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REVIEW ARTICLE

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Hematopoietic stem cell transplantation for the treatment of autoimmune diseases

Abstract Systemic autoimmune diseases that are resistant to conventional treatment cause considerable morbidity and mortality. Although aggressive new approaches to treating autoimmune diseases have been developed over the past decade, there are still patients with a severe, progressive, and life-threatening course. Based on animal studies and experience in the treatment of hematological disorders with preexisting autoimmune disease, hematopoietic stem cell transplantation has been proposed for the treatment of severe autoimmune diseases. Immunoablation and subsequent autologous peripheral blood stem cell transplantation using $CD34^+$ hematopoietic cells with T cell depletion have been used for selected severe autoimmune diseases at many institutes in Australia, Europe, and the United States. However, it is necessary to assess the efficacy and safety of this therapy compared with conventional and other newly emerging therapies.

Key words Autoimmune disease · Bone marrow · Hematopoietic stem cell transplantation · Therapy

Introduction

Autoimmune diseases are characterized by a chronic course with remission and relapse.[1,2] Despite recent therapeutic advances, severe autoimmune diseases with poor prognostic features have sometimes been experienced.[1–5] For severe autoimmune diseases that fail to respond to conventional therapy, several new approaches are being developed.[5–7] These include: (1) the use of genetically engineered molecules affecting B and T lymphocytes and their interactions; (2) immunosuppressive therapy for regulating T and B cell activity; (3) gene therapy focusing on the regulation of the self-destruction process; (4) hematopoietic stem cell transplantation (HSCT) to eliminate disease-causing B and T lymphocytes from the body and reconstitute the bone marrow with cells that are free of disease and which function normally.[5–19] In this paper, we review the animal study, early experiences, and current clinical trials of HSCT in autoimmune diseases.

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Experience of HSCT in animal models of autoimmune diseases

There are numerous animal models of autoimmune disease. They can be categorized into two groups. In one animal model, autoimmune diseases develop spontaneously, and in the other the disease is caused by antigen injection.[9,11,15] The therapeutic potential of HSCT in animal models of autoimmune disease is shown in Table 1.

Animal models of autoimmune diseases with spontaneous occurrence

The animal models of autoimmune diseases with spontaneous occurrence include Murphy Roth Lab lymphoproliferative (MRL/lpr) mice and New Zealand black/New Zealand white (NZB/NZW F1) mice.[9,11,15] MRL/lpr mice are characterized by lymphadenopathy, arthritis, glomerulonephritis, vasculitis, and positive anti-DNA antibody such as systemic lupus erythematosus (SLE). NZB/NZW F1 mice are characterized by hemolytic anemia, glomerulonephritis, and positive anti-DNA antibody such as SLE.[9,11,15] It was first shown by Denman et al.[20] that the transfer of spleen cells or bone marrow cells from NZB mice could develop autoimmune disease. In 1985, Ikehara et al.[21] first reported the successful treatment of lupus-prone mice by allogeneic bone marrow transplantation (BMT) from a nonsusceptible strain. After allogeneic BMT, improve-

Table 1. Treatment of animal models of autoimmune disease by bone marrow transplantation

Animal	Equivalent human autoimmune disease	Type of transplant	Conditioning	Outcome	References
Spontaneous occurrence					
NZB/NZW F1, BXSB	SLE	Allogeneic	TBI	Remission	Ikehara et al. (1985)[21]
MRL/lpr	SLE	Allogeneic	TBI	Remission and relapse	Ikehara et al. (1989)[22]
Induction by immunization					
Adjuvant-induced arthritis (BUF)	RA	Syngeneic, allogeneic, or autologous	TBI	Remission	Van Bekkum et al. (1989)[24] Knaan-Shanzer et al. (1991)[25]
Experimental autoimmune encephalitis (BUF)	MS	Allogeneic	TBI or CY + BU	Remission Prevention of relapse (90%)	Van Gelder et al. (1995, 1996)[26,27]
		Syngeneic or autologous	TBI	Remission Spontaneous relapse (30%)	Van Gelder et al. (1993, 1996)[28,29]
Collagen-induced arthritis (DBA/1)	RA	Syngeneic or allogenic	TBI	No remission Prevention of progression	Kamiya et al. (1993)[30]

NZB, New Zealand black; NZW, New Zealand white; BXSB, black-6 mouse crossed to an SB mouse; MRL/lpr, Murphy Roth lab/lymphoproliferative; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MS, multiple sclerosis; TBI, total body irradiation; CY, cyclophosphamide; BU, busulfan

ments in histological findings for glomerular damage and immunologically abnormal findings such as high titers of anti-DNA antibody, positive anti-Sm antibody, and circulating immune complexes have been observed in NZB/NZW F1 mice and Black-6 mice crossed to SB mice (BXSB). Furthermore, abnormal immunological functions of T cells, macrophages, and B cells were normalized.[15,22] In contrast, the occurrence of relapses has been demonstrated in MRL/lpr mice 5 months after BMT.[15,22] The reason for this is thought to be that abnormal radioresistant hemopoietic cells derived from the recipient react with abnormal B cells and T cells and lead to the relapse.[15] It has also been shown that thymic abnormalities might contribute to the occurrence of autoimmune diseases in these animal models.[15,23] The results from animal autoimmune disorders suggest that spontaneous autoimmune diseases are "stem cell disorders" and cannot be cured by autologous BMT and peripheral blood stem cell transplantation (PBSCT).[9,15]

