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Original Article

Long-term Outcomes of Autologous Peripheral Blood Stem Cell Transplantation for Refractory Rheumatic Diseases

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Objective. We investigated the long-term outcomes of autologous peripheral blood stem cell transplantation (PBSCT) to treat refractory rheumatic diseases. **Methods.** Patients who underwent PBSCT for refractory rheumatic diseases at our institution between 2002 and 2005 were assessed for outcomes including treatment response, adverse events, damage accrual, and survival at 6 months and last follow-up. **Results.** Eleven patients, including six with systemic lupus erythematosus (SLE), four with systemic sclerosis (SSc), and one with Still's disease were treated with PBSCT. In SLE patients, two showed complete response, two partial response, and two expired. One patient who expired responded completely two months after transplantation but discontinued treatment by choice and expired at six months due to an SLE flare. Long-term, two patients went into remission without organ damage, one patient went into remission with organ damage, and one had low disease activity with organ damage. Of the four patients with SSc, two showed a complete response, one a partial response, and there was one transplantation-related death at six months. At the last record notation, two remained in remission without relapse and one was lost to follow-up. The Still's disease patient partially responded at six months and was in remission at the last record notation. **Conclusion.** The ten-year survival rate was 70% with a 40% recurrence rate and 20% treatment-related mortality rate. **(J Rheum Dis 2017;24:149-156)**

Key Words. Peripheral blood stem cell transplantation, Systemic lupus erythematosus, Systemic scleroderma, Still disease

INTRODUCTION

Rheumatic diseases are systemic inflammatory disorders that can lead to pain, disability, morbidity, and mortality [1]. Immunosuppressants and corticosteroids are used for its treatment, but it can be ineffective. We currently lack safe and effective treatment for patients with major organ involvement who are refractory to conventional treatments. Hematopoietic stem cell transplantation (HSCT) has been proposed as an effective alternative treatment for refractory rheumatic diseases.

HSCT was first suggested as a treatment for severe refractory autoimmune diseases in 1996 [2]. The primary concept of HSCT is to eradicate autoreactive immunologic memory cells after intensive chemotherapy and to regenerate a new self-tolerant immune system using hematopoietic precursors [3]. There are two main treatment methods; allogeneic HSCT and autologous HSCT. Allogeneic HSCT is considered to be more effective and can lead to long-lasting remission with a lower rate of recurrence [4]. However, procedure-related complications such as graft-versus-host disease are more frequently reported and are associated with a higher risk of mortality than autologous HSCT. Autologous HSCT has a safer mobilization process and lower transplant-related mortality than allogeneic HSCT. Both peripheral blood stem cell transplantation (PBSCT) and bone marrow transplantation can be performed, but PBSCT, with more blood progenitor cells and better engraftment, is preferred [3,5]. European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT) published consensus guidelines and

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recommended indications for the use of HSCT [2]. In these guidelines, rheumatic diseases indication includes systemic sclerosis; refractory autoimmune pulmonary hypertension; refractory necrotizing vasculitis; refractory rheumatoid arthritis with severe complications or poor prognosis with rapid progression and destruction; refractory systemic lupus erythematosus (SLE) with major organ involvement; antiphospholipid syndrome; and severe uncontrollable cryoglobulinaemia. HSCT has since been used to treat over 2,100 cases of multiple sclerosis, systemic sclerosis (SSc), SLE, rheumatoid arthritis (RA), Crohn's disease, and others [4,6].

The short-term treatment response to HSCT treatment of refractory autoimmune diseases is significant reduction in disease activity and improvement in clinical symptoms [7]. We reaffirmed these short-term responses to HSCT in SSc and SLE patients [8,9]. The long-term analysis of 900 patients included in the EMBT database who underwent autologous HSCT up to 2007 showed an overall 5-year survival of 85% and progression-free survival of 43%. In addition, outcomes varied with age, diagnosis, and center experience [10]. In a randomized clinical trial for patients with diffuse SSc, HSCT was found to be more effective than monthly intravenous pulse cyclophosphamide (CYC); moreover, HSCT conferred a long-term survival benefit compared to conventional treatment [11]. However, HSCT is associated with a high early treatment-related mortality rate and serious adverse events and is therefore not yet the standard of care. Here we report a case series and describe short-term treatment responses and the long-term prognoses of 11 patients with refractory autoimmune disease who received autologous PBSCT.

