

# Hematopoietic Stem Cell Transplantation for Severe and Refractory Lupus

## Analysis After Five Years and Fifteen Patients

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**Objective.** To determine the safety and long-term efficacy of immune ablation and autologous hematopoietic stem cell transplantation (HSCT) in severe systemic lupus erythematosus (SLE).

**Methods.** Fifteen patients with persistently active SLE after intravenous (IV) cyclophosphamide (CYC) therapy underwent HSCT. Stem cells were mobilized with CYC (2.0 gm/m<sup>2</sup>) and granulocyte colony-stimulating factor (5 µg/kg/day). Lymphocytes were depleted from the graft by selection of CD34-positive cells. The conditioning regimen used was CYC (200 mg/kg), antithymocyte globulin (90 mg/kg), and methylprednisolone (3 mg/kg). Outcome was evaluated by the SLE Disease Activity Index (SLEDAI), serum complement levels, serologic features, function of diseased organs, and immunosuppressive medication requirements.

**Results.** Fifteen patients with persistent, severe SLE, 7 of whom were critically ill, were treated. No deaths occurred following treatment. The median followup after HSCT has been 36 months (range 12–66 months). All patients demonstrated a gradual, but marked, improvement. The SLEDAI score has declined to ≤5 in 12 patients. Complement and anti-double-stranded DNA levels have normalized and marked improvements in end organ function have occurred in

all subjects. Of the 12 patients followed up for >1 year after HSCT, 10 have discontinued immunosuppressive medications, and the prednisone dosage has been tapered to 15 mg/day in 1. Only 2 patients have demonstrated clinical evidence of recurrence of active lupus. One of these patients currently requires no immunosuppressive medication and has a normal performance status. The other patient is currently receiving IV CYC.

**Conclusion.** In patients experiencing the persistence of organ-threatening lupus following standard, aggressive therapy, HSCT may be performed safely, with marked improvement and sustained withdrawal of all immunosuppressive medication for most patients. A phase III randomized trial is warranted to determine the relative efficacy and durability of remission of HSCT compared with standard therapies.

Hematopoietic stem cell transplantation (HSCT) is most commonly applied to chemotherapy-sensitive “malignant” hematologic diseases, such as lymphoma or multiple myeloma. These malignancies are characterized by invasive or injurious clonal or oligoclonal lymphocyte proliferation. Diseases for which autologous stem cell transplants are used successfully are believed to be environmentally induced in a setting of genetic susceptibility. HSCT allows for normal, healthy hematopoietic stem cells to repopulate the bone marrow and peripheral blood after chemotherapy-induced elimination of the malignant clones. It may be anticipated that disease-mediating lymphocytes in patients with systemic lupus erythematosus (SLE) should be at least as prone to therapeutic eradication as malignant lymphocytes. If human SLE is also triggered by the hormonal and environmental milieu in a genetically susceptible host, then high-dose chemotherapy and HSCT should also induce sustained lupus-free remissions.

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**Table 1.** Organ system involvement and pre-HSCT and current use of immunosuppressive medications among the 15 patients who underwent HSCT for refractory SLE\*

