

Good outcome of severe lupus patients with high-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation: a 10-year follow-up study

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Abstract

Objective

This study aimed to examine the long-term efficacy, remission and survival of patients with severe systemic lupus erythematosus (SLE) after the combination treatment with high-dose immunosuppressive therapy (HDIT) and autologous peripheral blood stem cell transplantation (APBSCT).

Methods

Chinese patients with severe SLE receiving combination therapy with HDIT and APBSCT in Peking Union Medical College Hospital were enrolled from July 1999 to October 2005. Disease activity, treatment, and adverse effects of these patients were evaluated. The 10-year overall survival and 10-year remission survival were also analysed.

Results

Among the 27 patients, one patient failed to collect enough CD34+ cells and data was missing for two patients. In the end, 24 patients were included in the final analysis. After APBSCT, one patient died, two patients achieved partial remission and 21 (87.5%) achieved remission at 6 months. The median follow-up duration of the 23 patients was 120 months. Fourteen patients had completed a ten-year follow-up. The median proteinuria level of the 14 patients with LN with ten years of follow-up significantly decreased from 4.00 g/24 hours at pre-treatment to 0.00g/24 hours at year 5 and 0.00 g/24 hours at year 10 (both $p=0.001$). The 10-year overall survival rate and 10-year remission survival rate were both 86.0% (95% CI: 71.1-100.9%). After a median follow-up for 120 months, 16 patients (66.7%) remained in remission, 4 patients were lost to follow-up, 2 patients died and 1 patient remained active.

Conclusion

The combination of HDIT and APBSCT may be an option to improve the survival of severe lupus patients.

Key words

systemic lupus erythematosus, high-dose immunosuppressive therapy, autologous peripheral blood stem cell transplantation, survival

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease with high morbidity, mortality and variable prognosis and course (1). The mortality rate of SLE patients in Asia has been estimated as 9.2% (2). Although the prognosis has improved over the years with better therapeutic options, a substantial subset of SLE patients either fail to achieve optimal disease control or develop unacceptable levels of toxicity from the current available treatments. The 10-year survival rate of severe SLE patients ranges from 83% to 93% in recent studies, while the 15- and 20-year survival rates of these patients are 76–80% and 77–78%, respectively (3).

In contrast to some other systemic autoimmune diseases, there has been no significant breakthrough in the treatment of severe lupus even with the introduction of biologics such as rituximab and infliximab (4–5). Therefore, a more efficacious option with fewer side effects is needed for patients with severe lupus. Autologous peripheral blood stem cell transplantation (APBSCT) is proposed as a treatment option, which may arrest the autoimmune disease process and achieve sustained remission. Since the first consensus statement in 1997, approximately 300 autologous bone marrow or haematopoietic stem cell transplantations have been reported worldwide for SLE (6–7). The two largest experiences so far come from the European Group for Blood and Marrow Transplantation (EBMT) data registry (n=85; mean follow-up period: 25 months, range 2–123 months), and from the single-centre study by Northwestern University (n=50; mean follow-up period: 29 months, range 6–90 months) (8–9). The probability of 5-year activity free survival is 50% in both studies, consistent with the results of small pilot studies (10). The mechanism of efficacy of APBSCT on severe lupus remains unclear, but may be associated with the autoreactive immunologic memory depletion and resetting of the adaptive immune system (11).

Thus, this study aimed to evaluate the long-term efficacy, remission and survival of PBSCT followed by intensive immunosuppression in patients with severe SLE.

Materials and methods

This is an extension study on the treatment and follow-up of 18 severe systemic lupus erythematosus patients with stem cell transplantation (12).

Population

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital. The patients or their legal guardians (<18 years) signed the informed consent form approved by the IRB of Peking Union Medical College Hospital.

The eligibility of patients with severe SLE enrolled in this study was based on the SLE classification criteria of the revised American College of Rheumatology ≥ 4 (13): SLE patients with WHO class III or IV lupus nephritis (LN), progressive pulmonary dysfunction or pulmonary fibrosis, recurrent flares of lupus encephalopathy, transverse myelitis or catastrophic antiphospholipid syndrome.

