Autologous peripheral blood haematopoietic stem cell transplantation for systemic lupus erythematosus: the observation of long-term outcomes in a Chinese centre

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Abstract

Objective

We aimed to evaluate the safety and long-term efficacy of autologous peripheral blood haematopoietic stem cell transplantation (APHSCT).

Methods

We did not want to evaluate the efficacy of antibodies but rather the clinical response by investigating progression-free survival and serologic response by assessing autoantibody titres and complement levels.

Results

Overall, 22 patients with SLE (17 females; median age, 23 years) undergoing APHSCT were included. The 3-year progression-free survival (PFS) was 77.27% at our centre. We found that all the patients survived over three years. The 5-year PFS and overall survival (OS) rate was 67.90% and 95.20%. The titres of antinuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA), anti-Sm antibody, and 24-h urinary protein significantly decreased, while complements 3 (C3) and C4 normalised at 100 days after transplantation ($p<0.05$). Kidney re-biopsy revealed a decrease in immune complex deposits in patients with remission. The incidence of CMV reactivation was 59.09% after transplantation in 3 years. Pregnancy and childbirth were reported in three female patients after transplantation. The risk of post-transplantation complications persisted for many years.

Conclusion

Immunoablation followed by APHSCT has the potential to induce long-term clinical and serologic remissions despite withdrawal of immunosuppressive maintenance therapy. While relapses may occur, in our small cohort of patients we found no predictive markers for relapse development by analysing antibody and complement levels and urinary proteinuria.

Key words

haematopoietic stem cell, transplantation, systemic lupus erythematosus, progression-free survival, overall survival

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with heterogeneous clinical manifestations, involving any organ (1). The pathogenesis of disease includes genetic factors, immunologic derangement, viral infection, drugs, ultraviolet light radiation, mental factor, and others. It is an autoimmune disease mediated by complement and generation of pathogenic antibodies directed against a number of autoantigens such as antinuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibody, anti-Sm antibody, C3, and C4 (2) The prevalence of SLE has been estimated to be 1/1000 in Hong Kong, China (3). A composite study showed an estimated prevalence of 1 in 3500 women in the UK, 1 in 1000 women in China and 1 in 250 African-American women in the USA (4). The therapeutic regimen used internationally was often used as a standard in China, with dose reduction. SLE is responsive to treatment with immunosuppressants and steroids. Combining steroids with cyclophosphamide (CTX) has been the standard of care in the management of lupus nephritis for many years (5). However, SLE presents relapsing or refractory course resulting in increased incapacity and reduced survival (6, 7). Haematopoietic stem cell transplantation (HSCT) was introduced 50 years ago for the treatment of malignant and non-malignant disorders, and for autoimmune disease since 1996 (8, 9). A retrospective analysis of the European Group for Blood and Marrow Transplantation and European League against Rheumatism showed the efficacy of autologous HSCT for the induction of remission of refractory SLE (6, 7, 10, 35, 36). Autologous HSCT results in lower mortality rates than allogeneic transplantation mainly due to the absence of graft *versus* host disease (11, 12). Autologous peripheral blood haematopoietic stem cell transplantation (APHSCT) combined with immunosuppressants, chemotherapeutic drugs, and monoclonal antibody is a newer therapy with potential use in severe SLE. At our centre, APHSCT was used to treat 22 patients with SLE for 12 years. A series of indices such as ANA, anti-dsDNA antibody, anti-Sm antibody, C3, C4, urine protein, complications, cytomegalovirus (CMV) reactivation, pregnancy, progression-free survival (PFS), overall survival (OS), and transplantation-related mortality at 100 days were analysed.