HSCT patient	Cerebritis	Myelitis	Glomerulonephritis	Carditis	Lung disease		Peritonitis	Cytopenia	Skin disease	Immunosuppressive therapy	
					Active	Pleural only				Yes	Low platelets; anemia
SLE 1	HA; history of seizures	History of myelitis	Active; WHO class III	Active	Pleural only	Yes	None	Low platelets; anemia	None	IV CYC, AZA, pred., quin., MTX, plas. exch.	None
SLE 2	HA	None	Remitting; WHO class III	Active	Yes	None	None	Anemia, mild	None	IV CYC, quin., pred.	None
SLE 3	HA	None	Active; WHO class II	Active	Yes	Yes	Yes	Anemia, mild	None	IV CYC, AZA, pred.	None
SLE 4	Recent seizure; psychosis	None	Active; WHO class III	None	None	None	None	Anemia, moderate	None	IV CYC, quin., pred.	None
SLE 5	HA; cerebritis	None	None	None	Yes	None	None	Anemia, mild	None	IV CYC, quin., AZA, pred., MTX	None
SLE 6	Recent seizure	None	Active; WHO class III	None	None	Yes; diarrhea	None	Anemia, moderate	None	IV CYC, quin., pred., AZA	IV CYC, pred. (20 mg/day)
SLE 7	None	None	None	None	None	Yes; bowel vasculitis	None	Anemia, mild	None	IV CYC, AZA, pred.	None
SLE 8	None	None	None	None	None	Yes	Severe; oral ulcers	None	Severe; oral ulcers	IV CYC, quin., thalid., MTX	Quin., pred. (15 mg/day)
SLE 9	Recent seizure	None	Remitting; WHO class III	None	None	None	None	History of anemia; low platelets	None	IV CYC, pred., AZA, plas. exch.	Pred. (5 mg/day taper)
SLE 10	HA	None	Active; WHO class III	None	None	Yes	None	Anemia	None	IV CYC, pred., quin., AZA	Pred. (12 mg/day taper)
SLE 11	Cerebritis	Active myelitis	Active; WHO class III	None	None	None	None	Anemia, moderate	None	IV CYC, quin., AZA	Pred. (7 mg/day taper)
SLE 12	None	None	None	Previous	Yes	None	None	None	None	IV CYC, quin., pred.	None
SLE 13	Cerebritis; cranial nerves VI and III disease	None	None	None	None	None	None	Anemia, mild	None	IV CYC, quin., AZA	None
SLE 14	Cerebritis; cranial nerve III disease	None	None	None	None	None	None	Anemia, mild	None	IV CYC, MTX, AZA, quin., dex.	Dex. (4 mg qod taper)
SLE 15	Recent seizure; HA	None	None	None	None	None	None	Anemia, severe; thrombocytopenia	None	IV CYC, IVIG, pred., VCR, rituximab	Pred. (30 mg qod taper)

\* HSCT = hematopoietic stem cell transplantation; SLE = systemic lupus erythematosus; HA = headache; WHO = World Health Organization; IV = intravenous; CYC = cyclophosphamide; AZA = azathioprine; pred. = prednisone; quin. = quinacrine; MTX = methotrexate; plas. exch. = plasma exchange; thalid. = thalidomide; dex. = dexamethasone; IVIG = intravenous immunoglobulin; qod = every other day; VCR = vincristine.

Approximately 6 years ago, the first HSCT for SLE was performed by Marmont et al (1) in Genoa, Italy. That same year, our group of investigators began performing HSCT for SLE in the US (2–5). We report herein the 5-year outcome in our patients.

## PATIENTS AND METHODS

**Patient selection.** All patients met at least 4 of the 11 American College of Rheumatology criteria for SLE (6) and had failed to achieve sustained remission of SLE after treatment with monthly intravenous (IV) pulse cyclophosphamide (CYC; 500–1,000 mg/m<sup>2</sup>) and corticosteroids, thus necessitating a continued daily dosage of  $\geq 20$  mg of prednisone or its equivalent.

Patient eligibility criteria included an established diagnosis of SLE and 1 of the following 5 features: World Health Organization class III or class IV glomerulonephritis (7), uncontrolled with treatment according to the National Institutes of Health short-course CYC protocol (8); parenchymal disease of the heart or lung with biopsy-proven vasculitis, uncontrolled with IV CYC; cerebritis or transverse myelitis, uncontrolled with IV CYC; profound, refractory autoimmune cytopenias; or catastrophic antiphospholipid syndrome (9–12).

For nephritis, failure of CYC treatment was defined as persistent diffuse or focal glomerulonephritis after at least 6 months of CYC treatment. However, patients were not accepted for HSCT if glomerulonephritis constituted their only persistent major organ dysfunction. For other visceral organ involvement (such as cerebritis, pneumonitis, carditis, or mucocutaneous vasculitis), failure was defined as the persistence of active disease despite at least 3 months of IV CYC treatment.

Prior to registration or initiation of therapy, all patients read and signed an informed consent form that had been approved by the Institutional Review Board and the Food and Drug Administration. The eligibility of each patient screened was determined by consensus of the participating rheumatologist, nephrologist, pulmonologist, and hematologist who collaborated on this protocol. Each case was discussed individually among the subspecialists, without blinding.