Animal models of autoimmune diseases occurring after immunization

In some animal models, autoimmune diseases occurred after immunization with certain antigens, including adjuvant arthritis, experimental autoimmune encephalitis (EAE), and collagen-induced arthritis (CIA).[9,11,15] Adjuvant arthritis is induced by a single intracutanous injection of complete Freund adjuvant, and polyarthritis may appear within 3–4 weeks in more than 80% of in-bred Buffalo rats. EAE is induced by the injection of myelin, and is characterized by manifestations such as an inflammatory demyelinating relapsing/remitting disease which is similar to multiple sclerosis (MS). The appearance of characteristic clinical symptoms is seen in about 80% of rats. Recovery from the first attack is seen in most animals, but one or more relapses occur in 70% of animals. The treatment of adjuvant arthritis by allogeneic BMT was first reported by van Bekkum et al. in 1989.[24] In 1991, Knaan-Shanzer et al.[25] showed the efficacy of autologous BMT in the treatment of adjuvant arthritis in rats. Similar results showed that allogeneic, syngeneic, and autologous BMT could be used in the treatment of EAE in rats.[26–29] In the case of CIA in mice, it has been shown that BMT, especially allogeneic BMT, suppresses the immune reaction to type-II collagen (CII), decreases anti-CII antibody titer, and effectively suppresses CIA.[30] These results suggest that autologous BMT, PBSCT, or allogeneic BMT may be useful to cure autoimmune diseases caused by environmental stimuli such as immunization.

These animal studies clearly indicate the potential benefit of HSCT in human autoimmune diseases.

Experience of HSCT in patients with a hematological disorder with coincidental systemic rheumatic diseases

The clinical experience of HSCT for hematological disorder in patients with preexisting systemic rheumatic disease has been reported.[31–45] Allogeneic BMT has been performed in 15 patients with several systemic rheumatic diseases from human leukocyte antigen (HLA)-matched donors, as shown in Table 2.[31–39] Most patients received BMT for drug-induced aplastic anemia (AA). Twelve patients are in remission after a follow-up of 2–20 months. Either autologous BMT or PBSCT has been performed in seven patients with several systemic rheumatic diseases, as shown in Table 3.[40–45] In most cases the underlying hematological disorder was lymphoma, and that was the reason why autologous transplants were selected. Graft manipulation was not performed in all patients. Two of the seven patients are in

Table 2. Experience of allogeneic bone marrow transplantation in systemic rheumatic disease complicated with hematological disorder

No.	Systemic rheumatic disease	Complicated hematological disorder	Outcome of rheumatic disease	Prognosis	Follow-up period	Reference
1	RA	AA	Remission	Alive	2 years	Baldwin et al. (1977)[31]
2	RA	AA	Remission	Dead		Baldwin et al. (1977)[31]
3	RA	AA	Remission	Dead		Baldwin et al. (1977)[31]
4	RA	AA	Remission	Dead		Baldwin et al. (1977)[31]
5	RA	AA	Remission, relapse at 2 years	Alive	3, 14 years	Jacobs et al. (1986)[32], Snowden et al. (1998)[33]
6	RA	AA	Remission	Alive	8, 13 years	Lowenthal et al. (1993)[34], Snowden et al. (1998)[33]
7	RA	AA	Remission	Alive	6, 11 years	Lowenthal et al. (1993)[34], Snowden et al. (1998)[33]
8	RA	AA	Remission, relapse at 28 months	Alive	13 years	McKendry et al. (1996)[35]
9	RA	AA	Remission	Alive	20 years	Nelson et al. (1997)[36]
10	DLE	AA	Remission	Alive	13 years	Nelson et al. (1997)[36]
11	SLE-like disease	AA	Remission	Alive	9 years	Nelson et al. (1997)[36]
12	SLE	AA	Remission	Alive	15 years	Gur-Lavi (1999)[37]
13	Vasculitis	AML	Remission	Alive	7 years	Nelson et al. (1997)[36]
14	SS	CML	Partial improvement of serological abnormalities	Dead	11 months	Minowa et al. (1998)[38]
15	ShS	AA	Remission	Alive	34 months	Cetkovský et al. (1998)[39]

RA, rheumatoid arthritis; DLE, discoid lupus erythematosus; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; ShS, Shulman's syndrome; AA, aplastic anemia; AML, acute myeloblastic leukemia; CML, chronic myelogenous leukemia

remission after 22–30 months follow-up. These preliminary data encouraged us to believe that HSCT might cure some patients with systemic rheumatic disease, although the number of cases is limited and these case reports suffer from bias.

