

Autologous Stem Cell Transplantation for Systemic Lupus Erythematosus: Report of Efficacy and Safety at 7 Years of follow-up in 17 Patients

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ABSTRACT

Introduction. We observed the efficacy and toxicity of autologous stem cell transplantation (auto-SCT) for patients with systemic lupus erythematosus (SLE).

Methods. Seventeen patients with SLE were treated with auto-SCT. No prisoners were used in the study. Peripheral blood stem cells were mobilized with cyclophosphamide (Cy) and granulocyte colony-stimulating factor. After a conditioning regimen of Cy and antithymocyte globulin, we reinfused stem cells. The probabilities of overall survival (OS) and progression-free survival (PFS) were used to assess the efficacy and adverse experiences, to detect the toxicities of the treatment.

Results. The median follow-up time was 89 months (range 33–110). Probabilities of 7-year OS and PFS were $82.4\% \pm 9.2\%$ and $64.7\% \pm 11.6\%$, respectively. The principal adverse events included allergy, infection, elevation of liver enzymes, bone pain, and heart failure. Two patients died due to severe pneumonia and heart failure at 33 and 64 months after transplantation, respectively.

Conclusions. Our 7-year follow-up results suggested that auto-SCT seemed beneficial for SLE patients.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is a heterogeneous, multisystem disease responsive to treatment with corticosteroids and immunosuppressives. Many patients fail to achieve treatment-free remissions. Their long-term outcomes remain poor owing to the development of vital organ failure, cumulative drug toxicity, and an increased risk of cardiovascular disease and malignancy.¹ High-dose immunosuppression followed by autologous stem cell transplantation (auto-SCT) for SLE was proposed by Marmont et al in 1997.² It appears to be a feasible and promising strategy. Recent studies have suggested that high-dose chemotherapy and auto-SCT may be performed safely in patients with active SLE and impaired organ function, resulting in disease remission and improvement or salvage of residual organ function in the majority of patients.^{3–7} We applied this technique to Chinese patients with SLE and have reported preliminary findings previously.⁸ Since then, we have extend this study to report the results of 7-year follow-up herein.

PATIENTS AND METHODS

Patients

From April 2000 through August 2006, 17 patients including three males and 14 females who were diagnosed with clinically evident

SLE according to the previously published criteria⁹ were enrolled in this study. Patient eligibility criteria included transfusion-dependent autoimmune cytopenias, severe pericarditis (symptomatic pericardial effusions causing shortness of breath, hemodynamic compromise, or chronic and disabling pain despite narcotic use), involvement of the lung (vasculitis, pneumonitis, alveolar hemorrhage), involvement of the central nervous system (cerebritis or transverse myelitis), and World Health Organization class III or IV glomerulonephritis. Nephritis required failure of six or more monthly pulses of cyclophosphamide. Nonrenal visceral organ involvement required failure of at least 3 months of cyclophosph-

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amide. Twenty patients with SLE underwent conventional therapy in the same period as the control group. The Institutional Review Board approved this study, and all patients gave written informed consent. All patients were followed until July 1, 2010. No prisoners were used in the study. Patient characteristics are summarized in Table 1.

Stem Cell Mobilization and Transplant Procedure

Peripheral blood stem cells were mobilized with cyclophosphamide (Cy) at 2000 mg/m², followed by daily subcutaneous injections of granulocyte colony-stimulating factor (G-CSF) at 5 µg/kg body weight for 5 days or 6 days. When neutrophils reached 4.0 to 5.0 × 10⁹/L, a 10,000 mL leukapheresis was performed using a continuous flow blood cell separator (MCS+ version C, Haemonetics, Braintree, Mass, USA) to achieve an enriched CD34⁺ cell count to more than 2.0 × 10⁶ CD34⁺ cells/kg body weight. The stem cells were preserved at −80°C in dimethyl sulfoxide (5%), hydroxyethyl starch (3%), and human serum albumin (4%) for infusion within 3 weeks after collection.