**Procurement of HSCs.** Peripheral blood stem cells were mobilized with CYC (2.0 gm/m<sup>2</sup>) and beginning 72 hours later subcutaneous administration of granulocyte colony-stimulating factor (G-CSF; 5  $\mu$ g/kg/day) (Amgen, Thousand Oaks, CA). Leukapheresis was initiated when the white blood cell count rebounded to more than 1,000/ $\mu$ l ( $1.0 \times 10^9$ /liter) and continued daily until the number of stem cells exceeded  $1.4 \times 10^6$  CD34-positive cells per kg after positive selection using either the Ceparate (CellPro, Bothell, WA) or Isolex (Nexell, Irvine, CA) stem cell concentrator.

**Conditioning regimen.** CYC (total dose 200 mg/kg) was administered IV in divided doses of 50 mg/kg/day for 1–2 hours on days –5, –4, –3, and –2. Antithymocyte globulin (ATG; total dose 90 mg/kg) was infused for 10–12 hours in divided doses of 30 mg/kg/day on days –4, –3, and –2. Methylprednisolone (1 mg/kg) was given 30 minutes before each dose of ATG.

**Supportive care.** Patients were treated in a hospital unit in which the air was HEPA-filtered. A low microbial diet,

oral ciprofloxacin (500 mg twice a day), fluconazole (400 mg/day), and valacyclovir (500 mg 3 times a day) were started at the time of admission and were discontinued when the patient's neutrophil count reached 500/ $\mu$ l. During periods of neutropenia, fluconazole was changed to amphotericin B liposome (5 mg/kg/day) (AmBisome; Fujisawa, Deerfield Park, IL) and piperacillin tazobactam (3.75 gm every 4 hours) was added to the ciprofloxacin. G-CSF (5  $\mu$ g/kg/day) was started on the day of stem cell infusion and continued until the absolute neutrophil count was above 1,000/ $\mu$ l. For 6 months after discharge, patients received daily fluconazole (400 mg orally once a day) and monthly aerosolized pentamidine (300 mg). They continued to take valacyclovir twice a day for 1 year.

**Assessment of disease status.** Each patient was asked to return to the center 2 and 6 months following HSCT, and then yearly thereafter. Evaluations performed at those times included a physical examination, review of systems, measures of creatinine clearance, urinary protein excretion, antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, and serum complement, complete blood cell counts, pulmonary function testing with diffusion capacity for carbon monoxide, magnetic resonance imaging of the brain or spinal cord (if results were previously abnormal), and an echocardiogram (if results were previously abnormal).

Neurocognitive testing was performed prior to HSCT and at yearly followup beginning with patient 10, after we began to appreciate neurologic improvements in transplant recipients. Current medications were recorded at these time points as well. A SLEDAI score (13) was assigned at each baseline and followup time point for each registered patient.

## RESULTS

**Patient profiles.** The presenting symptoms and disease characteristics of the first 15 HSCT recipients are presented in Table 1. Included are all drug regimens they had received prior to HSCT and immunosuppressive medications being taken at the time of the most recent followup.

**Patients accepted for evaluation or registered, but did not undergo HSCT.** In addition to the 15 treated patients, 2 other SLE patients were registered on this protocol (intention to treat total 17) and underwent stem cell harvest, but died before receiving “immune-ablative” CYC or ATG therapy or stem cell infusion (Table 2). One died of *Mucor* mycosis 2 weeks following completion of stem cell harvest, and the other died of lupus cerebritis 4 months following completion of stem cell harvest, during an extended visit home.

Three additional patients with refractory SLE were accepted for transplant evaluation but, on screening at arrival, were found to be ineligible and were not registered or treated (Table 2). One patient was declined enrollment because of an extensive subdural hematoma (in the setting of antiphospholipid syndrome) that was diagnosed on screening magnetic resonance imaging

**Table 2.** Characteristics of the 5 patients with refractory SLE who were accepted for evaluation or were registered, but did not undergo HSCT\*

Patient	Age/sex	Performance status†	Major organ system involvement	Registered for NU95LU1 protocol	Stem cell harvest (reason declined)	High-dose therapy and HSCT performed	Cause of death (interval from NU evaluation to death)
SLE non-TP1	37/F	PS 4	Cerebritis	Yes	Yes	No	Cerebritis (5 months)
SLE non-TP2	28/F	PS 3	Catastrophic APS; GN	No	No (consensus about risk of recurrent subdural hematomas)	No	Sepsis (8 months)
SLE non-TP3	17/M	PS 3	Cerebritis; GN	Yes	Yes	No	Brain <i>Mucor</i> mycosis (<1 month)
SLE non-TP4	22/F	PS 2	Skin	No	No (consensus that standard IV CYC be given before high-dose therapy)	No	Sepsis (10 months)
SLE non-TP5	17/M	PS 4	Heart	No	No (patient died of heart failure on day 4 after arrival)	No	Cardiac failure (4 days)