Exclusion criteria included serum creatinine $>176.8 \mu\text{mol/L}$, glomerular filtering rate $<45 \text{ ml/min}$, alanine aminotransferase >2 times of normal upper limit, total serum bilirubin $>42.8 \mu\text{mol/L}$, left ventricular ejection fraction $<50\%$, pulmonary diffusion capability $<45\%$, over-growth of bacterial flora in gastrointestinal tract, active infection, history of severe drug allergy.

The study protocol followed the guidelines of the European Group for Blood and Marrow Transplantation and European League against Rheumatism in stem cell transplantation (6).

Pre-transplantation preparation

The disease activity of all the patients was assessed by SLE Disease Activity Index (SLEDAI) (14). Patients were screened for TB and cytomegalovirus (CMV) infections by CXR, PPD and CMV-pp65 testing.

Mobilisation, harvesting and selection of haematopoietic stem cells

Stem cells were mobilised into the peripheral blood using 2g/m^2 cyclophosphamide (CTX) over 2 days. Granulocyte-colony stimulating factor (G-CSF) $5 \mu\text{g/kg/day}$ was administered when the level of peripheral leucocytes $<1 \times 10^9/\text{L}$.

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at the end of harvesting. Peripheral leucocytes count was monitored and harvesting was performed when the level of peripheral white blood cell rebounded (usually 10 days after cyclophosphamide). Mononuclear cells were collected by apheresis and then purified with a CliniMACS device (Miltenyi Biotec GmbH, Germany). The graft was finally preserved at a temperature of -80°C for further use.

Regulation and reinfusion of stem cells

CTX (50 mg/kg over 4 days) plus porcine antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) (30 mg/kg over 3 days), or CTX (200 mg/kg) plus total body irradiation (TBI) (4–6 Gy) were selected depending on the patient's tolerance. The incidence of drug-related complications was decreased by hyperhydration, urine alkalinisation, and anti-emetic medication. The frozen haematopoietic stem cells were immediately warmed up to 37°C and intravenously reinfused in 10–30 minutes. A minimum of 2×10^6 CD34⁺ cells/kg was reinfused. G-CSF (0.5 $\mu\text{g}/\text{kg}/\text{d}$) was administered to each patient from the reinfusion day until the level of absolute peripheral neutrophil count was consecutively higher than $1.0 \times 10^9/\text{L}$ for 3–7 days.

Antibiotic administration

All these procedures were carried out in a HEPA-filtered haematology floor. Sputum cultures, throat swab cultures, nostril and external meatus cultures, perianal cultures were routinely used to monitor and treat infections during conditioning. One week before conditioning, the following were administered: low microbial diet, oral 80,000 IU gentamycin (twice a day), oral norfloxacin 0.2 g (three times a day), oral fluconazole 0.2 g (once a day), oral sulphamethoxazole 0.4g (once a day), gentamycin eyedrops (both eyes three times a day), chlortetracycline (both nostrils and external acoustic meatus), gargling three times per day using 0.02% chlorhexidine acetate and perineal bathing once per night with 0.05% chlorhexidine acetate. Antibiotic administration was terminated

once the level of absolute peripheral neutrophils was higher than $0.5 \times 10^9/\text{L}$. Intravenous ganciclovir (5 mg/kg every 12 hours) for 14–21 days or until CMV-pp65 negative as well as IVIG were administered once viral infection was suspected. Intravenous fluconazole (400 mg once a day) for 14–21 days was administered once fungal infection was suspected.

Follow-up

Close observation was carried out at mobilisation, transplantation, 3, 6, 12, 18, 24 months and then once a year after APBSCT. Low dosage of steroid and immune inhibitors were administered to maintain remission. Changes in symptoms, signs, and laboratory examination related to the disease activity were recorded. Side effects of high-dose immunosuppressive therapy (HDIT) and APBSCT were closely observed. Flow cytometry was used to evaluate the post-transplant immune reconstitution by determining the phenotypes of peripheral lymphocytes.

