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Nonmyeloblastic Hematopoietic Stem Cell Transplantation for Systemic Lupus Erythematosus

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Context Manifestations of systemic lupus erythematosus (SLE) may in most patients be ameliorated with medications that suppress the immune system. Nevertheless, there remains a subset of SLE patients for whom current strategies are insufficient to control disease.

Objective To assess the safety of intense immunosuppression and autologous hematopoietic stem cell support in patients with severe and treatment-refractory SLE.

Design, Setting, and Participants A single-arm trial of 50 patients with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement. Patients were enrolled from April 1997 through January 2005 in an autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) study at a single US medical center.

Interventions Peripheral blood stem cells were mobilized with cyclophosphamide (2.0 g/m²) and granulocyte colony-stimulating factor (5 µg/kg per day), enriched ex vivo by CD34+/H11001 immunoselection, cryopreserved, and reinfused after treatment with cyclophosphamide (200 mg/kg) and equine antithymocyte globulin (90 mg/kg).

Main Outcome Measures The primary end point was survival, both overall and disease-free. Secondary end points included SLE Disease Activity Index (SLEDAI), serology (antinuclear antibody [ANA] and anti–double-stranded (ds) DNA), complement C3 and C4, and changes in renal and pulmonary organ function assessed before treatment and at 6 months, 12 months, and then yearly for 5 years.

Results Fifty patients were enrolled and underwent stem cell mobilization. Two patients died after mobilization, one from disseminated mucormycosis and another from active lupus after postponing the transplantation for 4 months. Forty-eight patients underwent nonmyeloablative HSCT. Treatment-related mortality was 2% (1/50). By intention to treat, treatment-related mortality was 4% (2/50). With a mean follow-up of 29 months (range, 6 months to 7.5 years) for patients undergoing HSCT, overall 5-year survival was 84%, and probability of disease-free survival at 5 years following HSCT was 50%. Secondary analysis demonstrated stabilization of renal function and significant improvement in SLEDAI score, ANA, anti–ds DNA, complement, and carbon monoxide diffusion lung capacity adjusted for hemoglobin.

Conclusions In treatment-refractory SLE, autologous nonmyeloablative HSCT results in amelioration of disease activity, improvement in serologic markers, and either stabilization or reversal of organ dysfunction. These data are nonrandomized and thus preliminary, providing the foundation and justification for a definitive randomized trial.

Clinical Trial Registration ClinicalTrials.gov Identifier: NCT00271934

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shorten the interval of conditioning fused as a supportive blood product to phocytes before HSC reinfusion. In the resistant nonmitotic memory T lymphocytes before HSC reinfusion. In the second step of the treatment, autologous CD34-enriched HSCs are infused as a supportive blood product to shorten the interval of conditioning regimen–related neutropenia. The lupus-specific conditioning regimen was based on dose escalation of a standard lupus lymphotoxic drug, cyclophosphamide. In addition, antithymocyte globulin (ATG) was added to eliminate cyclophosphamide-resistant nonmitotic memory T lymphocytes before HSC reinfusion. In the second step of the treatment, autologous CD34-enriched HSCs are infused as a supportive blood product to shorten the interval of conditioning regimen–related neutropenia. 

HSCT is a salvage therapy designed to treat refractory disease. Therefore, physicians referred patients for HSCT after the exhaustion of available treatments. Patients were receiving and their disease was not responding to a number of newer treatments such as mycophenolate mofetil and rituximab before referral. Therefore, this study was undertaken to determine whether HSCT could be performed safely as a salvage therapy in patients with SLE refractory to current therapies and whether there is sufficient evidence of efficacy to justify a definitive randomized trial. Short-term outcome of the first 15 patients was previously reported. We now report outcome on all 50 patients enrolled in the study.