Methods

All the patients were diagnosed using lupus classification criteria of American Rheumatism Association (ARA), 1997 (13). The renal function before transplantation was evaluated using renal biopsy, 24-h urinary creatinine clearance, and 24-h urine protein. Glomerulonephritis was classified according to the World Health Organization (WHO)'s morphological classification of lupus nephritis (modified in 1982) (14). The progression of disease was evaluated using SLEDAI (15). The definition of failed previous therapy was based on resistance to treatment with prednisolone 0.5 mg/kg at least 2 months, or methylprednisolone pulse treatment for 6 months, or CTX 500 mg/m^2 three times in 3 months (16). In addition, we also created secondary criteria including: 1. neurological involvement, 2. lung disease caused by lupus, 3. refractory haemolytic anaemia, 4. SLEDAI >16, 5. anti-cardiolipin syndrome, 6. advanced nephritis caused by lupus. We defined the success of transplantation in terms of haematopoietic function recovery, symptom resolution, antibody elimination and complement recovery. The haematopoietic function recovery was based on white blood cell (WBC) (1.0×10^9/L) and blood platelet (20.0×10^9/L) count. We defined the remission of SLE could not be diagnosed using ARA lupus classification criteria again and had no increase in SLEDAI (Index <5). We defined the relapse of SLE was diagnosed using ARA lupus classification criteria again, and had increase in SLEDAI. The efficacy of treatment was evaluated using ANA, anti-dsDNA antibody, anti-Sm antibody, C3, C4, and urine proteins at 100 days after transplantation (2, 20-22). Due to technical limtations, the number of stem cells increasing after haematopoietic function recovery was

Table I. General characteristics of the patients and the plan for transplantation.

	n	Mean	Median	95% CI
Gender				
Women	17			
Men	5			
Age at onset (years)	9-34	19.36	16.50	16.11-22.61
Age at transplantation (years)	11-37	23.00	23.00	19.26-26.74
Overlap syndrome				
Merger of dermatomyositis	2			
Treatment before transplantation				
Prednisone maintenance (mg/day)	12.5-110	54.80	60.00	44.88-64.71
Hormone pulse therapy (methylprednisolone 500-1000 mg/day)	5			
Intrathecal injection	1			
Cyclophosphamide	12			
Mycophenolate mofetil	2			
Methotrexate	2			
Tripterygium wilfordii	9			
Azathioprine	2			
Thalidomide	1			
Organ damage				
Synovitis	11			
Serositis	2			
Neurological involvement	4			
Haemolytic anaemia	1			
Leucopenia	6			
Thrombocytopenia	5			
Nephritis	22			
Classification of lupus nephritis				
Class II	8			
Class III	3			
Class IV	5			
Class V	5			
24-h urine creatinine clearance (L/24 h)	31.8-226.9	118.46	113.40	94.57-142.39
24-h urine protein (g/24 h)	0.17-12.10	2.04	0.48	0.59-3.49
SLEDAI	9-36	19.32	18.50	15.92-22.72
Duration of interval (onset to homing, months)	4-156	41.77	28.50	23.89-59.66
the time between mobilisation and homing (days)	35-285	70.59	58.50	47.81-93.37
CD34+ stem cell infusion ($\times 10^6$ cells/kg)	2.80-27.00	10.61	7.55	7.27-13.95
CTX (g, total)	4.00-14.20	9.41	8.9	8.28-10.54
ATG (mg, total)	125-700	448.18	475	390.91-502.73

CI: confidence interval; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ATG: antithymocyte globulin; CTX: cyclophosphamide.

not estimated. The study protocol was approved by the Ethics Committees of Nanfang Hospital, Southern Medical University, Guangzhou, and all participants provided written informed consent. Peripheral blood stem cells were mobilised with cyclophosphamide (CTX) 2–4 g/m^2 over 2 to 3 days, followed by granulocyte colony-stimulating factor 5–8 μg/kg/d subcutaneously in all patients (17). Stem cells were selected using BAXTER CS-3000PLUS Blood Cell Separator (Baxter International Inc. Deerfield, Illinois, USA), circulating blood volume of 3–4 L, and flow velocity of 40-60 mL/min from peripheral blood (18). CD34+ stem cell was selected using CliniMACS Cell Sorter. The conditioning regimen of CTX and antithymocyte globulin (ATG) was selected because of its effectiveness in patients with aplastic anaemia, which may often represent autoimmune suppression of haematopoiesis (19). After preprocessing with CTX 4.00–14.20g (100–200 mg/kg, total), rabbit ATG 125–700 mg (2–10 mg/kg, total) (Table I), methylprednisolone (60–500 mg/day) was administered through intravenous drip (VD). Two patients received additional treatment, including total body irradiation in one patient for >2 days in addition, for her lupus encephalopathy after mobilisation. Another underwent intravenous administration of rituximab 375 mg/m^2 (d0, d+7) because of the low response to mobilisation. The number of CD34+ stem cells infusion was 2.80–27.00×10^6 cells/kg (Table I). The duration of interval between mobilisation and CD34+ stem cell homing was 35–285 days (Table I). The patients in the two groups were categorised based on remission or relapse at the endpoint of our observation. Progression-free survival was defined as survival of patients without evidence of relapse or progression. Progression was mainly considered on the basis of the increase in the SLEDAI score. Overall survival was defined as survival of patients with or without relapse or progression. The 100-day transplantation-related mortality was defined as death of patients without relapse or progression of SLE (23). The risk of treatment was judged by the complications during mobilisation and transplantation at 100 days because the complications were closely associated to 100-day transplantation-related mortality. The paired samples test was used to evaluate the changes in index before and after transplantation. Statistical analysis was performed using SPSS 20.0 (IBM, Armonk, New York City, USA) software packages. All data was from the database of Nanfang Hospital, Southern Medical University between January 2002 and November 2014. All patients' personal information was not revealed.