Allogeneic BMT

Rheumatoid arthritis (RA)

The preexisting systemic rheumatic disease for which the highest number of allogeneic BMTs have been performed is RA.[31–36] All nine patients developed AA. In 1977, Baldwin et al.[31] first reported four patients with RA who received allogeneic BMT for AA. Although all four patients showed remission of RA after BMT, three patients died of complications associated with BMT within 3 months, and only 2 years of follow-up was possible in the remaining case. Jacobs et al.[32] reported a patient with RA with 2 years remission after allogeneic BMT. However, patient case had a relapse during long-term follow-up.[33] In 1993, two cases of long-term remission of RA (13 and 11 years, respectively) after allogeneic BMT were reported by Lowenthal et al.[34] McKendry et al.[35] reported a 52-year-old woman with an 8-year history of RA who received an allogeneic BMT for gold-induced AA and had been followed up for 13 years. She had experienced complete remission for 2 years after BMT. However, a recurrence and progression of RA from 3 to 13 years of follow-up was observed in spite of complete donor hemopoietic reconstitution. This case report illustrates the possibility that the initial events in the development of RA are T-cell-dependent, and that the disease may be most susceptible to the appropriate immune therapy early in its course, but synovial cell hyperplasia resulting in bone and cartilage destruction may be driven by nonimmunologically mediated pathways.[35] To determine the frequency of long-term remission, Nelson et al.[36] reviewed experiences with allogeneic BMT at the Fred Hutchinson Cancer Research Center and an affiliated hospital for patients with a preexisting autoimmune disease who survived more than 3 years after BMT. Out of 901 patients, 13 patients with autoimmune disease were identified. Among them, a 30-year-old female patient who had RA and received a marrow graft from her HLA-matched sister was described. Although she had developed limited chronic graft versus host disease (GVHD) 2 years after BMT and Sjögren's syndrome (SS) 17 years after BMT, she had been free of RA more than 20 years after BMT.

Discoid lupus erythematosus (DLE) and SLE

For DLE and SLE, three patients have been reported who had complications from drug-induced AA and who were successfully treated by allogeneic BMT.[36,37] Nelson et al.[36] reported two patients with DLE or SLE in a long-term follow-up study after BMT. Both patients went into good clinical remission and had taken no immunosuppressive agents for 8 years or no medication for 5 years without recurring disease. Gur-Lavi[37] described a 15-year-old patient with SLE. There was a total resolution of all lupus clinical symptoms (malar rash, discoid lesions, photosensitivity, oral ulcers, arthritis, and neuropsychiatric symptoms) except for positive antinuclear antibodies (ANA) after allogeneic BMT. She still has complete remission with no treatment.

Table 3. Experience of autologous peripheral blood stem cell transplantation and bone marrow transplantation in systemic rheumatic disease complicated with hematological disorder

No.	Age/sex	Systemic rheumatic disease	Hematological disorder	Type of transplant	Graft manipulation	Outcome of rheumatic disease	Prognosis	Follow-up period	Reference
1	51/F	RA	NHL	APBSCT	(–)	No improvement	Alive	4 months	Euler et al. (1996)[40]
2	54/M	RA	IBL	APBSCT	(–)	Remission, relapse at 20 months	Alive	20 months	Cooley et al. (1997)[41]
3	56/F	RA + SS	NHL	APBSCT	(–)	Remission	Alive	22 months	Jondeau et al. (1997)[42]
4	28/F	SLE	NHL	APBSCT	(–)	Remission, relapse at 1 year	Alive	1 year	Euler et al. (1996)[40]
5	56/F	SLE	NHL	ABMT	(–)	Remission, relapse at 3 years	Alive	4 years	Snowden (1997)[43]
6	37/F	SLE	CML	ABMT	(–)	Remission	Alive	30 months	Meloni et al. (1997)[44]
7	33/F	SS	MALTL	APBSCT	(–)	Partial remission	Dead	20 months	Rosler et al. (1998)[45]

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; NHL, non-Hodgkin lymphoma; IBL, immunoblastic lymphoma; MALTL, mucosa-associated lymphoid tissue lymphoma; APBSCT, autologous peripheral blood stem cell transplantation; ABMT, Autologous bone marrow transplantation

Necrotizing vasculitis

Only one case report is available for vasculitis. A 14-year-old female with a 1-year history of necrotizing vasculitis and acute nonlymphoblastic leukemia was described by Nelson et al.[36] After allogeneic BMT, she subsequently developed chronic GVHD and treatment with prednisolone (PSL), cyclosporine, and azathioprine was started. No evidence of the recurrence of vasculitis has been observed, although she has continued immunosuppressive therapy for 7 years since BMT.

Sjögren's syndrome (SS)

Minowa et al.[38] described a 37-year-old woman with primary SS complicated with chronic myelogenous leukemia (CML). The patient received a transplant from a HLA matched brother after chemotherapy with busulfan and cyclophosphamide (CY). She developed chronic GVHD 18 weeks after BMT. Although she was treated with PSL and cyclosporin, she died of an infectious disease 11 months after BMT. In this patient, allogeneic BMT did not improve her serological abnormalities.

Shulman's syndrome (ShS, eosinophilic fasciitis)

Cetkovský et al.[39] reported the case of a 43-year-old man with severe Shulman's syndrome (ShS) associated with AA who received allogeneic BMT. His ShS symptoms completely disappeared. Although a relapse in ShS (probably induced by GVHD) occurred during chronic GVHD, he was successfully treated with corticosteroids.