MATERIALS AND METHODS

Patients

We reviewed the clinical course and outcomes of patients who underwent autologous PBSCT between March 2002 and July 2005. Of the 12 patients, 7 had SLE, one of which had overlap syndrome with RA, 4 had SSc, and 1 had Still's disease. Short-term treatment response was evaluated in 11 of the patients, as one patient was not able to receive HSCT due to development of Guillain-Barre syndrome during the mobilization process. Long- term outcomes were evaluated in 10 of the patients, excluding one patient with SSc who was lost to follow-up at 9 months after PBSCT (Tables 1 and 2). Patients were selected using the criteria of the EULAR/EBMT guidelines published in 1997 [2]. All patients gave informed consent.

PBSCT method

To collect hematopoietic stem cells, patients were injected intravenously with CYC (3 g/m^2) and then were subcutaneously injected with granulocyte-colony stimulating factor (G-CSF, 5 μg/kg/day) on day 7. Leukapheresis was initiated on the day when the leukocyte count exceeded 1,000/μL, and cells were collected until the number of monocytes reached 5×10^8 cells/kg. Of the collected cells, CD34+ cells were selectively separated and stored at -190°C. As pretreatment, CYC (50 mg/kg/day) and anti-thymocyte globulin (30 mg/kg/day) were injected intravenously for 4 and 3 days, respectively. Forty-eight hours after pretreatment was complete, the CD34+ cells that had been stored in a freezer were injected through a large vein. Subsequently, G-CSF was subcutaneously injected until the absolute neutrophil count reached 1,000/μL.

Outcome assessment

Short-term and long-term outcome measures were assessed. Complete response in lupus nephritis was defined as a 24-h proteinuria level less than 500 mg at 6 months after HSCT and no worsening of serum creatinine level from baseline [12]. Complete response in SSc was defined as a decrease in the modified Rodnan skin score over 25% at 6 months after HSCT [13]. Complete response in Still's disease was defined as a Juvenile Arthritis Disease Activity Score-27 (JADAS-27) lower than 2.7 [14]. Remission of lupus nephritis was defined as no clinical disease activity and low disease activity with low-dose prednisolone [15]. Remission of RA was assessed using the 2011 American College of Rheumatology remission definition [16]. Remission of SSc and Still's disease was defined as lack of requirement for immunosuppressive therapy and no clinical disease activity [13,14]. Low disease activity in SLE was defined as SLE Disease Activity Index $\leq$4 [17].

RESULTS

SLE

There was a total of 7 patients with SLE. One patient who did not receive PBSCT due adverse event with mobilization treatment was excluded. Regarding disease manifestations prior to stem cell transplant, 4 patients had lupus nephritis, 2 had neuropsychiatric SLE, and 1 patient