Results

100-day transplantation-related mortality, progression-free survival, overall survival

The patients were followed up for 51 to 147 months (95% CI: 99.94–125.69) up to now. The median follow-up time is 112.82 months. One patient relapse at 12 months after transplantation and accepted steroid treatment for many years. Unfortunately she died due to serious pulmonary infection at 57 months after transplantation. Other patients survived till now (Table II). The duration of PFS was 9 to 147 months (95%CI: 67.28~106.82 months). The 100-day transplantation-related mortality was

Table II. Years of transplantation and overall situation.

Year	Amount	Patient number	PFS (M)	Follow-up time (M)	Reduced ANA/ anti-dsDNA Antibody	Elevalted C3	ANA/ Anti-dsDNA At about 3 years	ANA/ Anti-dsDNA At about 5years	ANA/ Anti-DNA at relapse	SLEDAI Before APHSCT	SLEDAI at 100 Day/3/ 5years	SLEDAI at relapse	Current status
2002	one	Patient 1	147	147	-165.41/-58.18	+0.475	58.17/41.87	Neg/Neg	--	21	1/1/1	--	Remission
		Patient 2	141	141	-140.48/-9.48	+0.934	35.22/15.16	Neg/Neg	--	19	1/1/1	--	remission
		Patient 3	27	141	-100.49/-25.45	+0.08	136.91/144.32	Spos/Spos	504.5/140.5	23	0/10/10	18	relapse
2003	six	Patient 4	138	138	-121.52/-6.40	+0.514	70.5/41.5	Wpos/Wpos	--	9	1/4/4	--	remission
		Patient 5	73	134	-10.21/-63.26	-0.06	Pos/44.8	Pos/Pos	264.46/161.04	12	1/1/1	12	relapse
		Patient 6	132	132	-140.79/-32.95	+0.84	84.7/18.6	Wpos/Neg	--	26	4/4/4	--	remission
		Patient 7	88	131	-144.54/-98.32	+0.58	23/25	Neg/Neg	128.3/43.9	28	1/1/1	18	relapse
		Patient 8	126	126	-159.52/-42.16	+0.37	139/14.3	Wpos/Neg	--	10	4/1/1	--	remission
		Patient 9	33	126	-43.37/-8.32	+0.39	103.6/50.3	Pos/Pos	103.6/50.3	12	1/10/5	13	Relapse
2004	six	Patient 10	124	124	-72.85/-24.19	+0.29	43.36/16.95	Wpos/Neg	--	17	4/1/1	--	remission
		Patient 11	9	124	-71.71/-44.09	+0.71	68.1/12.4	Pos/Neg	70.50/18.65	13	2/2/2	7	relapse
		Patient 12	12	57	-23.03/+25.56	+0.21	141.1/93.4	139.5/90.2	141.38/207.05	14	1/6/24	8	Relapse (death, year: 2009)
		Patient 13	95	122	-144.23/-82.09	+0.68	24.00/20.51	Neg/Neg	265.42/449.71	26	2/1/1	10	relapse
		Patient 14	118	118	-91.5/-26.89	+0.54	23.2/22.7	Neg/Neg	--	35	1/1/1	--	remission
		Patient 15	115	115	-55.31/-11.40	+0.67	69.23/13.88	Neg/Neg	--	26	1/1/1	--	remission
2005	five	Patient 16	102	116	-29.42/-58.72	+0.18	115.7/43	Pos/Wpos	300/82.47	21	1/2/2	24	relapse
		Patient 17	113	113	-48.7/-28.81	+0.18	Pos/Neg	Pos/Neg	--	29	4/4/4	--	remission
		Patient 18	113	113	-14.16/-98.30	+0.44	164.1/16.1	6.83/18.67	--	24	1/2/1	--	remission
2008	two	Patient 19	79	79	-62.3/-37.90	+0.2	31.9/41.2	6.57/15.63	--	10	1/1/1	--	remission
		Patient 20	35	76	-141.80/-127.8	+1.1	175.7/140.3	Pos/Pos	175.7/140.3	26	1/19/7	27	relapse
2010	two	Patient 21	44	58	+25.90/-13.40	+0.33	91.39/14.46	89.92/9.27	118.48/24.45	17	2/2/8	13	relapse
		Patient 22	51	51	-38.30/-10.70	+0.52	24.7/7.5	Neg/Neg	--	9	1/1/1	--	remission