\* These 5 systemic lupus erythematosus (SLE) patients were the only patients who were conditionally accepted by referral for transplant and were seen at Northwestern University (NU), but did not complete the procedure (non-TP) for hematopoietic stem cell transplantation (HSCT). Two were registered on protocol, but did not receive high-dose therapy. The other 3 were not registered because of a consensus that one or more aspects of their presentation made it impossible to proceed directly with high-dose therapy, despite their threatened condition. No effort was made to select patients with better performance status for transplantation. Patients were encouraged to utilize every existing standard therapy before proceeding with high-dose therapy. APS = antiphospholipid syndrome; GN = glomerulonephritis; IV = intravenous; CYC = cyclophosphamide.

† Eastern Cooperative Oncology Group performance status (PS) scores were graded on a scale of 0–4, where 0 = normal (no impairment), 1 = restricted only in physically strenuous activity, 2 = capable of self-care only and spends the majority of waking hours out of bed, 3 = capable of only limited self-care and spends more than 50% of waking hours in bed, and 4 = completely disabled.

after arrival at our center. She died of sepsis 8 months later. The second patient presented to us with severe cardiomyopathy and was intubated in the coronary care unit the day following admission. He died within 4 days of admission. The third patient had heavily treated cutaneous disease, but was CYC naive. She was advised to undergo standard IV CYC treatment before proceeding with high-dose therapy. She died of sepsis less than 1 year later.

All other patients, who were considered eligible after their outside medical records were reviewed, were interviewed at our center and underwent HSCT here.

**Patients who underwent HSCT.** All 15 of the transplant recipients are currently alive at 2–66 months following HSCT (Table 1). The average number of days from stem cell infusion to achievement of an absolute granulocyte count  $>500/\mu\text{l}$  was day 8 (range 7–10 days). The average number of days to achievement of platelet transfusion independence was day 10 (range 9–12 days). The average duration of neutropenia was 5 days.

**Toxicities.** The toxicities noted among the 15 patients who underwent HSCT are outlined in Table 3. Patients with both active glomerulonephritis and concurrent pulmonary or brain manifestations at the time of admission had more complications during high-dose therapy and a longer hospitalization period than those who had cerebritis or pulmonary disease without concurrent active glomerulonephritis. Of the 8 patients with active (n = 6) or remitting (n = 2) glomerulonephritis at

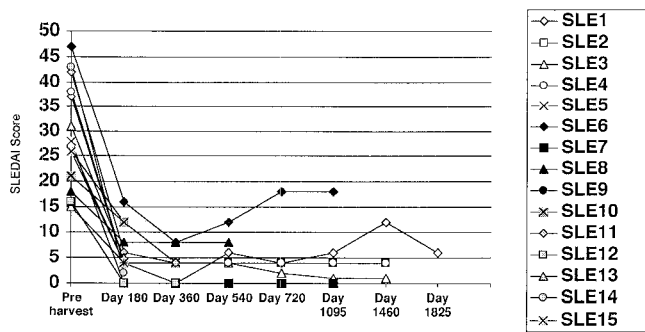
the time of presentation to our center, 4 were transferred to the medical intensive care unit and 2 received transient mechanical ventilation. In contrast, only 1 of the 7 patients without glomerulonephritis was transferred to the medical intensive care unit, and none received mechanical ventilation. Patient 15 developed hypotension following initiation of ATG, and the ATG was discontinued.

**Outcome. SLEDAI scores.** The SLEDAI scores tended to gradually normalize over the first year following HSCT (Figure 1). Eight patients have now been

**Table 3.** Toxicities among the 15 patients who underwent HSCT for refractory systemic lupus erythematosus\*

Toxicity	No. of patients (n = 15)
Neutropenic fever (culture negative)	12
Fluid retention necessitating dialysis	4
Plantar dysesthesia or foot drop	4
Bacterial pneumonia	1
Pulmonary edema and pulmonary exudates, requiring mechanical ventilation	2
Dermatomal zoster, days 60–120	2
Bacteremia, gram-positive	3
<i>Clostridium difficile</i> diarrhea	1
<i>Pneumocystis carinii</i> pneumonia following aerosolized pentamidine prophylaxis, day 60	1
Hypotension related to antithymocyte globulin	1

\* All toxicities were self-limited, and none were fatal. However, 2 patients died prior to receiving high-dose therapy/hematopoietic stem cell transplantation (HSCT), but after stem cell harvest.

