HCT. The rash and mouth ulcerations associated with chronic GVHD had resolved, and the immunosuppressive agents were being tapered. Her serum creatinine level was normal at 1.1 mg/dl but had been as high as 2.1 mg/dl several months earlier, which was likely related to the tacrolimus treatment. There was 100% donor chimerism in the peripheral blood mononuclear cells. The patient remained ANA positive (titer 1:160).

At 18 months after HCT, before returning to Seattle for subsequent evaluation including pulmonary function tests, the patient presented to a local hospital with overwhelming sepsis, and she died. The cause of death was confirmed on autopsy to be secondary to pneumonia, with blood cultures positive for *Pseudomonas aeruginosa*.

DISCUSSION

Although the experience is limited, these 2 cases demonstrate both the potential benefits and risks of allogeneic HCT after myeloablative conditioning. In both cases, the MRSS improved gradually after allogeneic HCT, and this occurred even though chronic GVHD developed in patient 2. The improvement in the MRSS in a patient with chronic GVHD is consistent with reports that diffuse scleroderma is an infrequent complication of chronic GVHD after allogeneic HCT from an HLA-identical sibling (12). On serial biopsy samples of skin from patient 1, there was improvement and then resolution of the dermal fibrosis at 5 years after HCT. The resolution of fibrosis suggests that there is a dynamic status to the deposition of collagen in the skin. The skin "remodeling" is comparable to the resolution of myelofibrosis after allogeneic HCT for myeloproliferative disorders (13). Improvements in the skin have also been observed after HDIT and autologous HCT (9,14). Two multicenter randomized clinical trials of HDIT and autologous HCT are being conducted in Europe (Autologous Stemcell Transplantation International Scleroderma [ASTIS] trial) and in North America (Scleroderma Cyclophosphamide or Transplantation [SCOT] trial).

Data from pulmonary function tests beyond 3 months after HCT were obtained in patient 1 only. The $DL_{CO_{adj}}$ was stable at 5 years after HCT. This likely reflected SSc-related damage to the lungs that was irreversible, even though the FVC improved by 28%. A transient decrease in the $DL_{CO_{adj}}$ observed with HCT after intensive conditioning with cytotoxic agents has been reported in transplant recipients with normal lungs and in SSc patients after HDIT (9). In neither of the reported cases was the transient reduction in $DL_{CO_{adj}}$ after treatment associated with increased symptoms of dyspnea or exercise intolerance. It was also documented in this study that acute alveolitis resolved or improved after allogeneic HCT, although a followup BAL fluid analysis was not performed after 3 months in patient 2, so conclusions are limited.

Patient 2 experienced skin toxicity, an observation not previously reported in clinical trials of total body irradiation–based high-dose immunosuppression and autologous HCT for SSc (9). Skin toxicity has previously been described with the combination of busulfan and cyclophosphamide (15). Patients with SSc may be at risk of renal crisis with the use of cyclosporine and prednisone for the management of GVHD. No significant renal dysfunction was observed during the 7 months of cyclosporine treatment in patient 1. The renal crisis that developed in patient 2 was temporally associated with the administration of high-dose prednisone (2 mg/kg/day). Effective antihypertensive therapy and a reduction in the prednisone dosage to 1 mg/kg/day were associated with resolution of the renal crisis. Although cyclosporine may have contributed to the development of the renal crisis, it was otherwise not associated with significant renal dysfunction even though the patient continued to take calcineurin inhibitors for an additional 17 months.

There has been another case report in which a patient with features of SSc and systemic lupus erythematosus (SLE) had an allogeneic HCT after a nonmyeloablative conditioning regimen (16). The patient was markedly improved at 24 months after HCT, with resolution of the scleroderma. However, the patient experienced a flare of SLE that required a course of moderate-dose prednisone, which was later discontinued. The level of donor hematopoietic chimerism was ~15% in the myeloid and T cell compartments. It is not clear if disease remissions will be associated with stable mixed hematopoietic chimerism or if full donor chimerism will be required.

Although the risk is substantial, the potential benefit of allogeneic HCT is durable disease remission that may improve the patient's quality of life and overall function. About 30–60% of patients may require treatment for GVHD after allogeneic HCT (2,3). However, if patients can be successfully supported during treatment of the GVHD, the majority will be successfully discontinued from immunosuppressive agents (2). A workshop sponsored by the National Institutes of Health was recently conducted on the rationale for allogeneic HCT in patients with severe autoimmune diseases, including SSc (17). Because sustained remissions may be induced, insights from prospective studies of allogeneic HCT may assist in the design of nontransplant clinical trials and guide other SSc-related research activities.