+: the index increased at 100-day after transplantation; -: the index decreased at 100-day after transplantation, --: none; M: months; Neg: negative; Pos: positive; Wpos: weekly positive; Spos: strongly positive.

0% as complications were treated actively. We used a Kaplan-Meier (KM) curve to show PFS and OS (Fig. 1). The 3-year PFS rate was 77.27%; all the patients survived over three years. The 5-year PFS and OS rate was 67.90% and 95.20%, respectively, predicted by the KM curve (Fig. 1).

Antibodies and complement

The levels of ANA, anti-dsDNA antibody, anti-Sm antibody, C3, and C4 pre-APHSCT and post-APHSCT at 100 days were tested. The results were significantly different ($p<0.05$), both in the relapse and the progression-free groups (Fig. 2 A-E). No significant difference between the relapse and the progression-free groups was found at 100 days after transplantation ($p>0.05$). All patients showed improvement at 100 days after transplantation following antibody removal and complement recovery. The increased level of ANA and anti-dsANA antibody could be detected in relapse (Table II). However, some patients accepted re-examination at a local hospital with poor testing equipment due to economic reasons or the long distance involved. Therefore, ANA and anti-dsANA antibody could not be confirmed as the predictive markers for relapse development due to lack of more valid data.

Renal function and classification of changes in nephritis

Renal function was evaluated using pre-transplantation renal biopsy and 24-h urine protein levels. The changes in 24-h urine protein level showed a significant difference at 100 days after transplantation, both in the relapse and the PFS groups (Fig. 2F; $p<0.05$). No significant difference was found between the relapse and progression-free survival groups (Fig. 2F; $p>0.05$). All the patients had nephritis proved by the first renal biopsy before transplantation and the changes in kidney could be a good sign for predicting remission or relapse, evaluating long-term efficacy. We advised all the patients to accept a second renal biopsy one year after transplantation, but the majority of patients thought there was no need to do this. They insisted that serologic examination and 24-h urinary protein were enough. Finally, so far, just six patients have undergone a re-biopsy. All patients and their family members had signed an informed consent. Based on the classification of nephritis (modified in 1982, WHO) the results of the second renal biopsy were not reversed in six patients in 12 to 95 months post-transplantation due to damaged renal structure, and the kidney function was simply maintained. However, the deposits of immune complex in kidney and 24-h urinary protein were obviously decreased in five patients (Table III). The classification of one of the patients changed from II to IV because of early relapse.

Virus reactivation

In the present study, 22 patients showed viral reactivation after transplantation. The viruses detected included CMV (13 patients), Epstein-Barr virus (EBV) (1 patient), herpes simplex virus (HSV) (none), and human parvovirus (none) based on detection of viral

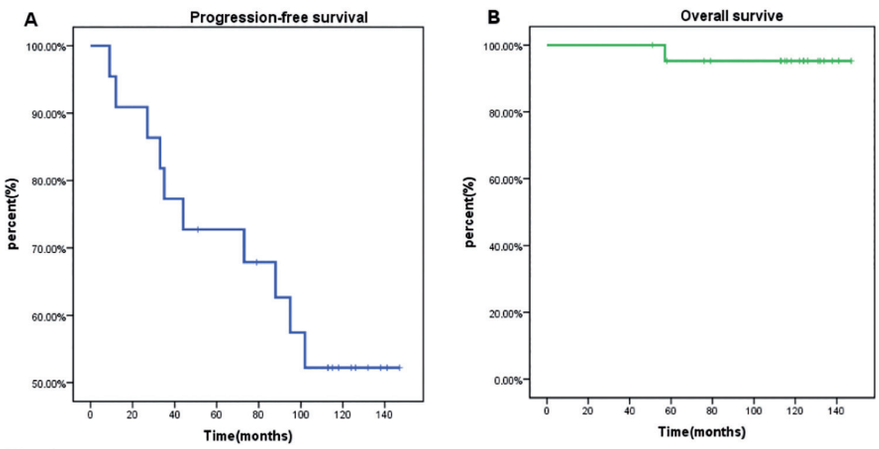

Fig. 1. Progression-free survival and overall survival. **A:** progression-free survival. **B:** overall survival.