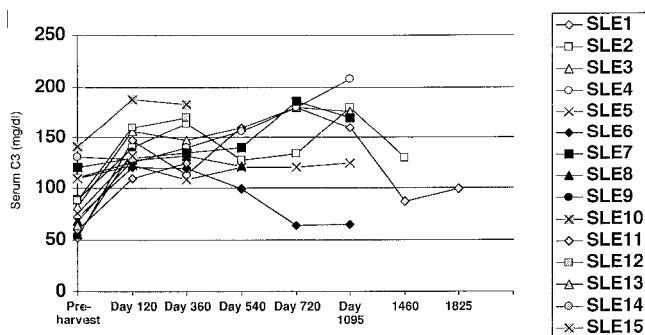


**Figure 1.** Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores immediately prior to entry into the study and during the period following hematopoietic stem cell transplantation in 15 patients with severe, refractory SLE. The SLEDAI score remained elevated (>10) in 1 of the 2 patients with disease reactivation.

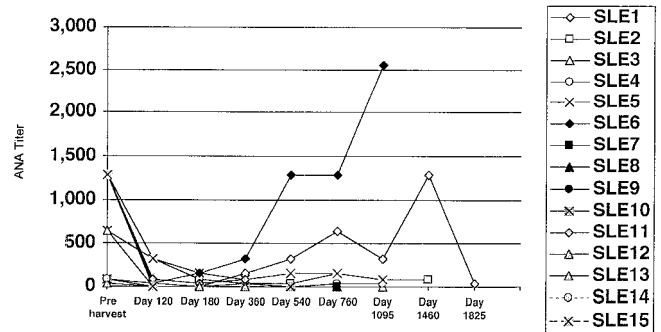
followed up for more than 24 months after HSCT. Abnormal SLEDAI scores that persisted at 24 months after HSCT have been attributable, in order of frequency, to one or more of the following: 1) residual, but greatly diminished, proteinuria (n = 3; range 300–2,000 mg/24 hours); 2) positive ANA serology result with positive concurrent anti-dsDNA (n = 1); 3) persistent, but improved, cutaneous vasculitis (n = 1); and 4) reactivation of urinary sediment and arthralgias, heralding reactivation of disease (n = 1; patient 6).

**Complement levels.** Approximately one-half of the 15 patients had a C3 level below normal at the time of study entry (Figure 2). Twelve patients had a low C4 level. All complement values normalized following HSCT and remained normal for the period of extended followup in all but 2 patients.

**Serologic findings.** Low-titer ANA antibodies were commonly seen during the period after HSCT



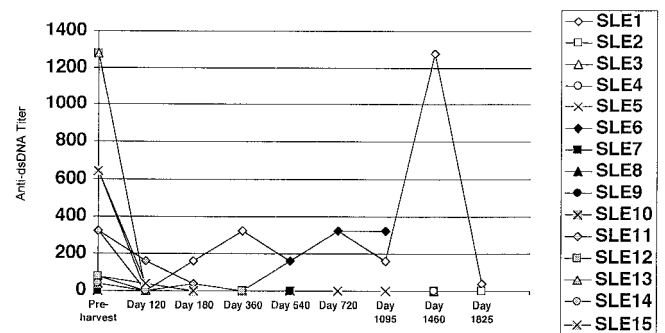
**Figure 2.** Serum C3 levels at the time of entry into the study and during the period following hematopoietic stem cell transplantation (HSCT) in 15 patients with severe, refractory systemic lupus erythematosus (SLE). Several patients had undergone therapeutic plasma exchange elsewhere in the weeks preceding referral for HSCT, and a lower C3 value had been obtained prior to plasma exchange.