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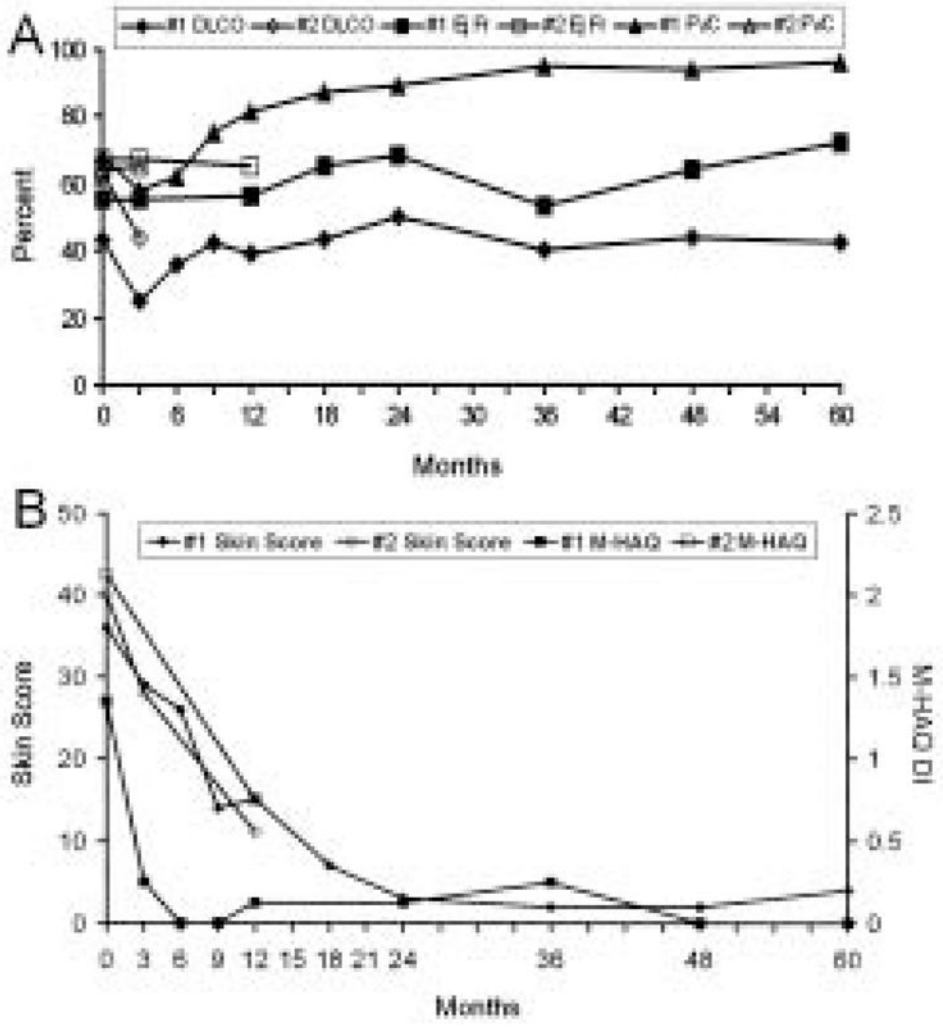

Figure 1.

Pulmonary and cardiac function, skin scores, and physical function after allogeneic hematopoietic cell transplantation (HCT) following myeloablative conditioning in 2 patients with severe systemic sclerosis (SSc). **A,** Pulmonary and cardiac function remained stable or improved after allogeneic HCT. Patient 1 was followed up for 5 years after allogeneic HCT and had significant improvement in forced vital capacity (FVC), and her diffusing capacity for carbon monoxide corrected for hemoglobin ($DL_{CO_{adj}}$) remained stable. Patient 2 did not have pulmonary function tests after the 3-month evaluation posttransplantation. Both patients experienced decreases in $DL_{CO_{adj}}$ during the first 3 months after HCT. The observed improvement in FVC in patient 1 is likely related to the nearly complete resolution of the scleroderma. Ej Fr = ejection fraction. **B,** The modified Rodnan skin thickness score and physical function, as measured by the Disability Index (DI) of the modified Health Assessment Questionnaire (M-HAQ), improved in both SSc patients after allogeneic HCT. The improvements in function documented by the M-HAQ DI after allogeneic HCT in both SSc patients are likely related to the decrease in the extent of scleroderma.

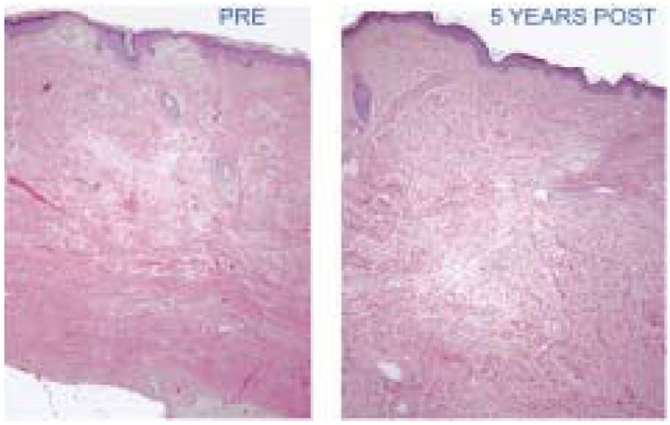

Figure 2.
Skin remodeling in systemic sclerosis (SSc) patients after allogeneic hematopoietic cell transplantation (HCT) following myeloablative conditioning. The skin biopsy sample obtained from patient 1 before HCT shows extensive collagen deposits in the dermis. At 5 years after allogeneic HCT, a skin biopsy sample taken from a site adjacent to the pretransplant biopsy site shows complete resolution of the dermal fibrosis, consistent with the occurrence of skin "remodeling." (Original magnification × 40.)