Table 1. Characteristics of the patients who underwent HSCT and their outcomes

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (yr)/Gender	22/female	39/female	38/female	18/male	19/female	42/female
Diagnosis	SLE	SLE	SLE	SLE	SLE	SLE
Clinical indications for HSCT	Refractory lupus nephritis with nephrotic syndrome Arthritis Hematologic disorder DVT with APS	Refractory lupus nephritis with nephrotic syndrome Seizure due to NPSLE Serositis Hematologic disorder	Cognitive disorder due to NPSLE Arthritis (RA overlap syndrome) Hematologic disorder	Refractory lupus nephritis with nephrotic syndrome Serositis Hematologic disorder	Refractory lupus nephritis with nephrotic syndrome Serositis Hematologic disorder	Refractory lupus nephritis with nephrotic syndrome (Class III+IV) Hematologic disorder Pulmonary artery hypertension
Disease duration (mo)	21	12	95	65	75	44
Previous treatment	PDS, CYC, HCQ	PDS, CSA, HCQ, IVIG	PDS, CSA, MTX, HCQ	PDS, CYC, MMF, AZA	PDS, CYC, CSA, MTX, HCQ, MMF, rituximab	PDS, CYC, CSA, AZA
Pre-transplantation disease activity	SLEDAI 2K − 16, SDI - 0	SLEDAI 2K − 23, SDI - 2	SLEDAI 2K − 12, SDI - 1 TJC 15 / SJC 11	SLEDAI 2K − 19, SDI - 1	SLEDAI 2K − 22, SDI - 2	SLEDAI 2K − 15, SDI - 3
Follow-up period (mo)	156	6	152	134	81 (follow-up loss)	2
Short-term response (6 mo)	Complete response	Complete response (2 months)	Complete response	Partial response	Partial response	Death at 2 months
Long-term outcomes	Remission 12 months after HSCT Relapse at 70 months (after NSVD) Remission 94 months after HSCT (drug-free)	Relapse at 3 months (medication self-stop) Death at 6 months (disease progression)	SLE − remission Arthritis − relapse at 7 months (Rituximab start at 84 months)	Remission (Low-dose PDS+HCQ after 52 months) Progression of organ damage (remnant proteinuria CKD stage 3 after 120 months)	Low disease activity with progression of organ damage ESRD on HD at 41 months	Death at 2 months (Sepsis due to systemic CMV infection)
Recent disease activity	SLEDAI 2K − 2 SDI - 0	*	SLEDAI 2K − 0, SDI - 1 TJC 0 / SJC 0	SLEDAI 2K − 6, SDI - 1	SLEDAI 2K − 10, SDI - 3	*

SLE: systemic lupus erythematosus, DVT: deep vein thrombosis, APS: antiphospholipid syndrome, NPSLE: neuropsychiatric SLE, RA: rheumatoid arthritis, PDS: prednisolone, CYC: cyclophosphamide, HCQ: hydroxychloroquine, CSA: cyclosporine, IVIG: intravenous immunoglobulin, MTX: methotrexate, MMF: mycophenolate mofetil, AZA: azathioprine, SLEDAI: SLE disease activity index, SDI: systemic lupus international collaborating clinics/American College of Rheumatology (SLICC/ACR) damage index, TJC: tender joint count, SJC: swollen joint count, HSCT: hematopoietic stem cell transplantation, NSVD: normal spontaneous vaginal delivery, CKD: chronic kidney disease, ESRD: end-stage renal disease, HD: hemodialysis, CMV: cytomegalovirus. *Not available.

Table 2. Characteristics and outcomes of patients who underwent hematopoietic stem cell transplantation (HSCT)

Characteristic	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Age (yr)/Gender	31/female	42/female	36/female	30/female	22/male
Diagnosis	Systemic sclerosis	Systemic sclerosis	Systemic sclerosis	Systemic sclerosis	Still's disease
Clinical indications for HSCT	Rapid progression scleroderma Pulmonary involvement	Rapid progression scleroderma Pulmonary involvement Acral ulcerations	Pulmonary involvement Cardiac involvement Pharyngeal muscle involvement Acral ulcerations	Pulmonary involvement	Refractory disease activity Recurrent flare
Disease duration (mo)	7	33	58	36	108
Previous treatment	PDS, CYC, D-penicillamine, colchine	PDS, MTX, D-penicillamine, limaprost	D-penicillamine, limaprost, cilostazol, streptokinase, ACEi	PDS, CYC, MTX, D-penicillamine, limaprost,	PDS, CSA, MTX, bucillamine infliximab
Pre-transplantation disease activity	mRSS 27	mRSS 31	*	mRSS 33	TJC 5 / SJC 4 JADAS-27 23.5
Follow-up period (mo)	158	148	1	9	151
Short term response (6 mo)	Complete response mRSS 7	Complete response mRSS 11	Death at 7 days	Partial response mRSS 27	Partial response Relapse at 1 month TJC 1 / SJC 1 JADAS-27 4
Long term prognosis	Remission (drug-free) No recurrence	Remission (drug-free) No recurrence	Death at 7 days (respiratory arrest)	*	Remission (drug-free)
Recent disease activity	mRSS 0	mRSS 0	*	*	TJC 0 / SJC 0 JADAS-27 0