The Cy/anti-human thymocyte immunoglobulin (ATG) regimen was chosen for conditioning all 17 SLE patients. Cy was given intravenously over 2 hours at 50 mg/kg/d on days −4 and −2. On day 0, the purged stem cells were thawed and infused. On days +1, +2, and +3 ATG (2.5 mg/kg/d of the Sangstat product, intravenously) was administered together with soluble methylprednisolone (1000 mg/d). G-CSF was injected subcutaneously (5 µg/kg/d) starting on the day of stem cell reinfusion and continued until the absolute neutrophil count was greater than 1.0 × 10⁹/L for 3 consecutive days. All patients were hospitalized in rooms with high efficiency particle-arresting (HEPA) air filters. To prevent infections, we prescribed oral ciprofloxacin, fluconazole, acyclovir, and intravenous immunoglobulin. All blood products were irradiated at 2500 cGy before infusion.

Table 1. Patient Characteristics

Variable	Auto-SCT	Conventional Therapy	P Value
No. of patients	17	20	
Age (y), median (range)	23 (16–38)	28 (14–62)	.069
Sex, n (%)			.315
Male	3 (17.6)	1 (5.0)	
Female	12 (82.4)	19 (95.0)	
Organ involvement, n (%)			
Lupus nephritis	12 (70.6)	10 (50.0)	.204
Cerebritis/myelitis	1 (5.9)	3 (15.0)	.373
Myocardial injury	8 (47.1)	3 (15.0)	.069
Idiopathic thrombocytopenic purpura	2 (11.8)	4 (20.0)	.667
Previous therapy, n (%)			<.001
Yes	17 (100)	3 (15.0)*	
No	0 (0)	17 (85.0)	
Duration from diagnosis to therapy (mo), median (range)	33.6 (6–108)	11.0 (1.0–49.0)	.007
Length of follow-up (mo), median (range)	89 (33–110)	68.5 (2–114)	

auto-SCT, autologous stem cell transplantation.

*These three patients with lupus nephritis failed treatment of six or more monthly pulses of cyclophosphamide.

Conventional Therapy

In the conventional therapy group, patients with nephritis and those with nonrenal visceral organ involvement were given 0.5 g/m² monthly pulses of Cy for at least 6 months and 3 months, respectively. The dose was then adjusted according to the patient's response and/or toxicity. Mercaptoethane sulfonate sodium was used for prophylaxis of hemorrhagic cystitis. The median total dose of Cy was 8.10 g (range: 3.25–15.10 g). Prednisone (0.5 mg/kg/d) was administered orally in conjunction with Cy. Four patients without visceral organ involvement were treated with prednisone (1 mg/kg/d). For three patients with refractory lupus nephritis, mycophenolate mofetil (1.5–2 g/24 h) was administered with prednisone (10–20 mg/d).

Efficacy and Toxicity Evaluation

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)¹⁰ was used to evaluate activity. Adverse experiences were recorded during stem cell mobilization, conditioning, reinfusion and post-transplant periods as well as among the conventional therapy group.

Statistical Analysis

The Mann-Whitney *U* (for continuous variables) as well as chi-square and Fisher exact (for categorical variables) tests were used to compare differences between the groups. Overall survival (OS) was defined as time to death, irrespective of the cause. Progression-free survival (PFS) was defined as survival without evidence of relapse or progression, which was considered to be any increase in disease activity index. The 100-day transplant-related mortality was defined as death without SLE relapse or progression. The Kaplan-Meier estimator was used to assess 7-year cumulative incidence of OS and PFS.

RESULTS

There were no significant difference in characteristics between patients in the conventional group and those in auto-SCT group, except that the auto-SCT group included more refractory subjects and a longer duration from diagnosis to therapy (Table 1).

Efficacy

All 17 patients were considered to respond to the auto-SCT, for glucocorticoids were discontinued at 6 (*n* = 12) or 12 months (*n* = 4) after transplantation, except for one patient who continuously takes prednisone (5 mg per day). At 5 years, the SLEDAI score significantly decreased from 32.3 ± 9.2 to 0.76 ± 0.92 (*P* < .01). No patient died within 3 months posttransplantation, which was considered to be a transplant-related death, according to the Milan consensus. But two patients (11.8%) died of severe pneumonia and heart failure, at 33 and 64 months after transplantation, respectively. The median follow-up was 89 (range = 33–110) months. Probabilities of 7-year OS and PFS were 82.4% ± 9.2% and 64.7% ± 11.6%, respectively. Successful pregnancies with live births of two healthy babies were observed in two female patients at 3 and 5 years after transplantation.