Autologous BMT and PBSCT

Rheumatoid arthritis (RA)

There are three reported cases of RA in which the patients had undergone unmanipulated autologous PBSCT.[40–42] Euler et al.[40] reported a 51-year-old woman with RA complicated with non-Hodgkin lymphoma (NHL) who received PBSCT. Her arthritis improved slightly for 5 weeks after HSCT and then the RA activity flared up again. A similar case was described by Cooley et al.[41] A 54-year-old man with RA developed immunoblastic T cell lymphoma and received PBSCT, and then he experienced a return of RA 20 months after HSCT. In contrast, in a case of RA with SS associated with NHL, the patient achieved complete remission of lymphoma and RA after PBSCT, as reported by Jondeau et al.[42]

Systemic lupus erythematosus (SLE)

There are three case reports describing autologous unmanipulated stem cell transplantation (ASCT) in patients with SLE and a hematological disorder.[40,43,44] Euler et al.[40] described a 28-year-old female patient with NHL. High-dose chemotherapy according to the BEAM protocol

(carmustine + etoposide + cytarabine + melphalan) followed by PBSCT was applied and achieved complete remission of the NHL and SLE. One year after PBSCT, active lupus symptoms such as oral ulcers and pancytopenia with severe thrombocytopenia reappeared. The importance of lymphocyte depletion in ASCT to cure autoimmune diseases was emphasized, along with four other cases showing early recurrence or persistence of disease after unmanipulated ASCT.[40] Snowden et al.[43] described a 56-year-old female patient with steroid-dependent SLE and NHL in whom clinical and serological remission was achieved after autologous BMT. It was interesting that she developed immune thrombocytopenia, that had not previously been seen, 3 years after BMT. Meloni et al.[44] described a 33-year-old woman with long-lasting SLE and subsequent CML who underwent autologous BMT after the remission of blastic crisis. Clinical and serological remission had been achieved 30 months later.

Sjögren's syndrome (SS)

Rösler et al.[45] first described a case of a 33-year-old woman with primary SS who developed a lymphoma which, after relapse, was treated with PBSCT. Remission of SS was short-lived, and was followed by a relapse and a steroid-dependent active disease. She acquired a therapy-resistant *Pneumocystis carinii* pneumonia and died 20 months after ASCT.

HSCT for treatment of systemic rheumatic disease

Based on studies in animal models and experience of HSCT in hematological disorders with preexisting systemic rheumatic diseases, the concept of treating severe systemic rheumatic diseases with ASCT has been developed. There have been several reports of cases in which ASCT was performed for the systemic rheumatic disease itself, as shown in Table 4.[10,40,46–58]

Rheumatoid arthritis (RA)

There are five published cases of RA in which the patient has undergone transplant, four with autologous PBSCT and one with syngeneic PBSCT for the treatment of RA itself.[46–49] In the basic protocol of PBSCT, peripheral blood stem cells (PBSCs) were mobilized with CY. Conditioning was performed by the administration of CY with or without antihymocyte globulin (ATG). The mobilized PBSCs were lymphocyte-depleted via positive selection for $CD34^+$ progenitor cells. Complete remission was achieved in two patients, one with unmanipulated stem cells and one with manipulated stem cells.[46,47] In contrast, Burt et al.[48] reported two patients with RA who did not achieve complete remission after PBSCT. A decreased number of swollen joints and an improvement in the activities of daily life (ADL) were seen in these cases. McColl et al.[49] reported the case of a 39-year-old man with severe, treatment-resistant RA who received high-dose CY and ATG and hematopoietic rescue with PBSCs from an identical twin. The patient achieved clinical remission after transplantation. This is the only case report in which syngeneic HSCT was performed. However, prolonged observation for efficacy and long-term side effects is required because syngeneic lymphocytes from a healthy donor might also modify the perturbed immune regulation which contributes to autoimmunity in the recipient or produces a graft-versus-autoimmunity effect, as pointed out by McColl et al.[49]

Systemic lupus erythematosus (SLE)

