Autologous Blood Stem Cell Transplantation in Refractory Systemic Lupus Erythematosus With Severe Pulmonary Impairment

A Case Report


For patients with severe forms of autoimmunity, including systemic lupus erythematosus (SLE), purging autoreactive T cells from the immune repertoire by transplanting autologous hematopoietic stem cells (ASCT) is a therapeutic option. We describe an 18-year-old woman with SLE who had been treated with corticosteroids, azathioprine, cyclophosphamide (CYC), and immunopheresis for 4 years, during which time mechanical ventilation for lupus pneumonitis had been repeatedly required. After the patient was conditioned by administration of CYC and antithymocyte globulin, a total of 8.87 × 10^6 purified CD34+ cells per kg of body weight was infused. Hematopoietic regeneration was observed within 9 days. Twenty-one months after ASCT, the patient continues to be in complete clinical remission, with no signs of SLE-related disease activity and without any immunosuppressive medications. Her pulmonary function has returned to normal. Although a longer followup is required for assessment of the durability of response, the patient's course indicates that ASCT may be a way to reinduce tolerance in patients with SLE.

CASE REPORT

The patient, an 18-year-old woman at the time ASCT was performed, presented in late 1996 at age 14 with cutaneous vasculitis, biopsy-proven pneumonitis, and lupus nephritis (World Health Organization class IV). Antinuclear antibodies were present at a titer of 1:640 (normal ≤1:40), and anti–double-stranded DNA antibody levels were elevated to 28.1 IU/ml (normal 0.0–7.0). The patient did not respond to treatment with corticosteroids and azathioprine, and mechanical venti-
After enrollment into the study, hematopoietic stem cells were mobilized by the administration of CYC at 2 gm/m² and granulocyte colony-stimulating factor (G-CSF) at 5 μg/kg/day. Nine days later, 2 leukaphereses (both of which were well tolerated by the patient) were required to obtain $8.87 \times 10^6$ CD34+ cells/kg of body weight. The cells were then enriched with the Isolex system (Clinimacs; Miltenyi Biotec, Bergisch Gladbach, Germany), and after enrichment, the cells demonstrated 89.6% purity. Three days after the second leukapheresis, she experienced respiratory deterioration without signs of infection, and mechanical ventilation was required for 2 days. The patient improved with corticosteroid treatment at a dosage of 12.5 mg/day.

In February 2000, at the time of admission for ASCT, the patient (who was then 18 years old) presented with significant impairment of pulmonary function, severe proteinuria, anemia, and arterial hypertension (Table 1). After administration of CYC at 200 mg/kg of her actual body weight and antithymocyte globulin (ATG) at 90 mg/kg of her actual body weight, the patient’s CD34+ cells ($8.87 \times 10^6$ CD34+ cells/kg of body weight) were reinfused. Aside from moderate intermittent fluid overload and mild mucositis, no toxicities were observed. On day 1 after ASCT, the patient experienced septicemia caused by *Pseudomonas aeruginosa*, which resolved with appropriate antimicrobial therapy. An absolute neutrophil count of $>0.5 \times 10^9$/liter and a platelet count of $>20 \times 10^9$/liter were observed on days 9 and 8 after ASCT, and the patient was discharged on day 14 after ASCT.

Twenty-one months after ASCT the patient is in excellent clinical condition, with a score of 100% on the Karnofsky performance scale, which rates the ability to perform one’s usual activities. Her physical condition is significantly improved, and the underlying disease has completely resolved (Table 1). No signs of SLE-related pulmonary activity can be observed on computed tomography scans of the chest (Figure 1). The patient is taking no immunosuppressive medication. Her ovarian function normalized 6 months after ASCT. Aside from a reactivation of herpes zoster in early 2001, her immune reconstitution was unremarkable.

**DISCUSSION**

Refractory autoimmune diseases cause a high degree of morbidity and mortality. Severe organ impairment or reduction in clinical performance scores due to disease activity or immunosuppressive therapies (13) can significantly increase a patient’s risk for treatment-
related complications when ASCT is performed late in the course of their disease. Thus, only a few patients with SLE who have been treated with high-dose immunosuppression and stem cell transplantation have been reported so far (2,5–12). Patients with pulmonary involvement due to SLE experienced toxic effects of ASCT, including pulmonary edema, and intermittent mechanical ventilation was required (5).

Herein we report the outcome of ASCT in an 18-year-old woman with SLE of 4 years’ duration. She had severe multisystem involvement and was refractory to multiple immunosuppressive regimens. The patient had survived 3 biopsy-proven flares of SLE pneumonitis that had required mechanical ventilation. Since ASCT, she has been in continuous clinical remission for 21 months and is in excellent clinical condition. Despite severe lung impairment prior to transplantation, her pulmonary function has completely normalized. So far, only Traynor et al (5) have reported the complete normalization of pulmonary function in 2 SLE patients who were treated with ASCT. Burt et al (2) recently described 1 SLE patient with alveolar hemorrhage prior to transplantation who had no pulmonary infiltrates after ASCT. The patient’s diffusing capacity for carbon monoxide, however, remained unchanged at 50% of predicted (2).