nucleic acid. Thirteen patients experienced CMV reactivation in 3 years, and the incidence of CMV reactivation was 59.09%, despite antiviral therapy. However, EBV was detected in a single patient alone and mortality due to virus was very low, prompting preemptive treatment, the use of antiviral drugs such as valacyclovir, or ganciclovir, which was effective (24). The dosage of valacyclovir and ganciclovir were both 300 mg bid (7–14 days) with oral or intravenous injection. Virus testing was necessary for all patients 3 years post-transplantation (24, 25).

Pregnancy

CTX is generally avoided during pregnancy because of its teratogenic effects (23, 26, 27). Pregnancies in patients with SLE pose a high risk to both mother and foetus because of increased rates of complications. The use of high-dose CTX during APHSCT affected patients' fertility. In the follow-up to the present study, a few patients experienced secondary menopause following the use of high-dose immunosuppressants after transplantation. We called all the patients to know about their marriage and children. Some patients were not married. Some patients worried about the progression of disease if they had pregnancy. Perhaps two patients developed premature ovarian failure. Two patients had an abortion because of diseases. Fortunately, only three female patients were pregnant and underwent cesarean section, although two of them relapsed before pregnancy (Table IV). Two patients experienced thrombocytopenia, with positive reaction to anti-SSA or anti-Ro52 antibodies, and were treated with prednisone or hydroxychloroquine. The infants' health was assessed by Apgar scores, and the growth and development based on weight, height, and intelligence. Apgar scores at 5 min after birth in all the infants were above 8. The weight, height, and intelligence of the infants were similar to their peers, with no any symptoms of neonatal lupus ery-