There are seven reported cases of SLE which have been treated with ASCT, one with bone marrow and six with PBSCs.[48,50–54] Graft manipulation was performed in all cases. In 1997, Marmont et al.[50] first reported the case of a 46-year-old female patient with severe long-lasting SLE who received an autologous BMT utilizing $CD34^+$ cells following a 3-log T cell depletion for the treatment of the SLE itself. The patient had been suffering from lupus nephritis which did not respond to immunosuppressive therapy. She obtained a good partial remission with an important reduction in steroid requirements. Burt et al.[48] reported the cases of two patients with severe SLE who received PBSCT with a 2-log T cell depletion via positive selection for $CD34^+$ following a CY and ATG conditioning regimen. The first patient was a 24-year-old woman who manifested World Health Organization (WHO) class IV glomerulonephritis with rapidly declining renal function, pancytopenia, and pleural–pericardial effusion. She achieved complete clinical and immunological remission 12 months after PBSCT, and was free of medication, including corticosteroids and immunosuppressive agents. The second patient was a 15-year-old girl who exhibited recurrent alveolar hemorrhage, vasculitis, and WHO class IV glomerulonephritis. Active lupus symptoms were resolved and anti-DNA antibody became negative with a tapering dosage of PSL during a follow-up period of 6 months after PBSCT. Musso et al.[51] reported the case of a 19-year-old woman with SLE, APS, and refractory Evans syndrome who had a transplantation with mobilized $CD34^+$ cells after conditioning with CY, ATG, and PSL. The patient was alive and well, with normal blood cell counts, and persistent low-titer direct antiglobulin and ANA tests. Anti-DNA antibody, lupus anticoagulant tests, and anticardiolipin antibody tests were negative. Fouillard et al.[52] reported the case of a 35-year-old with severe and progressive SLE manifested by WHO class III glomerulonephritis and cerebral vasculitis despite corticosteroids, CY, and plasmapheresis, but which clinically improved with PBSCT after conditioning with the BEAM regimen. Trysberg et al.[53] described an 18-year-old girl with severe progressive central nervous system (CNS) lupus despite treatment with corticosteroids, CY, T cell antibodies, and plasmapheresis. The patient received PBSCT mobilized with CY, and total body irradiation (TBI) following by depletion of T and B cells. The CNS symptoms improved

Table 4. Hematopoietic stem cell transplantation in systemic rheumatic dlsease

No.	Age /sex	Systemic rheumatic disease	Major clinical symptoms	Type of SCT	Graft manipulation	Outcome of rheumatic disease	Prognosis	Follow-up period	Reference
1	46/M	RA	Polyarthralgia	APBSCT	(−)	Remission	Alive	6 months	Joske (1997)[46]
2	46/F	RA	Polyarthralgia	APBSCT	(+)	Partial remission	Alive	1 year	Burt et al. (1998)[48]
3	42/F	RA	Polyarthralgia	APBSCT	(+)	Partial remission	Alive	3 months	Burt et al. (1998)[48]
4	22/F	RA	Polyarthralgia	APBSCT	(+)	Remission	Alive	10 months	Durez et al. (1998)[47]
5	39/M	RA	Polyarthralgia, fever	SPBSCT	(+)	Remission	Alive	2 years	McColl et al. (1999)[49]
6	46/F	SLE	Nephrotic syndrome, chest pain	ABMT	(+)	Partial remission	Alive	7 months	Marmont et al. (1997)[50]
7	24/F	SLE	Nephrotic syndrome (WHO4), pancytopenia, pleuritis/peritonitis	APBSCT	(+)	Remission	Alive	1 year	Burt et al. (1998)[48]
8	15/F	SLE	Recurrent pulmonary hemorrhage, nephritis (WHO4)	APBSCT	(+)	Remission	Alive	6 months	Burt et al. (1998)[48]
9	19/F	SLE	Antiphospholipid antibody syndrome, Evans syndrome	APBSCT	(+)	Remission	Alive	8 months	Musso et al. (1998)[51]
10	52/F	SLE	Pancytopenia	APBSCT	(+)	No improvement	Alive	3 months	Fassas et al. (1998)[54]
11	35/F	SLE	Nephrotic syndrome (WHO3), vasculitis of skin and brain	APBSCT	(+)	Remission	Alive	1 year	Fouillard et al. (1999)[52]
12	18/F	SLE	CNS lupus	APBSCT	(+)	Improvement	Alive	18 months	Trysberg et al. (2000)[53]
13	37/F	SSc	Myositis, pulmonary fibrosis, drug-induced renal injury	APBSCT	(+)	Improvement	Alive	6 months	Tyndall et al. (1997)[55]
14	12/F	SSc	Sclerosis of skin, arthritis, interstitial pneumonia	APBSCT	(−)	Improvement	Alive	2 months	Martini et al. (1999)[56]
15	47/F	CREST	Pulmonary hypertension	APBSCT	(+)	Improvement	Alive	6 months	Tamm et al. (1996)[57]
16	40/F	CREST		ABMT	(−)	Remission, relapse at 2 months	Alive	3 months	Euler et al. (1996)[40]
17	40/F	CREST	Polyarthralgia	ABMT	(−)	Remission, relapse at 2 months	Alive	2 months	Marmont (1997)[10]
18	28/F	PM	Myositis, polyarthritis, interstitial pneumonia	APBSCT	(+)	Remission	Alive	15 months	Baron et al. (2000)[58]

RA, rheumatoid arthrits; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; PM, polymyositis; CNS, central nervous system; APBSCT, autologous peripheral blood stem cell transplantation; SPBSCT, syngeneic peripheral blood stem cell transplantation; ABMT, autologous bone marrow transplantation

steadily during the 18 months of follow-up. However, it was interesting to note that she experienced autoimmune hemolytic anemia after PBSCT but not before. This observation suggests that the expression of different manifestations of SLE might be independently regulated. Although the results of these case reports are encouraging, a case of SLE presenting with pancytopenia in which HSCT therapy had not yielded a meaningful effect 3 months after PBSCT was reported by Fassas et al.[54]

