High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study

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More effective therapeutic strategies are required for patients with poor-prognosis systemic sclerosis (SSc). A phase 2 single-arm study of high-dose immunosuppressive therapy (HDIT) and autologous CD34-selected hematopoietic cell transplantation (HCT) was conducted in 34 patients with diffuse cutaneous SSc. HDIT included total body irradiation (800 cGy) with lung shielding, cyclophosphamide (120 mg/kg), and equine antithymocyte globulin (90 mg/kg). Neutrophil and platelet counts were recovered by 9 (range, 7 to 13) and 11 (range, 7 to 25) days after HCT, respectively. Seventeen of 27 (63%) evaluable patients who survived at least 1 year after HDIT had sustained responses at a median follow-up of 4 (range, 1 to 8) years. There was a major improvement in skin (modified Rodnan skin score, \(P < .001\)) and overall function (modified Health Assessment Questionnaire Disability Index, \(1.03; P < .001\)) at final evaluation. Importantly, for the first time, biopsies confirmed a statistically significant decrease of dermal fibrosis compared with baseline (\(P < .001\)). Lung, heart, and kidney function, in general, remained clinically stable.

There were 12 deaths during the study (transplantation-related, 8; SSc-related, 4). The estimated progression-free survival was 64% at 5 years. Sustained responses including a decrease in dermal fibrosis were observed exceeding those previously reported with other therapies. HDIT and autologous HCT for SSc should be evaluated in a randomized clinical trial.

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease with vasculopathy and progressive fibrosis that is highly variable in its clinical manifestations, but patients with diffuse cutaneous SSc and internal organ involvement have reduced life span.1,4 Although cyclophosphamide was recently observed to have a small beneficial effect, more effective therapies for the severe forms of SSc are required to improve outcome.5-9 In a report of the first 19 patients in this pilot study, it was observed that there was marked clinical improvement in the degree of the scleroderma and overall function with a median follow-up of 15 months.10 Now, in 34 patients, we report additional information on safety and show that there was a significant decrease in the degree of the scleroderma and dermal fibrosis, improved overall function and, in general, stability of internal organ function, and these responses were sustained at a median of 4 years after high-dose immunosuppressive therapy (HDIT).

Patients, materials, and methods

Patients

Between July 1997 and March 2005, 34 participants were enrolled in the study at the Fred Hutchinson Cancer Research Center (n = 19), University of Michigan (n = 7), Karmanos Cancer Institute (n = 4), Loma Linda University (n = 3), and Texas Transplant Institute (n = 1). The institutional review board at each center approved the study. Patients were registered for the study only after providing a signed consent to confirm that they had been fully informed, in accordance with the Declaration of Helsinki, of the investigational purposes of the study.

Study design

This pilot study was designed to assess the safety and potential efficacy of HDIT for severe SSc. Patients 65 years of age or less were eligible for study participation if they had early (4 years or less) diffuse scleroderma (modified Rodnan skin score [mRSS] 16 or greater) and significant visceral organ involvement as previously described.10 Patients were also included if there was progressive pulmonary disease with a decrease of at least 15% in forced vital capacity (FVC) or diffusion capacity of the lung for carbon monoxide adjusted for hemoglobin levels (DLCO/ht) in the previous 6 months with any skin involvement. The eligibility criteria selected patients with a mortality risk from SSc of approximately 50% at 5 years with conventional treatment, and these have been previously published.9,11 Study end points were safety of mobilization with granulocyte colony-stimulating factor (G-CSF), engraftment after transplantation of autologous CD34-selected hematopoietic cells (HCs), early and late regimen-related payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734.
of disease-modifying antirheumatic drugs (DMARDs). Disease response was defined as a decrease in mRSS (5 or more for baseline of up to 20, or more than 25% for baseline more than 20), improving pulmonary function (increase in FVC of more than 10% or DLCO$_{adj}$ of more than 15%), or a decrease in mHAQ (more than 0.4). Only patients who survived at least 1 year were considered evaluable for response because there were no scheduled evaluations performed 3 to 12 months after HDIT, and the duration of follow-up at 3 months was not adequate for evaluating response endpoints of fibrosis and organ function.