A further limiting factor for the prognosis of SLE is renal involvement. Our patient had lupus nephritis (World Health Organization class IV) with severe nephrotic syndrome and catabolism. After ASCT in our

Table 2. Results of autologous stem cell transplantation for systemic lupus erythematosus, as reported in the literature*

<table>
<thead>
<tr>
<th>Author, year (ref.)</th>
<th>No. of patients</th>
<th>Conditioning</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wulffraat et al, 2001 (11)</td>
<td>2</td>
<td>CYC, ATG, TBI</td>
<td>12–15 months of followup: remission, off IS agents</td>
</tr>
<tr>
<td>Traynor et al, 2000 (5)</td>
<td>7</td>
<td>CYC, ATG</td>
<td>12–40 months of followup (median 25 months): remission, off IS agents</td>
</tr>
<tr>
<td>Rosen et al, 2000 (10)</td>
<td>3</td>
<td>CYC, ATG</td>
<td>10–21 months of followup (median 14 months): remission, reduced steroids</td>
</tr>
<tr>
<td>Trysberg et al, 2000 (12)</td>
<td>1</td>
<td>CYC, TBI</td>
<td>18 months of followup: improved</td>
</tr>
<tr>
<td>Fouillard et al, 1999 (8)</td>
<td>1</td>
<td>BEAM</td>
<td>9 months of followup: remission, reduced steroids</td>
</tr>
<tr>
<td>Burt et al, 1998 (2)</td>
<td>2</td>
<td>CYC, ATG</td>
<td>12 months of followup: improved, 1 off IS agents, 1 reduced steroids</td>
</tr>
<tr>
<td>Musso et al, 1998 (9)</td>
<td>1</td>
<td>CYC, ATG</td>
<td>8 months of followup: remission, off IS agents</td>
</tr>
<tr>
<td>Burt et al, 1997 (7)</td>
<td>1</td>
<td>CYC, ATG</td>
<td>6 months of followup: remission, reduced steroids</td>
</tr>
<tr>
<td>Marmont et al, 1997 (6)</td>
<td>1</td>
<td>CYC, TT</td>
<td>7 months of followup: remission, reduced steroids</td>
</tr>
</tbody>
</table>

* CYC = cyclophosphamide; ATG = antithymocyte globulin; TBI = total body irradiation; IS = immunosuppressive; BEAM = chemotherapy with carmustine, etoposide, cytarabine, and melphalan; TT = thiotepa.
patient, complete remission of renal involvement and resolution of cytopenias was achieved. This is consistent with published findings (2,5–12), which are summarized in Table 2. In all 19 patients described in the literature, disease activity was stopped by high-dose immunoablation. The duration of followup, however, was short, and only 11 of the 19 patients were reported to be off all immunosuppressive medication. Six of 13 patients with renal involvement improved and, strikingly, another 4 patients experienced normalization of kidney function (2,5,7,10). In addition to our patient’s marked clinical improvement, normalization of antinuclear antibody and anti–double-stranded DNA antibody titers occurred; this had not been achieved at any previous point during treatment with traditional immunosuppressive agents.

Flares of autoimmune disease have been reported during stem cell mobilization and after ASCT, but these flares could be controlled by treatment with high-dose steroids (10,14). Whether the administration of G-CSF for stem cell mobilization had an influence on pulmonary involvement shortly after leukapheresis in our patient has to remain a matter for speculation.

The conditioning regimen of CYC and ATG was chosen because of its effectiveness in patients with aplastic anemia, which may often represent an autoimmune suppression of hematopoiesis. So far, the majority of patients who were undergoing ASCT for treatment of SLE were given CYC and ATG for immunoablation (Table 2). This regimen was tolerated reasonably well, considering the advanced disease status and reduced clinical condition of these patients with longstanding SLE. No transplant-related deaths have thus far been reported.

It is unclear if the autologous cells need to be depleted of autoreactive lymphocytes and inflammatory leukocytes or if there is a threshold dose of T cells that is acceptable for reinfusion. Most anecdotal case reports suggest nonsustained remission of the autoimmune disease after unmanipulated ASCT (15). For this reason, a CD34-enriched stem cell product with partial depletion of T cells was reinfused into our patient. Purging the cells of lymphocytes may prevent reinfusion of potential disease-causing cells. However, aggressive lymphocyte depletion may result in late fungal and viral infections and lymphoproliferative disorders. It is well known that patients with active lupus seem to be at increased risk of infection from immune suppression and disease-associated T cell abnormalities (13). As has been reported by other investigators (2,5), our patient also experienced fever and septicemia during ASCT and had an episode of herpes zoster after transplantation. After 100 days, concordant with resolution of disease activity, no opportunistic infections have occurred in any patient who has undergone transplantation. Furthermore, Traynor et al (5) observed a normalization of T cell phenotype, repertoire diversity, and responsiveness after ASCT.

In summary, this report confirms the efficacy of high-dose immunoablation and infusion of purified CD34+ stem cells in patients with SLE. Advances in identifying high-risk patients may allow for ASCT during an earlier stage of disease, before the development of severe end organ damage. The results obtained thus far with ASCT are promising and call for a wider use of ASCT in SLE in controlled clinical trials as has been started at our institution.

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REFERENCES