Autologous hematopoietic stem cell transplantation to treat systemic lupus erythematosus: The first case in Vietnam

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Summary

Background: Systemic lupus erythematosus (SLE) is a chronic disease that causes systemic inflammation which affects multiple organs. There is no cure for SLE. Conventional treatment options include antimalarial drugs, corticosteroids, and immune suppressants, but a number of patients are resistant to treatment or suffer from severe side effects. Stem cell transplantation has been used to treat SLE for the past 2 decades. We describe the first Vietnamese patient with refractory SLE who received an autologous hematopoietic stem cell transplant. *Case presentation:* The patient is a woman who was diagnosed 12 years ago with systemic lupus erythematosus. She was administered corticosteroids and high-dose immunosuppressive medicines, but the condition was refractory, manifesting as severe headache, arthralgia, chronic anemia, severe Cushing's syndrome, and proteinuria. At admission, the SLEDAI score was 28 and proteinuria was 6.7g/l. She received cyclophosphamide and G-CSF for HSCT mobilization. Peripheral blood stem cells were collected and selected for CD34+ cells. Antithymocyte, cyclophosphamide, and rituximab were used in conditioning regimens. The patient was then administered a CD34+ autologous hematopoietic stem cell transfusion with a CD34+ dose of 7.93 x 10^6 cells/kg body weight, T and B lymphocyte purity of the graft exceeded 99.99%. Post-transplant course was favorable, the patient did not experience serious complications. Recovery of neutrophils on post-HSCT day +9 and platelet on day +12. Six months after stem cell transplantation, the patient's clinical symptoms significantly improved, the SLEDAI score dropped from 28 to 0, and the patient discontinued receiving immunosuppressive drugs. *Conclusion:* Autologous hematopoietic stem cell transplantation promises to be a new, effective therapeutic method that can be implemented more broadly in Vietnam for SLE patients.

Keywords: CD34+ selection, SLE, CliniMACS, Autoimmune diseases, AD, HSCT, PBSC, systemic lupus erythematosus.

1. Background

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the generation of autoantibodies to the host and manifests clinically in many organs with diverse clinical forms. The condition disproportionately affects women of childbearing age, with an 8:1 female to male ratio. The inability to tolerate autoantigens is influenced by genetic and environmental factors, which are yet not fully understood. It is unknown to what extent interactions between aberrant genes and environmental variables contribute to the pathogenesis of the disease [1].

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In recent decades, treatment strategies for systemic lupus erythematosus have advanced with the development of numerous new immunosuppressive drugs and biologics. However, 10 to 15 percent of patients with systemic lupus erythematosus are resistant to treatment (unresponsive to current therapies) or experience numerous adverse effects from immunosuppressants, putting them at risk for death and a significantly diminished quality of life [2]. To expand the patient's lifespan and improve the patient's quality of life, it is necessary to develop both novel and conventional treatments.

Numerous hematologic, malignant, and autoimmune conditions have been successfully treated with autologous hematopoietic stem cell transplantation. Autoactivated T cells and B cells are considered to be crucial to the pathogenesis of systemic lupus erythematosus [1]. Therefore, systemic lupus erythematosus patients may benefit greatly from stem cell therapy that eliminate these autoimmune cells, restore healthy immune systems, and prevent disease relapse. Hematopoietic stem cell transplantation has been used to successfully treat approximately to 300 patients with systemic lupus erythematosus worldwide [5].

This approach was utilized to treat systemic lupus erythematosus for the first time in Vietnam. We describe the procedure for autologous hematopoietic stem cell transplantation for SLE patients as well as the outcomes of the first case.

2. Case presentation

46-year-old female patient, diagnosed with systemic lupus erythematosus 12 years ago. The patient was treated with corticosteroids and aggressive immunosuppressants, with a dose of medrol 40mg/day; mycophenolate mofetil 1000mg/day, and hydroxychloroquine 400mg/day; however, the disease reactivated with manifestations of severe headache, arthralgia, chronic anemia, severe Cushing's syndrome, proteinuria 6.7g/l, and SLEDAI score of 28 on admission. The patient was chosen for an autologous hematopoietic stem cell transplant at 108 Military Central Hospital.