### Assessment of skin biopsies

Serial 3- to 4-mm full-thickness punch biopsies of skin were taken from the same location in an individual patient, either the lateral aspect of the forearm or the upper arm in the triceps region, in a subset of patients. Coded slides stained with hematoxylin and eosin (H&E) were prepared from formalin-fixed blocks and were analyzed for changes in the various components of skin, including epidermis, papillary and reticular dermis, adnexae, and subcutis. Deidentification and coding of the slides was done so that a blinded evaluation of the dermal fibrosis could be performed. The histologic sections of the skin were assessed on a Leica DM 3000 microscope (Leica Microsystems, Wetzlar, Germany), relying primarily on the 2.5× plan/0.07 NA, 5× plan/0.12 NA, and 10×/HC plan Fluotar.30 NA objectives, and also using a 20× HC plan apo/0.70 NA. Images were processed using Adobe Elements 4.0 and Adobe Photoshop CS version 8. Changes in fibrosis were graded on a 0-to-5 semiquantitative scale (Table 1; Figure 1). Because of the local variability in skin, even within a given location, and some qualitative variability between biopsies, a meaningful reduction in overall fibrosis score required changes of at least 2 grades.

### Statistics

For each of the clinical parameters assessed, posttransplantation values were compared with pretransplantation (baseline) values at the last time point in each of several posttransplantation time windows. The 1-sample $t$ test was used to test the null hypothesis that the difference between posttransplantation and baseline values was equal to 0. In addition to comparisons in specific time windows, generalized estimating equations (GEEs) were used to determine if the value of a clinical parameter increased or decreased with time (from baseline to the last measurement available). For these analyses, we tested for linear associations between time and each clinical parameter. All reported $P$ values are 2-sided, and those resulting from regression models were derived from the Wald test.

### Results

#### Patient characteristics

Patient characteristics at baseline are described in Table 2. All patients were considered to have a poor prognosis and had failed a median of 2 (range, 0 to 5) different immune-modifying treatments before being included in the clinical trial. All patients had pulmonary disease, although this may not have been the primary internal organ considered for protocol eligibility. The only patient with a skin score less than 16 (1 subject with an mRSS of 3) had progressive pulmonary disease and a DLCO$_{adj}$ of 48%. One patient had pulmonary arterial hypertension, 1 patient required total parenteral nutrition, 3 patients had a history of significant renal...

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### Table 1. Grading of dermal fibrosis in systemic sclerosis

<table>
<thead>
<tr>
<th>Dermal fibrosis grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No homogenization but there may be atrophic, thin straightened collagen bundles with increased amounts of interstitial ground substance</td>
</tr>
<tr>
<td>1</td>
<td>Less than 25% sclerosis with residual foci; some residual straightening or eosinophilic collagen bundles may be present</td>
</tr>
<tr>
<td>2</td>
<td>Focal sclerosis—less than 50% overall</td>
</tr>
<tr>
<td>3</td>
<td>Incomplete homogenization with spaces between the collagen bundles with 50% to 75% sclerotic change</td>
</tr>
<tr>
<td>4</td>
<td>Pandermal sclerosis without obvious expansion of the lower reticular dermis with some sparing of perineurium adipose tissue</td>
</tr>
<tr>
<td>5</td>
<td>Pandermal sclerosis with homogenization from the papillary to the reticular dermis; includes obvious widening of the reticular dermis below the eccrine coils with extension into the hypodermis and formation of fibrous septa</td>
</tr>
</tbody>
</table>
Table 2. Patient characteristics before transplantation (n = 34)