Outcomes

The major outcomes were overall survival and remission survival. Overall survival was defined as time to death, irrespective of the cause, while remission survival was defined as survival without evidence of flare or activity. SLE patients achieving SLEDAI <3, Physician's global assessment (PGA) <1 and requiring physiologic doses of corticosteroids (≤ 10 mg/d of prednisone or low dose of immunosuppressant such as HCQ and MTX) as well as clinical evaluation of rheumatologists were considered to be in remission, while SLEDAI reduction >3 was considered to be improved, and partial remission included mild or moderate disease activity (defined as SLEDAI <4 and 4–8 respectively) (15–18). Flare was defined as a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements (19). Renal flare is defined as an increase in proteinuria or serum creatinine, abnormal urinary sediment or reduction in creatinine clearance due to active disease (7). The toxicity of high

dose immunosuppressants was evaluated by WHO (20).

Statistical analysis

SPSS statistical package 19.0 (Chicago, IL) was used to calculate the mean value and the standard deviation (SD) of the enumeration data. Wilcoxon signed ranks test was used to compare the change of indices before and after transplantation. The test was two-tailed with a significance level of 0.05. Kaplan-Meier survival analysis was used to assess overall survival and activity free survival.

Results

Twenty-seven patients with severe lupus were enrolled and followed. Among 27 patients, one patient failed to collect enough CD34⁺ cells and date was missing for two patients due to them being lost to follow-up. One of the patients dropped out at month 3 (SLEDAI pre-transplantation vs. post-transplantation: 13 vs. 3) while the other patient dropped out at month 6 (SLEDAI pre-transplantation vs. post-transplantation: 12 vs. 0). Three paediatric patients were included in the final analysis (15, 16, and 17 years). In the end, 24 patients were included in the final analysis. The median age of these patients was 22 years (range: 15–48 years) and 83.3% of them were female (n=20) (Table I). The median follow-up period of these patients was 120 months (range: 8–180 months). The immunosuppressants before APBSCT included cyclosporine (CsA), azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), CTX, hydroxychloroquine (HCQ), intravenous immunoglobulin (IVIG), or combinations while the immunosuppressants after APBSCT included HCQ, CTX, MMF, MTX, or combinations. The disease duration of all the patients before PBSCT was 1.17–16 years. The prednisone dosages of all the patients before PBSCT was mainly 40–60 mg/d. The involved organs of all the patients included renal, brain, haematologic system and others (e.g. lung, APS).

One patient with LN and lupus encephalopathy (18 years; disease duration: 3.3 years) died of transplant-related

Table I. Characteristics of patients.

Age, year, median (range)	22 (15-48)
Female (%)	83.3
Dx-Tx duration, month, median (range)	60 (14-192)
Follow-up duration, month, median (range)	120 (8-180)
Pre-APBSCT (%)	
CTX	25
CTX+MMF	16.7
CTX+MTX	12.5
Others*	45.8
Post-APBSCT (%)	
MTX	20.8
MTX+HCQ	34.2
HCQ	20.8
MMF+HCQ	4.2
Others	20
End organ involvement (%)	
LN	87.5
Non-LN	12.5
Conditioning (%)	
CTX+ATG	25
CTX+TBI	66.7
CTX+ALG	4.2
Other	4.2

APBSCT: autologous peripheral stem cell transplantation; CTX: cyclophosphamide; MMF: mycophenolate mofetil; MTX: methotrexate; HCQ: hydroxychloroquine; ATG: antithymocyte globulin; TBI: total body irradiation; ALG: anti-lymphocyte globulin.