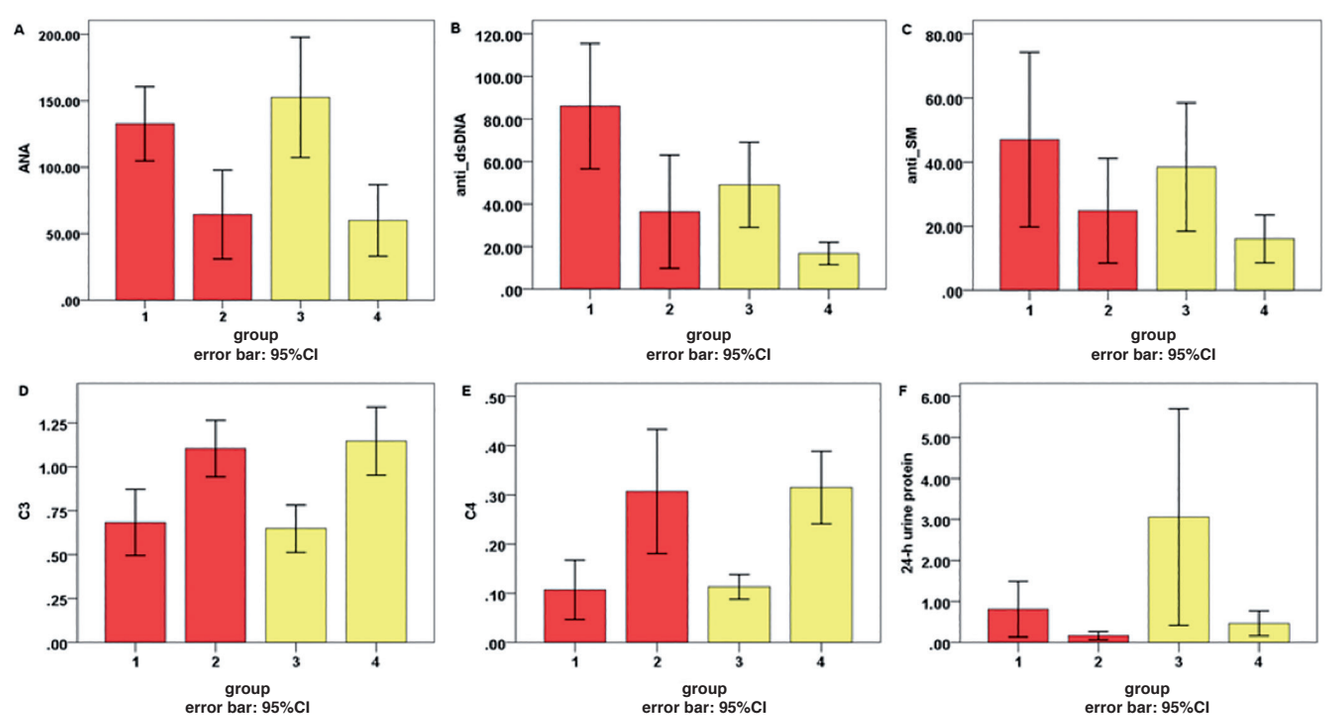

Fig. 2. Changes in antibodies, complement levels and 24-h urine protein at 100 days after transplantation.
Group 1: relapse group (before transplantation); Group 2: relapse group (after transplantation); Group 3: remission group (before transplantation); Group 4: remission group (after transplantation).
(A-F) Changes in ANA, anti-dsDNA antibody, anti-Sm antibody, C3, and C4, and 24-h urine protein show significant differences between pre- and post-transplantation levels ($p<0.05$). There is no significant difference between relapse and progression-free survival groups after transplantation ($p>0.05$).

Table III. The condition of patients who underwent renal biopsy twice.

	Patient 4	Patient 2	Patient 13	Patient 1	Patient 5	Patient 20
Classification of nephritis before transplantation	V-b	IV-d	IV-a	III-b	II-b	II
Depositional immune complex in kidney	IgG(3+) IgM(2+) IgA(3+) C3(3+) C1q(3+)	IgG(3+) IgM(2+) IgA(2+) C3(2+) C1q(2+)	IgG(3+) IgM(2+) IgA(3+) C3(3+) C1q(3+)	IgG(2+) IgM(1+) IgA(-) C3(3+) C1q(3+)	IgG(±) IgM(-) IgA(+) C3(±) C1q(-)	IgA(+) IgG(+) IgM(+) C3(+) C4(+) C1q(+)
24-h urine protein before the first renal biopsy	3.28	7.42	2.3	2.72	0.52	0.65
Classification of nephritis after transplantation	V-c	IV-d	IV-a	Mild mesangial proliferative glomerulonephritis with fiber crescents formation (lighter than III-b)	II-a	IV-a
Depositional Immune complex on kidney	IgG(-) IgM(1+) IgA(±) C3(±) C1q(1+)	IgG(1+) IgM(2+) IgA(2+) C3(±) C1q(1+)	IgG(+) IgA(+) IgM(+) C3(+) C1q(+)	IgG(-) IgM(+) IgA(-) C3(-) C1q(-)	IgG(-) IgM(-) IgA(-) C3(-) C1q(-)	IgA(>1+) IgG(>1+) IgM(>1+) C3(>1+) C4(>1+) C1q(>1+)
24-h urine protein before re-biopsy	1.63	0.21	0.08	0.48	0.31	6.58
Time between homing and re-biopsy(months)	12	17	95	16	26	36
Status pre-APHSCT	relapse	relapse	relapse	relapse	relapse	relapse
Status when he/she accepted re-biopsy	remission	remission	relapse	remission	remission	relapse
Status post-APHSCT till now	remission	remission	relapse	remission	relapse	relapse

Table IV. The condition of three female patients with pregnancy.

	Patient 5	Patient 13	Patient 19
Age at transplantation (years)	20	12	27
Total CTX amount(g)	28.6	12	18
Age of pregnancy(years)	29	21	30
Condition before pregnancy	Relapse	Relapse	Remission
The time between conditioning and pregnancy(months)	31	18	34
24-h urine protein(g) during pregnancy	<0.2	<0.04	<0.17
Drug therapy during pregnancy	Prednisone 15mg/d, hydroxychloroquine 0.2g bid	Prednisone 12.5mg/d	intravenous immunoglobulin 22g/d for 1 day, 25g/d for 3d (6 days before delivery)
Complication during pregnancy	Thrombocytopenia	None	Thrombocytopenia
Delivery type	Caesarean	Caesarean	Caesarean
Condition after pregnancy	relapse	relapse	remission
Apgar score of baby at 5 minutes	9	8	8
The condition of children till now	healthy	healthy	healthy

thematosus. The patients' condition improved after fertility and treatment with prednisone, indicated by the decrease in anti-dsDNA antibody and the recovery of platelet levels, C3, and C4. Transplantation is not absolutely effective in ensuring future pregnancies.