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Value</th>
<th>Frequency, no.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>41 (23-61)</td>
<td>34</td>
</tr>
<tr>
<td>Sex: M/F</td>
<td>8/26</td>
<td>34</td>
</tr>
<tr>
<td>Median skin score: mRSS (range)</td>
<td>30 (3-48)</td>
<td>34</td>
</tr>
<tr>
<td>Median DLCOadj, † % (range)</td>
<td>61 (40-83)</td>
<td>33</td>
</tr>
<tr>
<td>Median FVC, % (range)</td>
<td>71 (27-103)</td>
<td>34</td>
</tr>
<tr>
<td>Disease duration, mo (range)#</td>
<td>21 (4-51)</td>
<td>34</td>
</tr>
<tr>
<td>Immune-based therapy before HDIT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>15</td>
<td>34</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Etanercept</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>Relinax</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>Imuran</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>34</td>
</tr>
</tbody>
</table>

HRCT of chest
- Abnormal: 27
- Ground-glass: 12
- Interstitial fibrosis: 25
- Normal: 7
- Alveolitis by BAL: 16
- Median ejection fraction, % (range): 65 (47-80)
- Median serum creatinine level, mg/dL (range): 0.7 (0.4-1.7)
- Median mHAQ score (range): 1.88 (0.25-2.88)
- Hypothyroidism: 9

Organ dysfunction
- Lung‡: 34
- Kidney§: 2
- Heart: 9
- Gastrointestinal tract¶: 23

Autoantibodies
- Antinuclear antibodies: 25
- Scl-70: 11
- Anticentromere: 0
- Other: 9

**Table 3.** Apheresis, graft composition, and engraftment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobilization: no. of apheresis – back-up*</td>
<td>2 (2-7)</td>
</tr>
<tr>
<td>CD34-selected grafts</td>
<td></td>
</tr>
<tr>
<td>CD34⁺ cells × 10⁶/kg</td>
<td>4.02 (2.36-8.6)</td>
</tr>
<tr>
<td>CD3⁴⁺ cells × 10⁴/kg; n = 22</td>
<td>1.86 (0-25.2)</td>
</tr>
<tr>
<td>CD34 purity (%)</td>
<td>91 (55-99)</td>
</tr>
</tbody>
</table>

Engraftment after transplantation
- Days to neutrophil count above 500/μL† | 9 (7-13) |
- Days to platelet count above 20 000/μL‡ | 11 (7-25) |

**Table 4.** Summary of skin histology.

- Normal: 7
- Ground-glass: 12
- Interstitial fibrosis: 25
- Normal: 7
- Alveolitis by BAL: 16
- Median ejection fraction, % (range): 65 (47-80)
- Median serum creatinine level, mg/dL (range): 0.7 (0.4-1.7)
- Median mHAQ score (range): 1.88 (0.25-2.88)
- Hypothyroidism: 9

**Figure 1.** Dermal fibrosis grades 0 to 5.

- Grade 0 is normal—dermis with minimal fibrosis
- Grade 1 is mild fibrosis
- Grade 2 is moderate fibrosis
- Grade 3 is extensive sclerosis
- Grade 4 is pandermal fibrosis
- Grade 5 is markedly fibrotic

**Figure 2.** mRSS and mHAQ scores.

- mRSS: 0-5
- mHAQ: 0-3

**Figure 3.** Disease evaluations.

- Cardiac dysfunction was defined as ejection fraction below 50%, electrical dysfunction or renal crisis, and 5 patients had gastric antral vascular ectasia before HDIT.