METHODS

Patient Eligibility

From April 1997 through January 2005, 50 patients with SLE refractory to standard therapies were enrolled in an autologous HSCT trial at Northwestern Memorial Hospital (Chicago, Ill) after signing informed consent. The study was approved by an institutional review board and the US Food and Drug Administration (IDE 6559). The patients were from 20 states. Race was recorded as reported by the patient and was assessed to confirm that all ethnic groups were able to participate. All patients had at least 4 of 11 American College of Rheumatology criteria for SLE and required more than 20 mg/d of prednisone or its equivalent despite use of cyclophosphamide. Patient eligibility criteria included World Health Organization class III or IV glomerulonephritis, involvement of the lung (vasculitis, pneumonitis, alveolar hemorrhage), involvement of the central nervous system (cerebritis or transverse myelitis), vasculitis (confirmed by biopsy or angiogram), myositis (biopsy confirmed), transfusion-dependent autoimmune cytopenias, severe serositis (symptomatic pericardial or pleural effusions causing shortness of breath), hemodynamic compromise, or chronic and disabling pain despite narcotic use), ulcerative muco-cutaneous disease, or antiphospholipid syndrome (APS) as defined by the Sapporo criteria. Nephritis required failure of 6 or more monthly pulses of cyclophosphamide. Nonrenal visceral organ involvement required failure of at least 3 months of cyclophosphamide. The definition of APS required recurrent thrombosis despite therapeutic warfarin or low-molecular-weight heparin (LMWH) anticoagulation. Patient eligibility was confirmed by the transplantation physician, rheumatologist, and, where indicated, pulmonologists and nephrologists.

Outcome Characteristics

Primary outcomes were overall survival and disease remission, which is defined according to the Responder Index for Lupus Erythematosus (RIFLE) as requiring no immunosuppressive medications except physiologic doses of corticosteroids (ie, ≤10 mg/d of prednisone or corticosteroid equivalent or hydroxychloroquine). Secondary characteristics included Systemic Lupus Erythematosus Disease Activity Index (SLE-DAD), lupus serology (antinuclear antibody [ANA], anti–double-stranded [ds] DNA antibody), comple-

Stem Cell Mobilization and Conditioning

Peripheral blood stem cells were mobilized with cyclophosphamide (2.0 g/m²) and granulocyte colony-stimulating factor (G-CSF) at 5 µg/kg per day administered subcutaneously daily beginning 3 days later. Leukapheresis was initiated when the white blood cell count reached 1000/µL and continued daily until the number of stem cells exceeded 1.4 × 10⁶ CD34+ cells/kg after immunoselection with a stem cell concentrator (Isolux; Nexcel, Irvine, Calif or Ceprate; Cellpro, Bothell, Wash). The conditioning regimen consisted of intravenous cyclophosphamide, 50 mg/kg daily, 5, 4, 3, and 2 days before transplantation (total dose 200 mg/kg) and intravenous equine ATG, 30 mg/kg daily, 4, 3, and 2 days before transplantation (total dose 90 mg/kg). The conditioning regimen was not started until at least 14 days after stem cell apheresis to allow for 2-week microbial cultures on the CD34 selected product to demonstrate sterility.

Antibiotic Prophylaxis

The prophylactic antibiotic regimen included on the day of admission for HSCT aerosolized pentamidine (300 mg) once; daily fluoroquinolone (ciprofloxacin or levofloxacin) changed to intravenous cefepime on neutropenia; daily ambisome or voriconazole, and either daily acyclovir or valacyclovir. Injections of G-CSF (5 µg/kg per day) were started on day 0 (day of stem cell infusion) and continued until the resolution of neutropenia (absolute neutrophil count >1000/µL). Patients continued to take prophylactic monthly pentamidine or sulfamethoxazole/
trimethoprim 3 times per week and daily fluconazole or (if receiving >10 mg/d of prednisone) voriconazole for 6 months, whereas daily acyclovir or valacyclovir was administered twice a day for 1 year after the transplantation.

Fluid and Electrolytes
During and for 24 hours after cyclophosphamide administration, patients without compromised renal function underwent hyperhydration (normal saline at 150-200 mL/h) combined with diuretics to expedite cyclophosphamide excretion. Patients with compromised renal function who were unable to tolerate hyperhydration were treated with bladder irrigation and intravenous mesna, 50 mg/kg, infused during 24 hours with each cyclophosphamide dose. Patients receiving dialysis underwent the procedure the morning after each dose of cyclophosphamide.

Anticoagulation Prophylaxis
For patients receiving anticoagulation or with a history of APS, 1 to 2 weeks before admission, warfarin anticoagulation was discontinued and therapeutic anticoagulation was initiated with either subcutaneous enoxaparin, 1.0 mg/kg every 12 hours (reduced to once a day for creatinine clearance <30 mL/h), or subcutaneous dalteparin, 200 U/kg per day (reduced to 100 U/kg per day for creatinine clearance <30 mL/h). After the conditioning regimen, when platelet counts fell below 50,000/mL, LMWH was adjusted for a prophylaxis dose of either enoxaparin at 40 mg/kg per day or dalteparin at 5000 U/d.