Systemic sclerosis (SSc)/CREST syndrome

There have been two reported cases of systemic sclerosis (SSc) and three of CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia) which have been treated with PBSCT.[10,40,55–57] The first patient was 37-year-old woman with SSc manifested by diffuse skin involvement, myositis, fibrosing alveolitis, and penicillamine-induced glomerulonephritis who received intensive immunoablation followed by ASCT.[55] PBSCs were mobilized with CY and the transplant product was purged with a positive CD34 selection and T cell depletion with CD3 antibody. CY was administered for conditioning. This patient showed subjective improvement with more energy, minimum joint stiffness and pain, and less skin tightness. The second patient was a 12-year-old girl who had SSc characterized by progressive cutaneous, articular, and pulmonary involvement, and stunted growth since 4 years of age, who received PBSCT.[56] The patient experienced a marked improvement in alveolitis, skin score, growth rate, and parental global assessment of general well-being after PBSCT associated with infusion of CAMPATH-1G antibody which targeted a small glycoprotein (CD52) present on mature lymphocytes and some monocytes. The third patient was a 47-year-old woman with a CREST-like syndrome and severe pulmonary hypertension.[57] This was the first case in which HSCT was performed as a treatment for uncontrollable pulmonary hypertension. Priming was induced with CY, and PBSCs were harvested with positive selection for CD34. T and B cell depletion was achieved with anti-CD2/CD3 and anti-CD19/CD20 antibodies. The patient noticed a significant subjective improvement of effort tolerance in the first 2 months, and showed an improvement in mean pulmonary artery pressure and pulmonary vascular resistance in light heart catheter studies 6 months after HSCT. Euler et al.[40] reported the case of a 41-year-old woman with CREST syndrome who received an unmanipulated autologous BMT and had a relapse 3 months later. Marmont[10] described a 40-year-old woman with CREST syndrome who received an unmanipulated autologous bone marrow transplant. She achieved complete clinical remission for only 2 months and then experienced a relapse. As pointed out for patients with RA and SLE, persistent and recurrent symptoms were seen later in two cases of SSc/CREST syndrome in which unmanipulated autologous stem cells were used for transplantation.[40] Although the first three case reports showed that PBSCT was effective in improving symptoms and achieving remission, the follow-up times of those cases was very short (2–6 months).

Polymyositis (PM)

There has been only one case report of polymyositis (PM) treated with HSCT.[58] A 28-year-old woman with PM refractory to standard therapy received an autologous T cell-depleted PBSCT after conditioning with busulphan and CY. Although this case was complicated by severe adult respiratory distress syndrome (ARDS) and adenovirus-associated haemorrhagic cystitis, as well as cytomegalovirus reactivation, she achieved remission in both clinical symptoms and laboratory findings. At 15 months after the transplantation, she was off all therapy, including corticosteroids.

Pathology of autoimmune diseases and the concept of HSCT

Rheumatoid arthritis (RA)

Rheumatoid arthritis is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and sometimes with multiorgan involvement.[1,2,59] The pathology of RA is not well understood. However, it has been shown that certain class II major histocompatibility complex (MHC) alleles are associated with RA, and T cell recognition of antigens is important in disease initiation and persistence.[60] Synovial cell activation and hyperplasia, angiogenesis, lymphocyte infiltration into synovium, and the influx of granulocytes into the synovial fluid are seen at the tissue level.[13] Bone marrow abnormalities have been reported, which include the presence of abnormal myeloid cells, enhanced monocyte DNA synthetic activity, an increased number of mononuclear cells positive for HLA-DR and CD14, high activity of myeloid growth factor, and myeloid precursor numbers.[10] These bone marrow abnormalities may reflect an enhanced hemopoietic activity which is present as part of an immune or chronic inflammatory reaction associated with the development of RA.[10] Although the reason why HSCT is effective in treating RA is not known, it can be speculated that the intensive immunosuppressive conditioning used to prepare for a transplantation eliminates putative autoagressive immune cells, or that the procedure as a whole contributes to resetting the immune system, allowing tolerance toward autoantigens to be restored.[8,61] McColl et al.[49] analyzed the T cell repertoires of each patient before and after syngenic PBSCT as well as those of the healthy donor. The T cell repertoires of the twins before transplantation were similar but differed in *BV* gene usage, as shown in previous studies.[62–64] It was interesting that the recipient's T cell repertoires became almost identical to those of the disease-free donor after HSCT.

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus is a chronic inflammatory autoimmune disease with multiple organ involvement.[1,2] Although the etiology of SLE is unknown, it has been shown that genetic, immunological, hormonal, and environ-

mental factors are involved in its pathogenesis.[1,2] Trysberg et al.[53] speculated that HSCT might induce the remission of certain SLE manifestations by (1) the generation of disease-specific tolerance by the exposure of immature T cells to disease-provoking molecules, ending up in either anergy or deletion, or (2) the re-creation of the immune system so that it becomes unresponsive to the "self" unless re-exposure to the disease-initiating stimulus (or stimuli) occurs. Most recently, Traynor et al.[65] investigated whether T cell abnormalities associated with SLE normalize after dose-intense chemotherapy and ASCT. It was shown that (1) T cell responsiveness measured by resting and stimulated CD69 expression changed from hyper to normal, (2) a normal T-helper-1 profile returned from a skewed T-helper-2 profile with increased interleukin-4 and diminished interferon-γ production, and (3) T cell repertoire diversity became normal after transplantation. These results suggest that ASCT might fundamentally alter the immune system after transplantation.[65]