**Table 3.** Apheresis, graft composition, and engraftment

- CD34⁺ cells × 10⁶/kg
- CD3⁺ cells × 10⁴/kg; n = 22
- CD34 purity (%) 91 (55-99)

**Figure 4.** Engraftment after transplantation.

- Days to neutrophil count above 500/μL† | 9 (7-13) |
- Days to platelet count above 20 000/μL‡ | 11 (7-25) |
Table 4. Change in clinical parameters after HDIT

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Difference from baseline (CI; P)</th>
<th>Final evaluation†</th>
<th>n</th>
<th>Years 1-2</th>
<th>Years 3-4</th>
<th>Years 5-8</th>
<th>Final evaluation;†</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRSS (0-51)</td>
<td>-30.12 (-25.71, -16.45; &lt; .001)</td>
<td>25</td>
<td></td>
<td>34</td>
<td>20.72, 17.56 (-14.40; &lt; .001)</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mHAQ (0-3)</td>
<td>1.85 (-1.60, -3.23; &gt; .01)</td>
<td>21</td>
<td></td>
<td>25.42, 17.05 (-11.72; &lt; .001)</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, %</td>
<td>71.53 (4.80, 0.11; .06)</td>
<td>23</td>
<td></td>
<td>22.08 (-11.72; &lt; .001)</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCOadj, %</td>
<td>60.09 (-3.60, 3.18; &gt; .01)</td>
<td>20</td>
<td></td>
<td>21.82 (-11.72; &lt; .001)</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63.24 (-3.60, 3.18; &gt; .01)</td>
<td>19</td>
<td></td>
<td>22.08 (-11.72; &lt; .001)</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.78 (0.04, 0.47; .26)</td>
<td>18</td>
<td></td>
<td>2.37 (4.80, 0.07; .06)</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Scl-70, %</td>
<td>0.26 (0.04, 0.47; .26)</td>
<td>17</td>
<td></td>
<td>6.04 (3.52, 17.20; &lt; .001)</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean difference between baseline and last evaluation for 27 patients who survived more than 1 year in the indicated period. Confidence intervals (95%) are within parentheses. Each patient was compared with his own baseline result.

†Mean difference between baseline and final evaluation after HDIT.

Significance (decrease of 0.36 per year [95% CI, 1.42 to -0.69], P = .001, GEE; Figure 2C) and DLCOadj values were decreased, but this did not achieve statistical significance (decrease of 0.36 per year [95% CI, 1.42 to -0.69], P = .50; GEE; Figure 2D). The HRCT scans of the chest were centrally reviewed in 21 of the evaluable patients. No significant changes were observed after HDIT except for the 6 patients with reactivation of disease in the lungs. In 6 of 7 patients who survived at least 1 year and were centrally reviewed, “ground-glass” abnormalities at baseline decreased and evolved to interstitial fibrosis, and in the other patient the findings remained unchanged. There was a statistically significant but small increase in serum creatinine and decrease in ejection fraction (Table 4; Figure 2E,F).

No patient experienced renal crisis or a significant loss of kidney function after the early treatment-related events. There was no statistically significant change in the ANA titer (P = .26). Of 11 patients who had a positive test for anti-Scl-70, 2 had become negative at last follow-up (6 and 8 years).

Among patients who survived more than 1 year, overall function as assessed by mHAQ was improved in 19 of 25 and disease responses were observed in skin of 23 of 25 and lung of 8 of 27 patients. All responders in lung had an improved FVC, and 2 patients also had an improved DLCOadj. Disease activation was observed in 10 (37%) patients at a median of 1 (range, 1 to 6) years after HDIT. Disease activation or progression occurred in lung (n = 6), heart (n = 1), or in other systems that required DMARD treatment (n = 3). Four of 6 patients with lung disease activation/progression died at a median of 4 (range, 1 to 5) years after HDIT. A patient with disease activation in the lung also developed a new anti-Smith antibody at more than 3 years associated with new onset of thrombocytopenia. A second patient with disease activation who had the onset of a syndrome resembling rheumatoid arthritis and required DMARD therapy developed a newly positive rheumatoid factor at more than 1 year.

Infections

We previously reported a fatal Epstein-Barr virus (EBV)-associated posttransplantation lymphoproliferative disorder (PTLD) in 1 patient associated with changing from horse to rabbit ATG in the HDIT regimen. One case of CMV disease (gastroenteritis) occurred that resolved with antiviral treatment. Bacteremic episodes were observed in 11 patients and were usually associated with a central line. The microorganism identified in 6 of these bacteremic episodes was staphylococcus (coagulase negative). Three months after HDIT, infections were infrequent despite persistent lymphopenia. Reactivation of varicella zoster virus (VZV) (shingles) occurred in 6 patients at a median of 8 (range, 3 to 26) months after HDIT in patients not receiving preventive acyclovir (Table 5).