Blood Transfusions
Platelet transfusions were given to maintain platelet counts greater than 20,000/µL in patients without need of anticoagulation or greater than 30,000/µL if patients were receiving anticoagulation. Packed red blood cells (PRBCs) were transfused for hemoglobin level less than 8.0 g/dL. Platelets and PRBCs were irradiated, leukocyte depleted, and deemed free of cytomegalovirus (CMV).

Follow-up
All patients underwent treatment at Northwestern Memorial Hospital. After HSCT, patients returned for scheduled follow-up at 6 and 12 months and then yearly thereafter. Medical history, physical examination, serologic testing, and necessary imaging studies were performed during follow-up visits. If a patient was not able to return for follow-up, medical records and laboratory blood-testing results were collected from the local physician or medical facility. If a patient refused or did not complete a test, the patient remained in the study, provided that he or she participated with the next follow-up analysis.

Statistical Analysis
Nonparametric t test analysis using Statistica software (Tulsa, Okla) was used for pairwise comparisons of pre- and post-HSCT variables (SLEDAI, ANA, anti-ds DNA, C3, C4, creatinine clearance, and carbon monoxide diffusion lung capacity corrected for hemoglobin). Statistical significance was set at P < .05. Overall and disease-free survival was analyzed using the Kaplan-Meier method.

RESULTS
Pre-HSCT Patient Demographics
Fifty patients were enrolled in the trial. Forty-eight patients underwent HSCT. The mean follow-up was 29 months (range, 6 months to 7.5 years). Table 1 displays patient demographics and medication history. Twenty-one patients, all of whom had a history of lupus nephritis, were taking antihypertensive medications.

Pre-HSCT Disease Manifestations
Table 2 lists pre-HSCT disease manifestations and the number of patients...
affected. Central nervous system involvement (cerebritis/myelitis) manifested as seizures, psychosis, paraparesis, headache, aseptic meningitis, hallucinations, focal deficits, transient ischemic attacks, or transverse myelitis not explained by a non-SLE pathogenesis. Immunomediected cytopenias included idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), and disease-related pancytopenia and neutropenia.

**Stem Cell Mobilization**

Stem cell collection occurred 10 days after cyclophosphamide administration and required a mean of 2.5 apheresis procedures (range, 1-11) to harvest more than $1.4 \times 10^{10}$ CD34+ cells/kg after CD34+ immonoselection. The mean number of CD3+ T cells in the apheresis and final CD34+ -enriched product was $1.67 \times 10^9$ and $13.63 \times 10^9$ CD3+ cells/kg, respectively. The mean number of preimmunoselected and postimunoselected CD34+ cells/kg was 8.95 $\times 10^9$ and 5.46 $\times 10^9$, respectively.

**Toxicity**

Time to recovery of absolute neutrophil count greater than 500/µL and platelet count greater than 20,000/µL was a mean of 9 days (range, 7-13 days) and 10 days (range, 7-22 days), respectively (Table 3). The mean number of PRBC and single-donor platelet transfusions was 5.4 (range, 0-15 transfusions) and 6.5 (range, 0-20 transfusions), respectively. The mean day of hospital discharge was posttransplantation day 14 (range, 9-26 days).

One death occurred from disseminated mucormycosis presenting 1 week after stem cell mobilization but before transplantation was started, for a treatment-related mortality rate of 2% (1/50). One patient had *Pneumocystis jiroveci* pneumonia on bronchoscopy and esophageal candidiasis on endoscopy after mobilization. Four patients developed gram-positive bacteremia during mobilization, none of whom had bacteremia during transplantation. Fourteen patients had bacteremia (predominantly gram positive) during transplantation. No patient with bacteremia developed evidence of sepsis (hypotension or impaired organ perfusion). During transplantation, peritoneal fluid specimens from 1 patient receiving long-term peritoneal dialysis grew *Candida parapsilosis*, and blood specimens from 1 patient grew *Candida glabrata*. Four patients had positive stool-culture results: 3 for *Clostridium difficile* and 1 for *Salmonella*. Cytomegalovirus viremia without evidence for invasive CMV disease was documented in 2 patients within 100 days of transplantation.