*CsA, AZA, HCQ, and/or IVIG.

complications (irreversible liver failure) due to severe CMV infection at day 23 after APBSCT. Two patients achieved partial remission and twenty-one patients (87.5%) achieved re-

mission at 6 months after APBSCT. The median scores of SLEDAI were decreased from 16 before treatment (range: 9–24) to 0 (range: 0–8) and 0 (range: 0–9) at 5 years and 10 years (all $p < 0.001$). The median proteinuria level of fourteen patients with LN who completed ten years of follow-up significantly decreased from 4.00 g/24 hours (range: 0.29–10.4) at pre-treatment into 0.00g/24 hours (range: 0.00–1.57) and 0.00 g/24 hours (range: 0.00–1.00) at year 5 and 10, respectively (both $p = 0.001$). The 10-year overall survival rate and 10-year remission survival rate were both 86.0% (95% CI: 71.1–100.9%) (Fig. 1). The patients with APBSCT in the first three years had a higher risk of flare (46.2% vs. 7.1%, $p = 0.006$). After a median follow-up for 120 months, the remission rate of these patients was 66.7%. A decreased or negative result in anti-dsDNA antibody and recovery of serum complement (CH50, C3, and C4) were observed in patients with remission. The ANA and anti-ENA (anti-SSA, anti-SSA and anti-RNP, respectively) of six patients normalised at 6 months after transplantation. Only a slight decline of autoantibody titres in other patients was observed after APBSCT. The ANA and anti-ENA of three patients had transient negative changes with remission during the months of follow-up and

continued to have a low positive titre. Infections were observed in 12 patients after conditioning. Eight patients had CMV-infection and one of them died of severe CMV infection, which was the only death due to treatment-related mortality (TRM) for transplantation. Six patients had bacterial infection (two patients with both bacteria and CMV infection). Other side effects included nausea, vomiting and alopecia caused by CTX and/or TBI, as well as bone pain caused by G-CSF. Drug-related liver function abnormality and renal dysfunction also occurred, both of which improved after discontinuing medication. In one patient post-TBI radiation parotitis was observed, but no radiation-associated pneumonia was observed in the follow-up period.

During the follow-up period, eight patients experienced flares and the total flare times was 11 (two times for one patient, three times for another). The mean first flare duration was 25.1 months and the mean SLEDAI of the first flare patients was 7.8. The occurrence of flares seven times was due to LN. The other flare conditions included alveolar haemorrhage, thrombocytopenia, leucopenia and reduced haemoglobin. Among these flare patients, two patients died, one due to ESRD and one to multisystem organ failure (MSOF). The disease duration of the

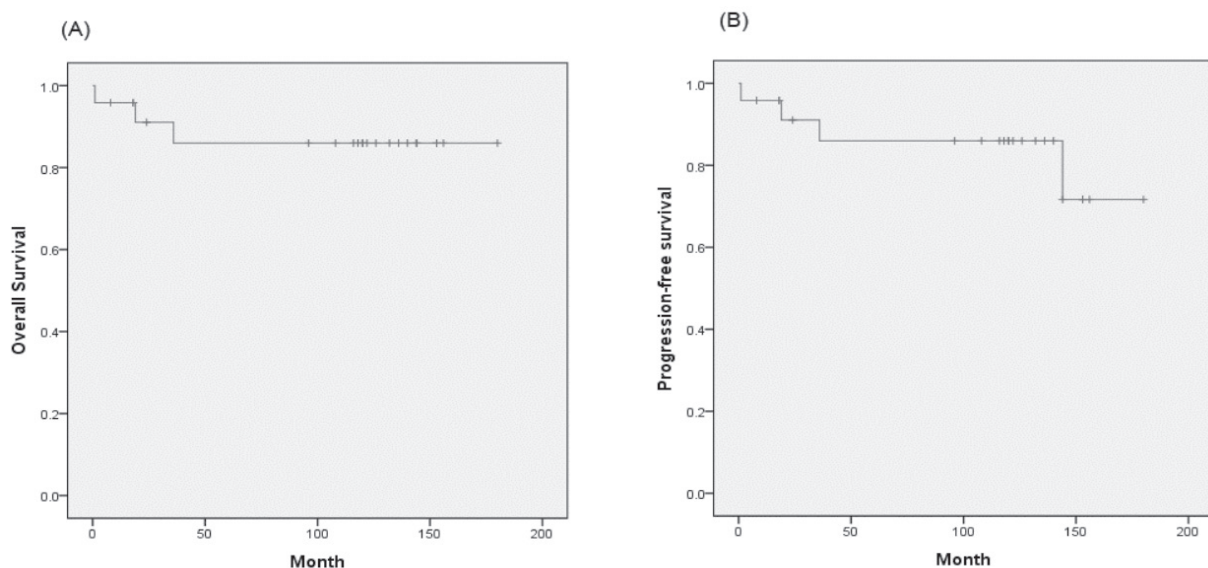


Fig. 1. Kaplan-Meier curves for the probability of overall survival and remission survival after autologous peripheral stem cell transplantation in patients with severe lupus. The 10-year overall survival rate (A) and 10-year remission survival rate (B) were both 86.0% (95% CI: 71.1–100.9%).