Regimen-related complications

Fatal pulmonary toxicities were observed in 2 of the first 8 patients on study and were previously reported. No further similar pulmonary events occurred after lung shielding was adopted for TBI. Renal crisis or dysfunction occurred in 6 patients, 3 of whom
had a history of renal crisis or renal dysfunction before study treatment. All adverse renal events first occurred less than 2 months after HDIT. Dialysis was required in 2 patients, but other complications developed after prolonged hospitalization and the patients died at day 123 and 191. A third patient required dialysis and died on day 14 after a sepsis syndrome (no microorganism isolated) and multiorgan failure. A fourth patient required dialysis for 20 months, both the estimated overall and required dialysis for 20 months. Both the estimated overall and disease-related deaths (Table 6). SSc-related organ dysfunction contributed to 6 of the 7 treatment-related deaths that occurred in the first year after HCT. There was 1 treatment-related event of renal failure that required dialysis for 20 months. Both the estimated overall and progression-free survival were 64% at 5 years (Figure 5).

Survival
There were 8 (23%) treatment-related and 4 (12%) disease-related deaths. SSc-related organ dysfunction contributed to 6 of the 7 treatment-related deaths that occurred in the first year after HCT. There was 1 treatment-related event of renal failure that required dialysis for 20 months. Both the estimated overall and progression-free survival were 64% at 5 years (Figure 5).

Discussion
This report demonstrates a major decrease of the dermal fibrosis by histopathology associated with an improvement of the mRSS after standard treatment regimens or HDIT and autologous HCT for SSc. This suggests that the dermal fibrosis of SSc is in a dynamic state and disease activity is required to maintain it. Improvements of the skin and resolution of dermal fibrosis have also been observed in SSc patients after allogeneic HCT.23,24 No differences in mRSS were observed in a randomized clinical trial of methotrexate.25 At 2 years in another clinical trial, patients with diffuse scleroderma

Figure 2. Change in modified Rodnan skin score (mRSS), modified Health Assessment Questionnaire (mHAQ) score, and organ function after high-dose immunosuppressive therapy (HDIT) and autologous hematopoietic cell transplantation. A determination was made as to whether a parameter value was statistically significantly increasing or decreasing over time using a generalized estimating equation (GEE) model. The bold black solid line represents the mean value over time for the parameter of interest. The bold black dotted line represents an estimate of the modeled linear relationship between the parameter value and time and summarizes the results of the GEE models. The gray solid lines are parameter values for individual patients. The mean mRSS and mHAQ values statistically significantly decreased with time after HDIT (both \( P < .001 \); panels A and B, respectively). The mean values for diffusion capacity of the lung for carbon monoxide (DLCO) adjusted for hemoglobin levels did not statistically significantly change (\( P = .50 \), panel C), and forced vital capacity statistically significantly increased with time (\( P = .01 \), panel D). The mean values for serum creatinine and ejection fraction statistically significantly increased and decreased with time (\( P = .01 \) and \( P = .04 \); panels E and F, respectively).
had a mean decrease in mRSS of 4.8 and 6.9 in the low- and high-dose arms of D-penicillamine, respectively. A very modest decrease in the grade of dermal fibrosis was observed in 4 of 10 patients that had a dermal fibrosis grade of 0 to 1 at the time of last skin biopsy. The median follow-up was 4 (range, 1 to 6) years after HDIT and autologous HCT.