Late infections (>100 days after HSCT) were uncommon. One patient developed *P. jiroveci* pneumonia and 5 patients developed herpes zoster. One patient with Libman-Sachs endocarditis complicated by a history of preenrollment methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis died from recurrent MRSA endocarditis at 18 months following HSCT while in remission and receiving no immnosuppression.

Two of the first 6 patients (both with nephritis) required intubation and mechanical ventilation for pulmonary edema as a result of volume overload. Pulmonary symptoms resolved with ultrafiltration. Thereafter, for patients with nephritis, treatment guidelines were changed from hyperhydration to continuous intravenous infusion of mesna and bladder irrigation without hyperhydration. In the last 44 patients, although 4 received additional supplemental oxygen, none required intubation. All preenrollment oxygen-dependent patients tolerated HSCT without further pulmonary deterioration. One patient was enrolled with acute alveolar hemorrhage requiring 40% oxygen by facemask, and 4 patients with home oxygen dependency underwent HSCT.

Three patients with end-stage renal failure who were receiving long-term peritoneal dialysis or hemodialysis and 2 patients with nephritis who were receiving acute hemodialysis underwent HSCT without complications. Hemodialysis was performed 12 hours after each dose of cyclophosphamide.

Although the regimen caused no mucositis, a cytokine release syndrome with combinations of fever, tachycardia, shortness of breath, rash, hypotension, or myalgias/arthritis occurred after ATG administration and was difficult to differentiate from symptoms of active SLE. Three patients without a history of pretransplantation immunomediated hematologic problems developed reversible post-HSCT–acquired factor VIII deficiency (2 patients) or ITP (1 patient) (Table 3). Idiopathic thrombocytopenic purpura responded to intravenous immunoglobulin (IV Ig). For patients with factor VIII deficiency, the condition in one responded to IV Ig, whereas in the other it remitted after treatment with IV Ig, rituximab, and pulse cyclophosphamide.

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**Table 2. Pretransplantation Disease Manifestations**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Patients</th>
<th>No. of Patients for Whom Manifestation Was a Primary Indication for HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Cerebritis/myelitis</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Serositis</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Nephritis</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Raynaud syndrome</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Myositis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: HSCT, hematopoietic stem cell transplantation.

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*Note:* The table lists the number of patients with each condition and the number of patients for whom the condition was a primary indication for hematopoietic stem cell transplantation (HSCT). The data are based on a review of patient records and clinical outcomes.
Overall and Disease-Free Survival

One patient died from pulmonary/cerebral mucormycosis presenting as a seizure 1 week after collection of peripheral blood stem cells. A second patient died 4 months after enrollment from active disease after postponing transplantation for 4 months. Of the 48 patients who underwent transplantation, no treatment-related deaths occurred. Six of 48 patients died after HSCT from non–treatment-related events. Two patients died without evidence of active SLE. While in remission, 1 patient died at 6 months after an unintentional injury; another individual who had a pre-HSCT history of Libman-Sachs endocarditis and MRSA endocarditis died at 18 months from MRSA endocarditis despite being in remission and receiving no immunosuppressive medications. Four patients died after HSCT from complications of active SLE. One died at 11 months while hospitalized after cord blood stem cell transplantation for relapsed ITP, AIHA, and central nervous system vasculitis; 1 death occurred at 15 months after the patient was placed in hospice for refractory lupus-related mucocutaneous disease; 1 patient died unexpectedly during sleep at 24 months while receiving numerous immunosuppressive medications; and 1 patient died at 33 months from sepsis in the setting of pancytopenia and bone marrow aplasia after treatment with high-dose cyclophosphamide (200 mg/kg) without stem cell support for relapsed SLE. For patients undergoing HSCT, the probability of 5-year survival was 84% (Figure 1).

The probability of disease-free survival defined as requiring no immunosuppressive medications except physiologic doses of prednisone (≤10 mg/d) or hydroxychloroquine was 50% at 5 years (Figure 1). The longest continuous duration of remission has been 7.5 years. Four patients never entered remission, and 2 of them subsequently died of active disease or its complications, whereas the other 2 continue to receive long-term immunosuppressive therapy. The time to entering remission varied from 1 to 29 months (mean, 6.2 months), often because of long-term high-dose pre-HSCT corticosteroid therapy that had to be withdrawn gradually to avoid addisonian symptoms. In addition, a rapid corticosteroid taper precipitated SLE-like symptoms of arthralgias and myalgias that responded to a temporary increase in corticosteroid dose.