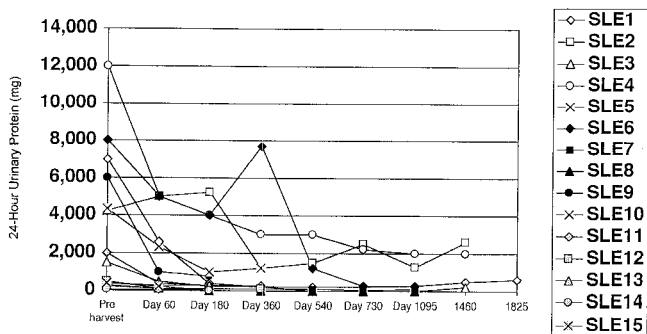
**Figure 3.** Antinuclear antibody (ANA) titers at the time of entry into the study and during the period following hematopoietic stem cell transplantation in 15 patients with severe, refractory systemic lupus erythematosus (SLE). The 2 patients in whom disease reactivation occurred developed consistently rising ANA titers. Low-titer ANA is commonly seen without clinical disease reactivation.

(Figure 3). A steadily rising ANA titer with positive anti-dsDNA antibodies was predictive of disease reactivation (Figure 4). Low-titer ANA occurring after many months of aggressive therapy did not preclude registration, provided that the same disease manifestations that had been associated with higher ANA titers persisted.

**End organ function.** Urinary protein excretion (Figure 5), forced vital capacity (Figure 6), arthritis (data not shown), and neurologic symptoms (data not shown) uniformly improved in a sustained manner following HSCT. Creatinine clearance (Figure 7) improved in 4 of the 7 patients with a creatinine clearance <80 ml/minute at study entry. The creatinine clearance value stabilized in 2 patients, but deteriorated further in patient 6, who developed a recurrence of lupus activity. A recent pretransplant decline in creatinine clearance



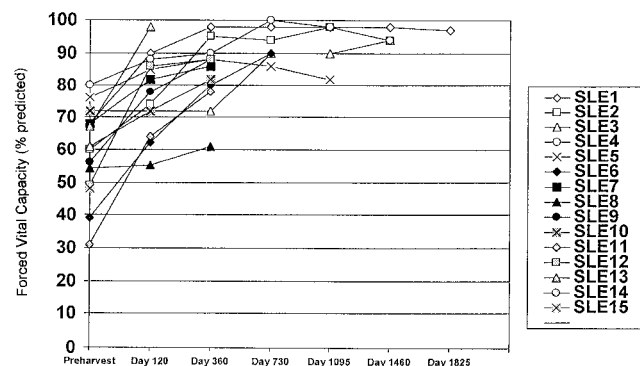
**Figure 4.** Anti-double-stranded DNA (anti-dsDNA) antibody titers at the time of entry into the study and during the period following hematopoietic stem cell transplantation in 15 patients with severe, refractory systemic lupus erythematosus (SLE). A rising anti-dsDNA antibody titer can predict clinical relapse 2 years before there is clinical evidence. Low-titer anti-dsDNA is not necessarily significant, and the antibodies may become undetectable.



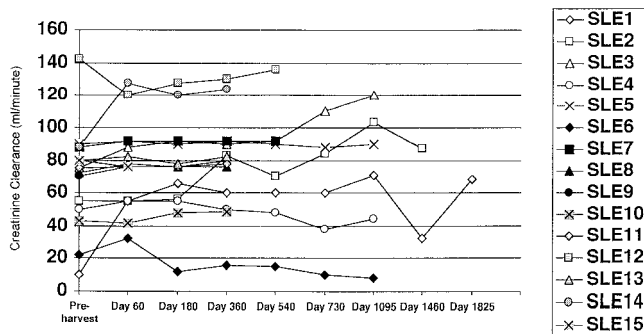
**Figure 5.** Twenty-four-hour urinary protein excretion at the time of entry into the study and during the period following hematopoietic stem cell transplantation in 15 patients with severe, refractory systemic lupus erythematosus (SLE). Urinary protein excretion uniformly improved, independently of serum creatinine levels, except in patient 6, who experienced a recurrence of autoimmune reactivity at 12 months.

and a creatinine clearance that had been lower than 50 ml/minute for fewer than 3 months prior to HSCT were each a good prognostic indicator for recovery of glomerular function.