PDS: prednisolone, CYC: cyclophosphamide, MTX: methotrexate, ACEi: angiotensin converting enzyme inhibitor, CSA: cyclosporine, mRSS: modified Rodnan skin score, TJC: tender joint count, SJC: swollen joint count, JADAS-27: juvenile arthritis disease activity score-27. *Not available.

had both manifestations. In the short-term, 2 patients showed complete response. Another patient had shown complete response after 2 months, but died after 6 months due to disease relapse because she stopped taking medication by her choice. Two patients had a partial response, and 1 patient died due to a transplantation-related infection. In the long-term, 4 patients were alive, and 2 patients died. One of the survivors was in remission without organ damage, and the other was also in remission but had organ damage. The overlap patient showed remission of SLE but a relapse for RA, while the other surviving patient maintained low disease activity without relapse but showed ongoing irreversible organ damage. The 2 deaths were related to relapse with disease progression and transplantation-related death, respectively.

Systemic sclerosis

A total of 4 patients underwent autologous PBSCT to treat systemic sclerosis. Over the short term, 2 patients showed a complete response, 1 showed a partial response, and 1 patient died of transplantation-related complications. Long-term outcomes showed 2 patients in remission and 1 patient lost to follow up.

Still's disease

One patient with Still's disease was treated with PBSCT. After 6 months, JADAS-27 decrease to 4 from 23.5. The patient has remained in complete remission at last follow up 144 months after PBSCT.

DISCUSSION

The long-term treatment effects and outcomes of HSCT have been reported in several studies. In a multi-center study of the long-term prognosis of 55 patients who underwent HSCT between 1997 and 2009, reported by the British Society of Blood and Marrow Transplantation, the 5-year overall survival rate was 56% in patients with connective tissue disease [18]. A retrospective analysis of 900 patients who underwent autologous HSCT, conducted using the EBMT database, showed that the 5-year overall survival rate was 85%, and the treatment-related mortality rate was 6.5% [4]. In addition, a study including 50 SLE patients who were treated with HSCT at a single center reported a 5-year survival rate of 84% and a recurrence rate of approximately 50% [19]. In the present study, of the 11 patients who underwent PBSCT, 4 showed a stable complete response, 4 showed a partial response, and 3 died. One of the patient who died had complete response after 2 months stopped taking all medications and died at 6 months. With respect to long-term outcomes, 5 remained in remission, 1 was in clinical remission but had progression of organ damage, 1 was in low disease activity state with progression of organ damage, and 1 was lost to follow-up. The 10-year overall survival rate was 70%, the recurrence rate was 40%, and the treatment-related mortality rate was 20%. Considering the high ratio of diseases such as SLE or SSc in our patients, the overall prognosis is not substantially different from that reported previously (Table 3).

We were unable to conduct statistical analysis on our data because of the limited sample size; however, the results strongly suggest that the observed treatment effect is related to disease duration. Short-term responses were favorable in patients who had a relatively short disease duration. When results were compared between the 5 patients with a shorter disease duration and the 5 patients with a longer duration, 4 of the 5 patients who showed a complete response in the short term were in the shorter disease duration group. In addition, the effect of PBSCT was insufficient when it was performed in cases with more severe damage. In patients 4 and 5, irreversible organ damage was expected, because the disease duration was relatively long and lupus activity was not controlled despite more than 10 CYC infusions. Both patients showed a relatively insufficient response in the short term, and organ damage progressed irrespective of disease activity. With regard to previous organ damage, emphasis should be placed on immune tolerance to prevent additional organ damage, rather than focusing on recovery of previous organ damage.