Serology and Complement

Antinuclear antibody, anti-ds DNA antibody, and complement C3 and C4 improved after HSCT. The level of ANA was significantly lower (all P<.05) at 3, 6, 12, 24, and 48 months; anti-ds DNA significantly improved (all P<.05) at 3, 12, and 24 months; and C3 significantly improved (all P<.05) at 3, 6, 12, 24, and 36 months after HSCT (Figure 2). C4 also improved in parallel with C3 after HSCT (data not shown). Improvement and normalization of serology and complement occurred in patients entering remission. In addition, levels of lupus anticoagulant and anticardiolipin antibodies improved after HSCT, as previously reported.21

Disease Activity and Organ Function

Patient scores on the SLEDAI, a validated instrument of disease activity, significantly improved and remained significantly lower (all P<.05) for up to 5 years after HSCT (Figure 3). Pulmonary function assessed by carbon monoxide diffusion lung capacity corrected for hemoglobin was also significantly improved at 12, 24, 36, and 60 months after HSCT (Figure 3). On enrollment, 5 patients were dependent on supplemental oxygen; 1 was using 40% oxygen delivered via facemask for acute alveolar hemorrhage, and 4 were receiving long-term home oxygen at 2 to 5 L/min. All became and have remained independent of supplemental oxygen after HSCT.

Renal function evaluated by creatinine clearance remained stable before and after HSCT. No patient without pretransplantation renal involvement developed posttransplantation nephritis or renal failure. Of the 25 patients with a history of nephritis (Table 4), 3 were receiving long-term hemodialysis for more than 2 years and were enrolled for other SLE-related indications. Two entered remission, had subsequent successful renal transplants, and have remained independent of dialysis without evidence of SLE (Table 4). The other continued to receive dialysis and died...
of relapsed SLE. Two patients developed renal failure during HSCT, one because of a preadmission flare-up of nephritis; that patient's renal function recovered, and the patient has subsequently remained independent of dialysis for 7.5 years. The other patient received an aminoglycoside during HSCT and never became independent of dialysis. Four patients with pretransplantation nephritis but not receiving dialysis before or during HSCT subsequently became dialysis dependent (Table 4) because of exposure to dye contrast, urate nephropathy, chronic

![Figure 1. Probability of Survival and Relapse in Lupus Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT)](image)

![Figure 2. Serology and Complement Before and After Hematopoietic Stem Cell Transplantation](image)

![Figure 3. SLE Disease Activity Index (SLEDAI) and Carbon Monoxide Diffusion Lung Capacity (DLCO) Corrected for Hemoglobin Before and After Hematopoietic Stem Cell Transplantation](image)

ANA indicates antinuclear antibody; anti-ds, anti–double-stranded. Blue bars indicate median values.
hypertension, or recurrent lupus nephritis (1 case each) (Table 4). Sixteen patients with nephritis did not require post-HSCT dialysis. Their posttreatment creatinine clearance generally remained stable or improved (Table 4). Prenrollment posttreatment renal biopsies were not obtained.

Pretransplantation AIHA and ITP were relatively common. Seven patients had ITP before enrollment: 5 have maintained remission, 1 had ITP relapse, and 1 never entered remission. Similarly, 5 patients had AIHA: 3 are in remission, 1 relapsed, and 1 never entered remission after HSCT. In patients with AIHA or ITP that relapsed or failed to remit, SLE also relapsed or never achieved remission, respectively.

Anticoagulation was common in this cohort of severely ill patients. Eighteen of 22 were able to discontinue anticoagulation a mean of 4 months after HSCT, and 78% have remained free of subsequent thrombotic events. As previously reported, levels of antiphospholipid antibodies and lupus anticoagulant markedly improved or normalized after HSCT. The elimination of anticoagulation was not standardized.

The toxicity of autologous HSCT is a result of patient selection, the conditioning regimen, and supportive care during and after transplantation. We selected a subset of very ill patients who had active disease refractory to standard therapy and who had multiorgan dysfunction. Therefore, it is unlikely that patient selection accounted for our lower mortality rate. The difference in treatment-related mortality between our single-center study and the European multicenter analysis is most likely due to a center effect related to the conditioning regimen used, supportive care guidelines, and experience in transplanting patients with SLE. A center effect on survival has been reported for HSCT in malignancies.