*Immunosuppressive medications.* Withdrawal of steroid therapy was gradual and generally sustained. The pace of the withdrawal was determined by the referring and managing rheumatologist, according to the manner in which he or she would usually taper the prednisone dosage in a previously severely affected patient. The time to discontinuation of prednisone, therefore, reflected the clinical judgment of the rheumatologist who was most familiar with the patient's case. The most rapid taper was completed by 60 days and the most prolonged by 18 months. We generally encouraged a withdrawal schedule that aimed to have all prednisone stopped by



**Figure 6.** Forced vital capacity of the lung at the time of entry into the study and during the period following hematopoietic stem cell transplantation in 15 patients with severe, refractory systemic lupus erythematosus (SLE).

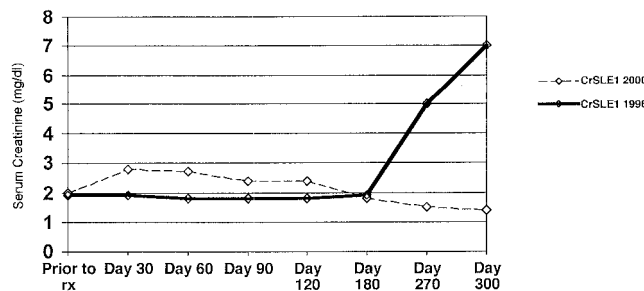


**Figure 7.** Creatinine clearance at the time of entry into the study and during the period following hematopoietic stem cell transplantation (HSCT) in 15 patients with severe, refractory systemic lupus erythematosus (SLE). Eight patients had experienced acute renal failure within 4 months prior to presentation at our center, but most of them had responded to intravenous cyclophosphamide treatment before being referred for HSCT. Of the 7 patients whose creatinine clearance was <80 ml/minute at study entry, the values improved after HSCT in 4, stabilized in 2, and deteriorated in 1 (patient 6, who is beginning dialysis).

12 months after HSCT if the patient's status was continuing to improve.

Of the 8 patients who have been followed up for more than 18 months after HSCT, only 2 are currently taking any oral prednisone. Patient 8 is taking 12 mg/day, and patient 6, who experienced a full relapse of disease, is taking 40 mg/day. Patient 8 is taking oral hydroxychloroquine, and patient 6 is receiving monthly IV CYC. All other patients are taking no immunosuppressive medications or are undergoing a continuous taper of the prednisone dosage after HSCT (Table 1).

**Disease course in patients who relapsed.** At the 30-month followup (n = 7 patients), patient 6 had a



**Figure 8.** Response of the serum creatinine (Cr) value to treatment with intravenous cyclophosphamide immediately before hematopoietic stem cell transplantation (in 1996) and after recurrence of active systemic lupus erythematosus (SLE) (in 2000) in patient 1. Reintroduction of conventional therapy resolved all symptoms in this patient in 2002, whereas in 1996, this therapy had failed.

reactivation of lupus. This patient continues to be treated with intermittent CYC and oral prednisone (20 mg/day). A second patient relapsed at 40 months after HSCT. She was treated according to the National Institutes of Health short-course CYC protocol at the time of that relapse and is now without active lupus and is currently not receiving any immunosuppressive medication. She had been refractory to standard IV CYC and high-dose prednisone immediately prior to HSCT (Figure 8).

### DISCUSSION

The introduction of IV CYC has been a useful, steroid-sparing maneuver for patients with SLE whose disease has remained aggressive despite the use of oral agents (8,14). It appears from the outcomes identified in the present study that escalation of IV CYC dosing, in conjunction with administration of ATG and reinfusion of autologous stem cells, achieves sustained freedom from disease activity in patients for whom standard-dose IV CYC has failed to stop disease activity. This sustained freedom from disease was associated with normalization of organ function.

HSCT was associated with resolution of nephrotic syndrome, which decreased the dependence on diuretics, lipid-lowering agents, and antihypertensive medications (which may also lower the risk for accelerated atherosclerosis in young patients) (15), and tapering or discontinuation of glucocorticoids, which contribute to the high risk of death from infections in SLE (16,17). Whether HSCT will curtail the accelerated risk of hypertension, osteoporosis, and atherosclerosis associated with lupus (18–21) or diminish the risk of death from lupus-related sepsis or atherosclerosis will require long-term followup of patients in randomized trials.