In patients who undergo autologous PBSCT, recurrence can occur relatively frequently and should be managed appropriately. In patient 2, the short-term response after the transplant was complete remission, but the disease recurred after she decided to discontinue drug therapy. Subsequently, the patient did not respond to aggressive immunosuppressive treatment and ultimately died. Patient 1, who had been in complete remission after the transplant, relapsed after normal childbirth. With her second delivery, her anti-dsDNA antibody results changed from negative to positive, and low-dose prednisolone was prescribed to reduce the possibility of recurrence. Therefore, during medication tapering after PBSCT, clinical symptoms should be carefully observed, and the rate of tapering and medication dose should be appropriately con-

Table 3. Comparison of long-term prognosis in patients who underwent autologous hematopoietic stem cell transplantation to values reported in previous studies

Variable	Hanyang University Hospital data	EBMT data (1996～2007) [10]	BSBMT data (1997～2009) [18]
Patient (n)	11	900	55
Disease manifestation	SLE (n=6) SSc (n=4) Still's disease (n=1)	MS (n=345) SLE (n=85) SSc (n=175) RA (n=89) JIA (n=65) Other (n=141)	Inflammatory arthritis (n=20, 36%) Connective tissue disease (SLE, SSc, myositis) (n=17, 31%) Bowel disease (n=8, 15%) Other (vasculitis, MS, n=10, 18%)
Age at HSCT (range), yr	30.8 (18～42), female 81.8%	35 (2.7～76), female 64%	38 (4～72), female 64%
Disease duration (range), mo	50.3 (7～108)	62 (0.5～494)	62 (3～299)
Follow-up (range), mo	90.7 (1～158)	34 (0.5～148)	*
Overall survival			
3 yr	70%	Category of autoimmune disease ($p<0.0001$) (80% for SSc, 87% for SLE, 82% for JIA) Center experience ($p=0.0001$) Number of patients≤13 (n=441) 83% (CI, 79～87) Number of patients>13 (n=421) 92% (CI, 90～94)	85% (1-year overall survival)
5 yr	70%	Overall 85% (CI, 79～83) (76% for SSc, 76% for SLE, 82% for JIA)	56%
10 yr	70%	*	65%
Non-relapse mortality	100-day non-relapse mortality 18% (n=2/11) 16.7% for SLE 25.0% for SSc 0% for Still's disease Overall non-relapse mortality 18% (n=2/11)	100-day overall TRD 5% (n=45/900) Before 2001, 12% Category of autoimmune disease ($p<0.0001$) 6% for SSc, 11% for SLE, 11% for JIA Center experience ($p=0.004$) Number of patients≤13 (n=441) 7% (CI, 5～9) Number of patients>13 (n=421) 3% (CI, 1～5) 5-year overall TRD 6.5% (n=59/900) Category of autoimmune disease ($p<0.0001$) 6.8% for SSc, 12.9% for SLE, 11% for JIA (n=7/65)	100-day non-relapse mortality 13% 1 year non-relapse mortality 29%

EBMT: European Group for Blood and Marrow Transplantation, BSBMT: British Society of Blood and Marrow Transplantation, HSCT: hematopoietic stem cell transplantation, SLE: systemic lupus erythematosus, SSc: systemic sclerosis, MS: multiple sclerosis, RA: rheumatoid arthritis, JIA: juvenile idiopathic arthritis, CI: confidence interval, TRD: treatment-related death. *Not available.

trolled depending on the test results and disease activity.

Last, the safety of treatment is critical for PBSCT to be an effective option for incurable autoimmune disease. Conditions that can arise during the procedure, such as infection and pancytopenia, can greatly impact a patient's prognosis. To reduce transplant-related mortality, possible conditions that can arise in association with PBSCT should be sufficiently anticipated and appropriately handled on the basis of the treatment protocol for each disease manifestation. In addition, as seen in Patient 5, complications such as vasculitis can occur from G-CSF used during the surgery, although this is rare [20]. Thus, care should be taken regarding the use of G-CSF, and additional review of these risks and effects would be valuable.

CONCLUSION

Despite the first PBSCT transplant to treat autoimmune disease in 1996, only a limited number of patients are currently treated with PBSCT. A few studies have validated both the short-term and long-term treatment effectiveness of PBSCT, and we reaffirmed these findings in this study. However, high transplant-related mortality is an important problem that must be resolved. More prospective studies are required to validate treatment effectiveness, and retrospective analyses should be performed to provide cautious guidelines for treatment indication and methods to reduce transplant-related mortality. Moreover, potentially safer treatments such as mesenchymal stem cell therapy should be considered as alternative treatment options.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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