In this clinical trial of HDIT, there were sustained responses at a median of 4 years consisting of a marked reduction in mRSS, had a mean decrease of 3 grades of a possible 5, and 7 of 10 patients had dermal fibrosis grades of only 0 or 1 at last follow-up after the more intensive HDIT including TBI. More importantly, both grading systems reflect the improvement in the skin score. The skin “remodeling” that has been reported after HDIT and either autologous or allogeneic HCT may be comparable to the “remodeling” of fibrotic bone marrow that was observed after successful allogeneic HCT for myeloproliferative disorders. Progression in other organs was observed in some patients even though a skin response occurred.

In this clinical trial of HDIT, there were sustained responses at a median of 4 years consisting of a marked reduction in mRSS, had a mean decrease of 3 grades of a possible 5, and 7 of 10 patients had dermal fibrosis grades of only 0 or 1 at last follow-up after the more intensive HDIT including TBI. More importantly, both grading systems reflect the improvement in the skin score. The skin “remodeling” that has been reported after HDIT and either autologous or allogeneic HCT may be comparable to the “remodeling” of fibrotic bone marrow that was observed after successful allogeneic HCT for myeloproliferative disorders. Progression in other organs was observed in some patients even though a skin response occurred.

In this clinical trial of HDIT, there were sustained responses at a median of 4 years consisting of a marked reduction in mRSS,
Table 6. Cause of death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No.</th>
<th>Time to event, mo after HDIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure: idiopathic pneumonitis + SSc</td>
<td>2</td>
<td>2, 2</td>
</tr>
<tr>
<td>EBV-PTLD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal crisis/failure</td>
<td>2</td>
<td>4, 6</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Multorgan failure and pulmonary hemorrhage</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Myelodyplastic syndrome</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>Disease related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure*</td>
<td>4</td>
<td>12, 44, 50, 59</td>
</tr>
</tbody>
</table>

*In 1 patient the terminal event was a gastrointestinal bleed.

Improved overall function and, in general, clinically stable internal organ function. Although overall mortality at 5 years was 36% and treatment-related mortality was 23%, revisions to the treatment plan and better patient selection based on the experience obtained in the pilot study should significantly decrease the risk of treatment-related deaths even further. In the early phase of the experience with HDIT and autologous HCT reported by the European League Against Rheumatism-European Group for Blood and Marrow Transplantation (EULAR/EBMT), treatment-related mortality was 17%. In an update of a randomized clinical trial conducted by the same group, there has been no treatment-related mortality or unexpected severe toxicities. This was ascribed to better patient selection but also may relate to increased experience in managing patients with SSc in a transplantation program.

Although limited in number, other clinical trials of HDIT have been conducted. In a single center study of high-dose therapy with a single agent (cyclophosphamide or melphalan) and autologous HCT, major or partial responses were observed in 8 of 11 patients, but at a median of 18 months, 8 patients had not responded or had relapsed. Four (36%) patients had died by 18 months after HDIT. In a report from the European Group of Blood and Marrow Transplantation on 57 patients in their registry with a median follow-up of 20 months, the cumulative probability of disease progression at 5 years was 48% after treatment with mostly high-dose cyclophosphamide with or without T-cell–specific antibodies. The cumulative probability of survival at 5 years was 72%. Skin responses were observed in both studies. The higher response rate that we observed in this study and was sustained for a median of 4 years may have resulted from the increased intensity of the pretransplantation immunosuppressive regimen with cyclophosphamide and ATG in combination with TBI. Increased intensity of the high-dose immunosuppressive therapy regimen has been associated with a lower relapse rate of the autoimmune disease.

Compared with baseline, there was a statistically but not clinically significant decrease of 7% in DLCO_adj at the final evaluation. There was a predictable, transient, early decrease in DLCO_adj with recovery by 6 to 12 months after HDIT, which is also observed in patients with normal lungs after HCT for hematologic malignancies. Six patients had disease activation/progression in the lungs, 4 of whom died. However, the average DLCO_adj remained stable over time when evaluated using the general estimating equation, and FVC remained stable or improved. There were small but statistically significant changes in serum creatinine levels and ejection fraction at final evaluation compared with baseline, but these changes were not clinically relevant for most patients. Visceral organ function in general remained stable after HDIT for most patients.