Table 4. Renal Outcome in the Subset of Patients With a History of Pre-HSCT Nephritis

<table>
<thead>
<tr>
<th>Patients With Pre-HSCT Nephritis</th>
<th>Pre-HSCT Creatinine Clearance, mL/min</th>
<th>Most Recent Post-HSCT Creatinine Clearance, mL/min</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving dialysis at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>24</td>
<td>54</td>
<td>Remission</td>
</tr>
<tr>
<td>Acute</td>
<td>22</td>
<td>ESRF from aminoglycosides</td>
<td>Relapsed</td>
</tr>
<tr>
<td>Long term</td>
<td>Hemodialysis</td>
<td>Cadaveric kidney transplantation</td>
<td>Remission</td>
</tr>
<tr>
<td>Long term</td>
<td>Hemodialysis</td>
<td>Sibling kidney transplantation</td>
<td>Remission</td>
</tr>
<tr>
<td>Long term</td>
<td>Hemodialysis</td>
<td>NA</td>
<td>Died during cord blood allogeneic HSCT for relapsed SLE</td>
</tr>
</tbody>
</table>

Developed ESRF after HSCT

<table>
<thead>
<tr>
<th>Did not develop ESRF</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>87</td>
<td>Remission</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>106</td>
<td>Relapsed</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>110</td>
<td>Remission</td>
</tr>
<tr>
<td>4</td>
<td>87</td>
<td>82</td>
<td>Relapsed</td>
</tr>
<tr>
<td>5</td>
<td>126</td>
<td>85</td>
<td>Relapsed</td>
</tr>
<tr>
<td>6</td>
<td>84</td>
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<td>Remission</td>
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<tr>
<td>7</td>
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<td>Relapsed</td>
</tr>
<tr>
<td>8</td>
<td>93</td>
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<tr>
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<td>114</td>
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<td>Remission</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>76</td>
<td>Remission</td>
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<tr>
<td>12</td>
<td>29</td>
<td>55</td>
<td>Remission</td>
</tr>
<tr>
<td>13</td>
<td>83</td>
<td>69</td>
<td>Remission</td>
</tr>
<tr>
<td>14</td>
<td>117</td>
<td>119</td>
<td>Remission</td>
</tr>
<tr>
<td>15</td>
<td>123</td>
<td>Refused to give 24-h urine</td>
<td>Remission</td>
</tr>
<tr>
<td>16</td>
<td>55</td>
<td>82</td>
<td>Remission</td>
</tr>
</tbody>
</table>

Abbreviations: ESRF, end-stage renal failure; HSCT, hematopoietic stem cell transplantation; NA, not applicable; SLE, systemic lupus erythematosus.

*Remission is defined by Responder Index for Lupus Erythematosus criteria, as described in the text.

COMMENT

In a European analysis from 23 centers reporting 53 patients with SLE who were undergoing autologous HSCT by using several conditioning regimens, the probability of disease-free survival at 5 years was 55%, surprisingly similar to that in our study. The European mortality, however, was much higher at 23% (12/53) predominantly because of an increased treatment-related mortality rate of 13% (7/53). The European analysis, being a composite of diverse regimens and protocols, did not in general report quantitative serologic, complement, or organ outcome.
patients with malignancies, emphasizing the importance of experience in treating lupus patients with high-dose chemotherapy and autologous HSCT. In contrast to eligibility criteria for malignancies in which organ dysfunction is a contraindication for transplantation, ongoing lupus-related organ impairment is often the indication for stem cell transplantation in SLE. Although cancer patients tolerate hyperhydration, SLE patients with impaired renal function are unusually susceptible to volume overload and pulmonary edema, as well as electrolyte abnormalities, if given hyperhydration during the conditioning regimen. Refractory or poorly controlled hypertension would be a contraindication for transplantation in patients with malignancies. In patients with lupus nephritis, poorly controlled hypertension is common. Pulmonary compromise with a diminished carbon monoxide diffusion lung capacity or dependence on supplemental oxygen, although considered an SLE-related eligibility criterion for transplantation, is a contraindication for HSCT in patients with malignancies.