Systemic sclerosis (SSc)

Systemic sclerosis is characterized by scleroderma, fibrosis of multiple organs, and vasculopathy.[66] The etiology and pathogenesis of SSc are still not well understood. However, genetic and environmental factors leading to immune-cell activation, cytokine release, vascular endothelial damage, and collagen synthesis have been suggested.[66,67] Thus, a strong rationale for the potential benefit of myeloablation and HSCT could be offered.[66,67]

Future direction of autologous stem cell transplantation in the cure of autoimmune diseases

Clinical study

There have been reports of several prospective clinical studies on the use of ASCT for the treatment of various autoimmune diseases based on findings from animal studies and preliminary case reports, as shown in Table 5.[65,68–70] Snowden et al.[68] conducted a single-center open-label phase I/II dose-escalation study of intensified CY and ASCT in RA. In this study, PBSCs were mobilized with granulocyte-colony stimulating factor (G-CSF) alone and used without graft manipulation. High-dose immunosuppressive therapy was performed with escalating dosages of CY (total 100 mg/kg and 200 mg/kg, respectively). This study has provided baseline findings for future clinical trials. It has been shown that (1) the use of CY at a dose of 200 mg/kg induced encouraging clinical responses with acceptable dose-dependent toxicity compared with using 100 mg/kg of CY, (2) clinical improvement was obtained without graft manipulation, although the number of patients was limited, and (3) the use of disease-modifying antirheumatic drugs (DMARDs) in combination with ASCT might extend clinical responses. Traynor et al.[65] investigated the safety and efficacy of immunosuppressive therapy and ASCT in pa-

Table 5. Clinical studies of immunoablation and autologous stem cell transplantation in autoimmune disease

No.	Institute	Disease	Number of patients	Type of transplant	Mobilization	$CD34^+$ selection	Conditioning	Outcome (number of patients)	Prognosis (number of patients)	Follow-up period	Reference
1	St. Vincent's Hospital	RA	8	APBSCT	G-CSF	(+)	CY (100 mg/kg)	Improvement and exacerbation ($n = 4$)	Alive ($n = 4$)	3–4 months	Snowden et al. (1999)[68]
							CY (200 mg/kg)	Remission ($n = 1$) Improvement ($n = 3$)	Alive ($n = 4$)	17–19 months	
2	Northwestern University	RA	4	APBSCT	CY (2.0 g/m^2) + G-CSF	(+)	CY (200 mg/kg) + ATG (90 mg/kg) +− TBI	Improvement ($n = 2$) Improvement and exacerbation ($n = 1$) No improvement ($n = 1$)	Alive ($n = 4$)	9–20 months	Burt et al. (1999)[69]
3	Northwestern University	SLE	7	APBSCT	CY (2.0 g/m^2) + G-CSF	(+)	CY (200 mg/kg) + ATG (90 mg/kg)	Remission ($n = 7$)	Alive ($n = 7$)	12–40 months	Traynor et al. (2000)[65]
4	University Hospital Charite	SLE	3	APBSCT	CY (2.0 g/m^2) + G-CSF	(+)	CY (200 mg/kg) + ATG (90 mg/kg)	Remission ($n = 3$)	Alive ($n = 3$)	16–19 months	Rosen et al. (2000)[70]
		SSc	3	APBSCT	CY (2.0 g/m^2) + G-CSF	(+)	CY (200 mg/kg) + ATG (90 mg/kg)	No improvement ($n = 2$)	Alive ($n = 2$) Dead ($n = 1$)	6–13 months 2 days	
		RP	1	APBSCT	CY (2.0 g/m^2) + G-CSF	(+)	CY (200 mg/kg) + ATG (90 mg/kg)	Remission ($n = 1$)	Alive ($n = 1$)	21 months	

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; RP, relapsing polychondritis; APBSCT, autologous peripheral blood stem cell transplantation; CY, cyclophosphamide; G-CSF, granulocyte-colony stimulating factor; ATG, antithymocyte globulin; TBI, total body irradiation

tients with SLE unresponsive to CY therapy. In this study, PBSCs were mobilized with CY (2.0 g/m^2) and G-CSF, followed by CD34$^+$ selection. Conditioning was performed with CY (200 mg/kg), methylprednisolone (1.0 g), and ATG (90 mg/kg). Seven patients with progressive lung disease and hypoxia (n = 2), alveolar hemorrhage (n = 1), and WHO class III–IV glomerulonephritis and nephrotic syndrome (n = 4) remained free of active lupus symptoms and improved continuously after ASCT. These patients required no immunosuppressive therapy or small doses of PSL only. Furthermore, it was confirmed that T cell abnormalities normalized after HSCT in all the patients analyzed, as described above. Rosen et al.[70] performed a phase I/II study to investigate the feasibility, toxicity, and efficacy of immunoablation and ASCT in patients with autoimmune disease refractory to conventional immunosuppressive therapy. Mobilization was achieved by CY (2.0 g/m^2) and G-CSF. Immunoablation was performed with CY (200 mg/kg) and ATG (90 mg/kg). Of seven patients, complete remission was achieved in relapsing polychondritis (n = 1) and SLE (n = 3). In contrast, two patients with SSc did not show either clinical or serological improvement. One patient with SSc died 2 days after ASCT owing to cardiac failure. The reason for the lack of response in SSc patients was presumed to be that insufficient immunoablation might play a role.