For patients such as those treated in the context of this trial, HSCT seemed beneficial, since conventional treatment options had been exhausted or were failing. The role of HSCT in patients with less-refractory disease can only be determined within the context of a randomized trial. A prospective comparison of HSCT and monthly pulse CYC with respect to 1) cumulative alkylator exposure, 2) cumulative glucocorticoid use, 3) incidence of therapy-related and disease-related morbidity, 4) overall sustained quality of life, and 5) overall survival is being planned.

### REFERENCES

- Marmont AM, van Lint MT, Gualandi F, Bacigalupo A. Autologous marrow stem cell transplantation for severe systemic lupus erythematosus of long duration. *Lupus* 1997;6:545–8.
- Traynor AE, Schroeder J, Rosa RM, Cheng D, Stefka J, Mujais S, et al. Treatment of severe systemic lupus with high dose chemotherapy and haemopoietic stem cell support. *Lancet* 2000;356:701–7.
- Traynor AE, Burt RK. Haematopoietic stem cell transplantation for active systemic lupus erythematosus. *Rheumatology (Oxford)* 1999;38:767–72.
- Burt RK, Traynor AE, Pope R, Schroeder J, Cohen B, Karlin KH, et al. Treatment of autoimmune disease by intense immunosuppressive conditioning and autologous hematopoietic stem cell transplantation. *Blood* 1998;92:3505–14.
- Burt RK, Traynor A, Ramsey-Goldman R. Hematopoietic stem cell transplantation for systemic lupus erythematosus. *N Engl J Med* 1997;337:1777–8.
- Smith EL, Shmerling RH. The American College of Rheumatology criteria for the classification of systemic lupus erythematosus: strengths, weaknesses, and opportunities for improvement. *Lupus* 1999;8:586–95.
- Schwartz MM, Bernstein J, Hill GS, Holley K, Phillips EA, for the Lupus Nephritis Collaborative Study Group. Predictive value of renal pathology in diffuse proliferative lupus glomerulonephritis. *Kidney Int* 1989;36:891–6.
- Austin HA III, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986;314:614–9.
- Ferro D, Pittoni V, Quintarelli C, Basili S, Saliola M, Caroselli C, et al. Coexistence of anti-phospholipid antibodies and endothelial perturbation in systemic lupus erythematosus patients with ongoing prothrombotic state. *Circulation* 1996;95:1425–32.
- Kornberg A, Blank M, Kaufman S, Shoenfeld Y. Induction of tissue factor-like activity in monocytes by anti-cardiolipin antibodies. *J Immunol* 1994;153:1328–32.
- Alarcón-Segovia D, Perez-Vázquez ME, Villa AR, Drenkard C, Cabiedes J. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. *Semin Arthritis Rheum* 1992;21:275–86.
- Wang Y, Schrieber L, Cohen MG, Furphy L, Webb J, Chivers T, et al. Antiphospholipid antibodies in systemic lupus erythematosus: clinical and laboratory associations in 111 patients. *Rheumatol Int* 1990;10:75–80.
- Gladman DD, Ibanez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. *J Rheumatol* 2002;29:288–91.
- Zimmerman R, Radhakrishnan J, Valeri A, Appel G. Advances in the treatment of lupus nephritis. *Ann Rev Med* 2001;52:63–78.
- Falaschi F, Ravelli A, Martignoni A, Migliavacca D, Sartori M, Pistorio A, et al. Nephrotic-range proteinuria, the major risk factor for early atherosclerosis in juvenile-onset systemic lupus erythematosus. *Arthritis Rheum* 2000;43:1405–9.
- Trager J, Ward MM. Mortality and causes of death in systemic lupus erythematosus. *Curr Opin Rheumatol* 2001;13:345–51.
- Ward MM. Hospital experience and expected mortality in patients with systemic lupus erythematosus: a hospital level analysis. *J Rheumatol* 2000;27:2146–51.
- Ward MM. Cardiovascular and cerebrovascular morbidity and mortality among women with end-stage renal disease attributable to lupus nephritis. *Am J Kidney Dis* 2000;36:516–25.
- Aranow C, Ginzler EM. Epidemiology of cardiovascular disease in systemic lupus erythematosus. *Lupus* 2000;9:166–9.
- Thomas GN, Tam LS, Tomlinson B, Li EK. Accelerated atherosclerosis in patients with systemic lupus erythematosus: a review of the causes and possible prevention. *Hong Kong Med J* 2002;8:26–32.
- Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000;43:1801–8.