Complications

Complications often occurred during mobilisation and transplantation, resulting in transplantation-related mortality at 100 days (Table V). Infections caused by virus, bacteria, PCP, and tuberculosis mostly occurred because of the administration of very high-dose immunosuppressant. Secondary autoimmunity, lymphoma, malignancy and others often occurred later (Table V). A few patients experienced these events after several years. The reason may be due to impaired function of regulatory T cells resulting in uncontrolled autoimmune response (28). One of the patients showed phthisis and Evans syndrome for 1 year. The patient with class IV lupus nephritis developed chronic renal failure 7 years after transplantation, but the ANA and anti-dsDNA antibodies were negative. The reasons for epilepsy in two patients could be attributed to relapse, and the symptoms persisted for several years even after

Table V.

	Mobilise-related complication	100-day transplant-related complication	complication over 100 days after tranplantation
Infections(virus, bacteria, PCP, tuberculosis)	7	18	14
Heart failure or myocarditis	2	1	0
Gastrointestinal symptoms (nausea, vomiting, diarrhoea, liver injury)	15	5	0
Neurological symptoms (headache, epilepsy)	1	2	2
Urological symptoms (kidney injury, haematuresis, chronic renal failure)	6	5	1
Allergic dermatitis	5	6	0
Secondary autoimmunity (Evans, thyroiditis, erosive osteoarthritis)	0	0	3
Thrombocytopenia (except CTX or ATG caused)	0	0	3
Lymphoma	0	1	0
Malignancy	0	0	1

SLE was managed well. It is difficult to distinguish between diseases caused by relapse or transplantation-related complications. However, control of relapse and treatment of complications are important. All the patients showed good response to treatment, although a few still needed drugs or other therapy for a longer period. To prevent mortality due to complications, the patients underwent follow-up observation.

Discussion

We carried out a long-term observation of patients with APHSCT and we always kept close contact with the patients during follow-up. The data shows that APHSCT may be a potential method of inducing sustained remission in SLE patients without sensitivity to conventional treatment. The 5-year PFS and OS (67.90% and 95.20%) are higher than Burt *et al*. (8) reported (50% and 84%). The increased level of ANA and anti-dsDNA antibody could be detected earlier than clinical symptoms in relapse. The relapse was not obviously related to changes in ANA, anti-dsDNA antibody, anti-Sm antibody, 24h urine protein, C3 and C4 at 100 days due to early good response with APHSCT. The re-biopsy showed the immune complex deposits in the kidney were significantly decreased in a very long time after transplantation. The female post-transplantation patients were able to have successful pregnancies and give birth to healthy babies. The re-biopsy and pregnancy should be taken into account due to finding more biomarkers and improved quality of life. Snowden *et al*. (9) showed graft *versus* host disease (GVHD) in allogeneic HSCT, though the APHSCT avoided the GVHD. But the risk of complications should be taken into account in both all the time, which is important to decrease mortality. Nonetheless, APHSCT shows efficacy for SLE due to: 1. the use of high-dose immunosuppressants for complete elimination of aberrant or self-reactive immune system during mobilisation and pretreatment; 2. the redistribution of altered cellular and humoral immune network or thymic re-education, development, and regeneration of a new and hopefully self-tolerant immune system from haematopoietic stem cells (8, 29-33); 3. susceptibility gene of SLE trend to negative expression or weekly expression. However, this study has its limitations. We were not able to confirm whether ANA and anti-dsANA antibody are the predictive markers for relapse development due to lack of more valid data. The number of re-biopsies is not enough to analyse more information about remission, nor did we find the relationship between complications and relapse. Perhaps the unchanged genetic predisposition of patients is probably related to relapse (28). Genetic susceptibility and biomarkers to SLE could be the key factor determining successful transplantation (34, 37). The long-term efficacy of APHSCT should be assessed based on clinical data over the years. Moreover, patients should pay more attention to regular re-examination even if they have had no clinic symptoms.

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