In patients with cancer, cytopenias would generally be considered an HSC defect and, consequently, a contraindication for autologous HSCT. In contrast, cytopenias in patients with lupus are common and multifactorial because of AIHA, ITP, antiphospholipid antibodies, or therapy and may be the major indication for transplantation. Aside from having impaired visceral function, a significant percentage of lupus patients had ongoing and life-threatening thrombotic events and continued receiving anticoagulation during transplantation.21 This prothrombotic tendency was multifactorial because of active inflammation, vasculitis, and APS. Finally, compared with patients with cancer, patients with lupus have a long history of chronic immunosuppression and appear unusually prone to infections during mobilization and transplantation, mandating aggressive preemptive antimicrobial prophylaxis.

In our study, the immunosuppressive conditioning regimen was based on the concept of lymphoablation without myeloablation.6,10-13 We did not use a malignancy-specific myeloablative conditioning regimen, as was used by some centers in the European study, but instead used dose-escalated cyclophosphamide, a standard lupus medication.6,13 Equine ATG was also added to the regimen for further immunosuppression. In patients with SLE, the adverse effects of equine ATG can mimic the manifestations of active disease, including fever, rash, myalgias, arthralgias, hypotension, and shortness of breath. By entry criteria, all patients were receiving long-term and often high-dose corticosteroids, and a gradual corticosteroid taper was necessary to avoid adrenal insufficiency or early flare-up of SLE-like symptoms, especially myalgias, arthralgias, and serositis. Because equine ATG is specific for T lymphocytes and does not target B lymphocytes,24,25 we cannot exclude that persistence of cyclophosphamide-resistant memory B cells contributed to a prolonged corticosteroid taper.

Compared with patients with malignancies, patients with lupus are immunocompromised for a long period before enrollment, and transplantation-related neutropenic infectious complications are common.26 Bacteremia, especially gram-positive bacteremia, was common. Fungal infections or fungemia also occurred, mandating aggressive broad antibacterial and antifungal prophylaxis. The risk of infection during postchemotherapy mobilization did not correlate with the risk of infection after the conditioning regimen. Patients who developed bacteremia after mobilization did not become bacteremic after HSCT and vice versa. No patient developed CMV disease after HSCT, even though we did not routinely monitor or treat CMV viremia. Positive CMV surveillance assay results could prompt treatment with ganciclovir, causing neutropenia-related bacterial or fungal infections27 or initiation of G-CSF that could trigger SLE.28,30 In contrast to CMV, post-transplantation dermatomal herpes zoster was relatively common.

Because SLE is a heterogeneous disease in terms of clinical course and manifestations,31 the SLEDAI19 and RIFLE10 definitions of disease activity and remission, respectively, were used to standardize outcome. HSCT had a disease-ameliorating effect, with significant improvement in the SLEDAI and a 50% probability of 5-year remission. In addition, serology, complement, immunomodulated hemolysis and thrombocytopenia, thrombotic events, and pulmonary function as monitored by carbon monoxide diffusion lung capacity corrected for hemoglobin markedly improved. Renal function as monitored by creatinine clearance remained stable or, for the subset with pre-HSCT nephritis, generally improved after HSCT. Future studies should consider a preenrollment renal biopsy to determine reversibility of renal function before HSCT.

Some centers are treating lupus with a similar dose of cyclophosphamide (200 mg/kg) without stem cells. In comparison, by using cyclophosphamide to mobilize stem cells, HSCT allows administration of a higher dose of cyclophosphamide (250 mg/kg). HSCT further maximizes immunosuppression by addition of ATG. However, the main reason for collection and reinfusion of HSC in this study was to shorten the duration of cyclophosphamide-induced neutropenia by 4 to 5 days and thus decrease the risk of infection. The majority of HSCT-related infections occur during the 10-day peritransplant neutropenic interval. Infections after hospital discharge are minimized by the corticosteroid taper and absence of other immunosuppressive medications.

When this protocol was conceived 10 years ago, other lymphocyte-specific agents such as rituximab, which selectively targets B cells,32-34 or alemtuzumab, directed against both T and B cells,35,36 were not available. Equine ATG caused acute toxicities that mimicked active SLE and did not target memory B cells. Future SLE transplant-
HEMATOPOIETIC STEM CELL TRANSPLANTATION IN LUPUS

REFERENCES