To mobilize peripheral blood stem cells, the patient received chemotherapy with cyclophosphamide 2g/m^2 on day 1 and G-CSF 10mg/kg on days 4 through 9. Stem cells were harvested on day 10 using the density-based cell separation method by TERUMO BCT Spectra Optia system. The PBSC product was subsequently processed and CD34+ cells were selected using the CliniMACS system. The final stem cell product was quantified using flow cytometry on a Facscanto II instrument, to determine CD34+, T, and B cell count and CD34+ cells viable percentage with a dye containing 7-aminoactinomycin D (7-ADD). The stem cell product was then stored at -196°C. The patient received conditioning regimens of myelosuppressive chemotherapy with rituximab, cyclophosphamide, and ATG, followed by a transfusion of stored stem cells and observation for clinical and biochemical improvement following transplantation.

Our results are as follows:

2.1. Performance of CD34+ cells selected procedure

Table 1. Performance of CD34+ cells selected procedure

Index	PBCS product	CD34+ cell selected product	CD34+ cell recovery/ T, B cell removal efficiency (%)
Total CD34+ cells (cells)	1021.76×10^6	660.87×10^6	64.5
CD34+ viability (%)	99.87	99.58	
Total lympho T (cells)	860400.25×10^4	6.4×10^4	99.99
Total lympho B (cells)	50934.44×10^4	1.65×10^4	99.99
Bacteria culture	Negative	Negative	

According to the findings of the study, the CD34+ selected process using the CliniMACS system eliminated 99.99% of the T and B lymphocytes, while maintaining the majority of CD34+ cells with a recovery rate of 64.5%. The patient received a purified stem cell transplant with a CD34+ dose of 7.93×10^6/kg body weight and T and B cell doses of 0.11×10^4/kg and 0.029×10^4/kg, respectively along with a totally no bacteria contamination (Table 1).

2.2. Characteristic of CD34+ cells selected product

Table 2. Characteristic of CD34+ cells selected product

CD34+ cell dose (cells/kg)	7.93×10^6
CD34+ viability (%)	92.6
T cell dose (cells/kg)	0.112×10^4
B cell dose (cells/kg)	0.029×10^4
Bacterial culture	Negative

The final stem cell product met the standard criteria in terms of CD34+ cell dose, T cell dose as well as sterile quality.

2.3. Time to engraftment following HSCT

Figure 1. Time to engraftment following HSCT

D0 is the date of stem cell infusion. After 9 days, our patient received neutrophil engraftment, and on day +12, platelet engraftment.

2.4. Therapeutic approaches and clinical features after transplantation

Before the stem cell transplant, the patient was on high-dose therapy with Medrol 40mg/day; Cellcept 1000mg/day, and HCQ 400mg/day but the SLEDAI score was 28. After 1 month of HSCT, the SLEDAI score decreased to 2 and continued to decline to 0 at 3 and 6 months. Proteinuria dropped from 6.7 g/l to 0.13 g/l. At the same time, the patient was withdrawn entirely from corticosteroids, hydroxychloroquine, and only using mycophenolate with a dose reduced in half compared to pre-transplant at 1 month, and eventually stopped immunosuppressive drugs at 3 months post-transplant.

3. Discussion

Hematopoietic stem cell transplantation (HSCT) has evolved as an advanced treatment for individuals with autoimmune diseases throughout the past three decades. More than 3000 people with autoimmune disorders, including more than 300

patients with systemic lupus erythematosus, have received hematopoietic stem cell transplantation to treat the disease, with remarkably successful outcomes [5]. The patients achieve long-term remission and minimize their need of immunosuppressive drugs. Stem cells from healthy donors have the potential to generate an entirely new immune system, free of disease and capable of destroying the patient's remaining cancer and autoimmune cells, but there is a risk of life-threatening graft-versus-host disease and a limited donor source because of the need for HLA matching. Due to its availability without the risk of graft-versus-host disease, autologous hematopoietic stem cell transplantation has become the primary source of stem cells used in treatment; however, it carries a potential risk of disease recurrence as autoimmune cells are harvested alongside the stem cells and re-infused into the patient's body.