It has been previously reported that there was recovery of CD4+ T-cell counts at 2 years after HDIT. However, sustained responses were observed in 63% of patients at a median of 4 years. Immune recovery after HDIT is associated with increasing thymic-derived naïve CD4+ T cells with a decrease in memory T cells, an increase in regulatory T cells, and broader clonal diversity than was present before HDIT. These late immune changes support the conclusion that sustained responses may have resulted from the immunomodulatory effects of HDIT in addition to the early immunosuppression and depletion of autoreactive T cells. The development of new autoantibodies and clinical changes in the manifestations of the autoimmune disease after HCT might have been the natural history of the disease process. However, the immunomodulatory effects of HDIT and autologous HCT may have also resulted in the development of a second autoimmune disorder.

In the early phase of the pilot study, risks of HDIT specific to SSc were identified. Shielding of the lungs during TBI reduced the risks of pulmonary toxicity. EBV-associated PTLD developed only after equine ATG was replaced by rabbit ATG, so caution is necessary when adjustments to the intensity of the regimen are made and should be limited. Renal crisis/dysfunction was observed after HDIT, and it is not clear if some component of the treatment or supportive care contributed to this. Close monitoring of blood pressure and early intervention may mitigate the risk for development of renal crisis. Late adverse effects previously associated with higher doses of TBI such as hypothyroidism and cataracts were infrequent. MDS was diagnosed in 2 patients, 1 in whom pretransplantation chromosomal abnormalities were observed that were similar to the karyotypic changes of the MDS after HDIT and the other in whom a total dose of cyclophosphamide (more than 27 g) was administered before study treatment. Although high-dose chemoradiotherapy has been associated with an increased risk of secondary MDS or acute myelocytic leukemia (AML), the intensity of the pretransplantation chemotherapy appears to be an additional risk factor. A contributing factor to the development of the stage I non–small cell carcinoma of the lung in one of the patients was a history of smoking. In the modified HDIT regimen, lung radiation exposure is only 200 cGy. A higher risk of secondary solid tumors has also been observed after high-dose chemoradiotherapy for treatment of hematologic malignancies. However, TBI at doses below 1000 cGy did not increase the risk of secondary MDS/AML or solid tumors compared with chemotherapy-only regimens. All patients will require continued follow-up after HDIT to monitor stability.
of the disease and for late effects of treatment. Limiting cytotoxic therapy (eg, cyclophosphamide) before HDIT may help reduce the risk of late secondary malignancies.

In this pilot study with a median follow-up of 4 years, substantial improvement in skin involvement occurred, confirmed by clear histologic improvement or resolution of dermal fibrosis. This is the first description of this grading system for dermal fibrosis, and further studies on a second data set are required for validation if it is to be used as a clinical tool. There was also substantial improvement in overall function, and there was general stability of internal organ involvement over time. Patients included in this study were within 4 years from diagnosis with non-Raynaud symptoms of SSc, so it is unknown if similar results would be observed after HDIT in patients with longer duration of disease. Important clinical issues in the use of HDIT and autologous HCT for SSc were identified and led to successful protocol modifications. Future studies should consider renal shielding during TBI. The observations of sustained disease stabilization and improved function in this study were encouraging; however, we cannot be certain that this outcome is a significant improvement over the natural history of the disease. A National Institutes of Health (NIH)–sponsored randomized clinical trial (Scleroderma: Cyclophosphamide or Transplant [SCOT]) based on the pilot study described in this report is now being conducted in the United States that compares HDIT and autologous HCT to pulse cyclophosphamide.

In addition, a second randomized clinical trial (Autologous Stem Cell Transplantation International Scleroderma Trial [ASTIS]) is being conducted in Europe in which high-dose cyclophosphamide and autologous HCT are compared with pulse cyclophosphamide.

References


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High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study