Fifteen of 20 patients receiving the conventional therapy achieved remissions. At 5 years follow-up, their SLEDAI scores had significantly decreased from: 18.21 ± 5.71 to 6.28 ± 4.48 ($P < .01$). Nine patients had disease flares. Five subjects died at a median of 20 months (range: 2–74). The causes of death included severe pneumonia ($n = 3$), renal failure ($n = 1$), and respiratory failure ($n = 1$). Probabilities of 7-year OS and PFS were $66.7\% \pm 11.4\%$ and $24.7\% \pm 10.3\%$, respectively. The PFS of patients in the conventional therapy group was significantly lower than that of those in the auto-SCT group, although there was no significant difference in OS.

Safety

During mobilization, four patients experienced adverse events, including allergic reactions to Cy ($n = 1$), fever related to G-CSF in ($n = 3$), and bone pain ($n = 4$). During conditioning and early posttransplant, transplant-related toxicity included allergy to ATG ($n = 1$), fever of unknown origin (FUO; $n = 8$), documented infection ($n = 8$), nausea and vomiting ($n = 17$), and transient elevation of liver enzymes ($n = 1$). During the follow-up period, one patient experienced spinal tuberculosis (TB) at 15 months posttransplant and relapsed at 24 months following transplantation.

The adverse events in 20 patients who underwent conventional therapy included FUO ($n = 6$), documented infection in ($n = 10$), nausea and vomiting ($n = 15$), elevation of liver enzymes ($n = 3$), and ovarian failure ($n = 1$). During the follow-up, two patients displayed varicella zoster virus infections that were successfully cured. There was no significant difference in the adverse events among patients in the conventional therapy versus auto-SCT group.

DISCUSSION

The present study reported follow-up data of SLE patients treated with auto-SCT. Consistent with two recent studies,^{6,7} the PFS of patients in the auto-SCT group was $64.7\% \pm 11.6\%$, which was significantly higher than that of patients in the conventional therapy group, suggesting that auto-SCT induced sustained remissions and was superior to conventional therapy. Another interesting point was the successful pregnancies with live births of two healthy babies in two female patients, further highlighting the efficacy and safety of auto-SCT although currently no definite conclusion can be drawn as to whether SLE is cured by auto-SCT.

The rationale for using auto-SCT to treat SLE is based on the principle of complete ablation of an aberrant immune system through high-dose Cy or total body irradiation followed by reconstitution of a new immune system from in vivo or in vitro T-cell depletion.¹¹ Moreover, the capacity of G-CSF to switch T-cell cytokine profiles toward T-helper cell type-2 elements and to promote tolerogenic dendritic cell and regulatory T cell differentiation previously demonstrated by us and others is based upon exper-

imental models of autoimmune diseases.^{12,13} Zavala et al¹⁴ showed that nephritis, the end-stage of lupus disease, was prevented in mice given a high-dose G-CSF regimen (200 $\mu\text{g/kg}$). In an animal model, our study indicated that application of G-CSF on day +5 posttransplant may further regulate T-cell functions.¹⁵ Taken together, the therapeutic effects of G-CSF may be expected, because it was used to mobilize stem cells and to promote engraftment posttransplantation.

Transplant-related complications were observed during the mobilization, conditioning, and posttransplant period. Allergy, FUO, infections, elevations of liver enzymes, and heart failure were the major adverse events, although there was no significant difference in adverse events between the transplant and the conventional therapy groups. In this study, one patient died of severe pneumonia at 33 months and another of heart failure at 64 months posttransplantation, suggesting that SCT should be undertaken before irreversible organ impairment. Another important finding was that one female patient experienced a relapse after a spinal TB infection. Some studies have suggested that mycobacterial infection may act as a possible trigger infection for autoimmune diseases, including SLE.¹⁶ The possible mechanisms for this phenomenon are^{17,18}: (1) the presence of autoantibodies such as antinuclear antibody in the sera of patients with active TB infection due to cross-reactivity between mycobacterial and self antigens; (2) molecular mimicry due to antigenic resemblance between mycobacterial cell wall glycolipids and DNA, as well as reactivity of monoclonal anti-*Mycobacterium tuberculosis* with DNA (simulating an antinuclear antibody). These results suggested that more attention should be paid to supportive care, although auto-SCT is safer than allogeneic transplantation.

In summary, our study showed that auto-SCT may be of benefit to SLE at 7 years follow-up. However, recruitment of more patients into multicenter, randomized, comparative studies versus conventional treatment of SLE, such as high-dose cyclophosphamide,¹⁹ is warranted to assess the efficacy and safety of auto-SCT.

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