Our CD34+ stem cell selection outcomes are comparable to those of other authors, including Despre's at al with CD34+ recovery of 69.5% (46.9-87.3), T cells depletion of 97.7% (89.4-99.8) [6], Imai at al report CD34+ recovery and T cells depletion of 72% and 93.3% (32.6-99.3) respectively [7], Leong et al. show the recovery of CD34+ cells is 66% and the T cell-depleted efficacy of 79% (18-86). The final stem cell product met the standard criteria in terms of CD34+ cell dose, T cell dose as well as sterile quality. Most guidelines recommend a CD34+ dose of 2×10^6 cells/kg body weight, preferably in the range of 3-8 $\times 10^6$ cells/kg body weight [3, 4]. The remaining recommended T-cell dose in the CD34+ selective graft is less than 2.5×10^4 cells/kg body weight [8, 9]. Self-activated T and B lymphocytes are considered to play a crucial role in the pathogenesis of systemic lupus erythematosus [1]. Using stem cell grafts to eliminate these cells theoretically help patients achieve long-term remission and reduce the risk of disease recurrence.

The time to neutrophil engraftment was defined as the first day in which the patient did not need to administer G-CSF for three consecutive days. The time to platelet engraftment was calculated as the first day in which the patient did not require platelet transfusion for three consecutive days [3, 4]. The time it took for neutrophils and platelets to engraft in our study was comparable to that of other investigations.

Table 3. Time to neutrophil and platelet engraftment in published reports

Study	Time to neutrophil engraftment	Time to platelet engraftment
Our study	D+9	D+12
Rosen, O et al (2000)	D+12 (9-15)	D+14 (12-16)
Ann E Traynor (2000)	D+9 (8-11)	D+11 (10-13)
Xianghua Huang (2019)	D+8 (7–9)	D+9 (6-10)

Although it is known that a transplant that eliminates the majority of T cells can slow engraftment, the patient is susceptible to fungal infections and viral reactivation [4]. Fortunately, our patient experienced neutrophil engraftment on day +9 and platelet engraftment on day +12, with no infection during the transplantation period.

The pre-transplant SLEDAI score of 28 decreased to 2 at 1 month (because the patient kept losing hair, but hair loss may be due to the conditioning agent), and continued to decline to 0 at 3 and 6 months. Proteinuria dropped from 6.7g/l to 0.13g/l while the patient was completely withdrawn from corticosteroids, hydroxychloroquine, and only using mycophenolate with a dose reduced in half compared to pre-transplant at 1 month, and completely stopped immunosuppressive drugs at 3 months post-transplant.

Compared to other trials, Rosen O et al (2000) found that autologous hematopoietic stem cell transplantation for 4 SLE patients, followed for 6 to 21 months, resulting in clinical remission,

normalization of ANAs, dsDNA, and cardiolipin levels, and a reduction in proteinuria [10]. Ann E. Traynor (2000) treated 9 patients with SLE with autologous hematopoietic stem cell transplantation, with a median follow-up of 25 months (12-40) revealing full remission, discontinuation of the treatment, or low-dose prednisolone [11]. Leng XM (2013) reported a significant reduction in proteinuria in SLE patients undergoing stem cell transplantation from 4.00g/24 hours to 0.00g/24 hours. The overall survival rate and the disease-free rate at 10 years were both 86% [12]. Burt RK (2018) reported that 30 SLE patients treated with autologous stem cell transplantation experienced disease remission and drug-free treatment in 92% of cases after one year, 81% after two years, 71% after three years, and 62% after four and five years [13].

Reducing the dose and discontinuing immunosuppressive medicines, relieving patients of drug-related side effects, and enhancing quality of life are the objectives of stem cell transplantation for treating diseases, as well as the desires of patients receiving this therapy. However, research is still ongoing to determine the long-term consequences of this therapy in terms of obtaining long-term remission and minimizing the need for immunosuppressants.

4. Conclusion

The first case of systemic lupus erythematosus has been successfully treated by CD34+ selective autologous hematopoietic stem cell transplantation. The initial outcomes are quite excellent and promising. Autologous hematopoietic stem cell transplantation holds promise as a new, effective treatment for lupus erythematosus patients in Vietnam that can be used more broadly. However, additional research and prolonged follow-up are required for a comprehensive evaluation.

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