female patient with ESRD (32 years) who died of renal failure 19 months after transplantation was eight years. She had partial remission after transplantation and continued on a moderate dosage of steroids and MMF. The male patient with MSOF (37 years), with a disease duration of 5 years, died of uncontrolled diffuse alveolar haemorrhage induced by pulmonary vasculitis 3 years after transplantation. He had remission after transplantation and maintained treatment with pred 10 mg+MTX 10 mg/w+HCQ 0.2 QD. Among the other 6 patients, 5 remained in remission at the last follow-up after treatment and one patient was active. Four patients dropped out at the last follow-up.

Discussion

The long-term remission and survival of HDIT and APBSCT with CD34⁺ cell selection in patients with severe SLE were investigated in this prospective study. The overall remission rate of severe SLE patients after APBSCT and in 120 months of follow-up were 91.7% and 66.7%. The 10-year overall survival and 10-year remission survival were both 86.0%.

The mechanism of the effectiveness of APBSCT on lupus remains unclear, however immune reconstitution is considered to play an important role. During the post-transplant immune reconstitution, we observed that the recovery of CD8⁺ cells and CD45RO⁺ (memory T cells) cells was faster than the recovery of CD4⁺ cells and CD45RA⁺ (naïve T cells) cells (data not shown). After haematopoietic system for at least 6 months, immunoreactive cells were reconstituted. We observed a change in the T cell pool, inversed ratio of CD4/CD8 and the increased natural suppressive cells in early immune reconstitution (data not shown). This remission may be due to the significant reduction of CD4⁺ cells after transplantation and inversion of T4/T8 ratio.

Two patients achieved partial response and one patient died after transplantation. Furthermore, flare was much easily controlled by previously refractory DMARDs in patients who achieved remission after APBSCT. During the

follow-up period, only eight patients experienced flares. This may be due to the de novo generation immune system (7). A small sample size study found that APBSCT is effective for children with severe lupus. The quality of life was also significantly improved (10). However, only five children with severe or refractory lupus were included in this study. The maximum follow-up duration of the five children was 7 years.

The 5-year overall survival rate in our study was 86%, which was similar to the previous study. However, the 5-year remission survival rate was higher than the previous study (9, 21-24). This may be due to the combination of low dose MTX, HCQ, and MMF in patients (25-26). The long-term data demonstrated that APBSCT was a therapeutic option for progressing lupus patients despite standard therapy.

Only one patient died of CMV infection after APBSCT in this study indicating the well safety of HDIT and APBSCT. CMV-pp65 monitoring was mandatory after the first CMV-related death case. Confirmed CMV infection cases would receive anti-virus treatment, and there was no other CMV-related death case. Two patients died of ESRD and MSOF (induced by nephritis). These data indicate that renal function was a critical factor in the long-term outcome of severe SLE patients. However, this risk for patients with severe organ dysfunction or possible fatal complication from underlying disease during the process of transplantation might outweigh the benefit. This further implied the importance of judicious recruitment of patient for APBSCT. Strict patient enrolment excluding those with irreversible organ involvement may reduce mortality. The rate of flare was significantly decreased without TRM case since September 2002 in our centre, which was consistent with the EMBT experience (23, 27). The outcome of lupus patients including relapse and mortality may be associated with anti-ds DNA antibodies and long disease duration before ASCT (28).

In conclusion, this study demonstrated the short-term and long-term effectiveness of APBSCT in patients with severe

SLE. Importantly, the present study highlights that the experience of the transplant centre is also an important factor in transplant-related mortality and overall survival.

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