Disease indication and patient selection

For what types of disease and for which patients should this new treatment be applied? To choose a candidate for HSCT, it is necessary to consider (1) disease severity and duration, (2) the criteria for an assessment of treatment failure with conventional therapies, (3) whether the established disease is potentially reversible, (4) short- and long-term side effects, (5) cost, and (6) degree of risk.[13] The use of HSCT in the treatment of human autoimmune disease was discussed at the first International Symposium on Haemopoietic Stem Cell Therapy in Autoimmune Diseases in September 1996.[71] HSCT for autoimmune diseases should be viewed as an experimental procedure to be carried out only after gaining informed consent from the patient, after consultation by two independent experts in the field, and according to a protocol approved by the institutional review board or a research ethics committee. Essentially, only diseases which are severe enough to have an increased risk of motility and which have clinically relevant reversibility should be considered.[71] Rheumatological disorders which are possible candidates for HSCT have been listed in a consensus statement from the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT)[71]:

1. SSc (scleroderma);
2. autoimmune pulmonary hypertension (after an adequate trial of immunosuppression);
3. nercotizing vasculitis (following induction with standard immunosuppression);
4. RA with severe complications, e.g., nercotizing vasculitis, scleritis;
5. RA with poor prognosis, rapidly progressive and destructive, and resistant to adequate treatment:

- Busulphan/CY regimen is preferred in RA (Busulphan is radiomimetic and possibly more effective against memory cells);
- CY alone is not excluded;

6. SLE with major organ threat, failed conventional therapy;
7. APS;
8. severe, uncontrollable cryoglobulinaemia;
9. pediatric rheumatology:

- SSc variants with pulmonary fibrosis;
- severe dermatomyositis (especially with pulmonary fibrosis);
- severe narcotizing vasculitis.

NOT juvenile arthritis at this stage.

At Northwestern University, patients with RA and SLE were considered to be candidates for ASCT under certain circumstances.[48]

In RA, patients less than 60 years of age at the time of pretransplant evaluation who fulfilled all of the following criteria were selected:

1. an established clinical diagnosis of RA by the American College of Rheumatology criteria;
2. a positive rheumatoid factor;
3. failure of at least two disease-modifying agents (methotrexate, gold, penicillamine, and hydroxychloroquine), where failure is defined as at least six swollen joints, and either 30 or more involved joints (swelling, tenderness, deformity, pain on motion, decreased motion), or answering less than 75% of the Activities of Daily Living (ADL) Health Assessments Questionnaire "without any difficulty."

In SLE, patients less than 60 years of age at the time of pretransplant evaluation who fulfilled any one of the following criteria:

1. biopsy-proven WHO class III or IV glomerulonephritis that has failed to respond to NIH short-course CY therapy (500–1000 mg/m^2 monthly for at least 6 months), with treatment failure defined as a failure of serum creatinine to return to normal or preexacerbation level;
2. vasculitis and/or immune complex deposition causing organ signs or symptoms, e.g., cerebritis, transverse myelitis, pulmonary hemorrhage, or cardiac failure, not controlled with corticosteroids and CY;
3. transfusion-dependent cytopenias that are immune-mediated and not controlled with danazol, PSL, and an alkylating agent (CY or vincristine);
4. catastrophic antiphospholipid syndrome (APS), which is defined as an antiphospholipid titer greater than five standard deviations above the mean and two or more antiphospholipid-related manifestations, including either cytopenias or vascular thrombosis that failed to respond to anticoagulant therapy.

Protocol of ASCT

The common mobilization regimen involves CY (2.0–4.0 g/m^2) with G-CSF. The PBSCs are harvested later by apheresis. Some investigators have suggested that it appears to be essential to purge lymphocytes from stem cells in reinfusing for successful ASCT for autoimmune disease.[40] Positive selection for CD34$^+$ cells or several established T cell depletion procedures may be employed.[10,19,71] The most common conditioning regimen includes CY combined with either TBI or other alkylating agents.[10,19,71]

Type of transplant

It has been suggested by Ikehara[15] that most autoimmune diseases are "stem cell disorders," and therefore that autologous BMT or PBSCT cannot be used for treatment of autoimmune diseases. There is no doubt that allogeneic BMT would have the advantage of supplying a "normal stem cell" in place of the potentially abnormal stem cells of the autoimmune host.[13] However, autoimmune diseases are not "malignant diseases" and their prognoses are continuously improving.[10] Although the mortality rate among patients with SLE is at least three times that of the general population, survival rates are about 80% at 10 years after diagnosis and about 65% at 20 years.[1–4] It should be noted that allogeneic BMT (15%–35% mortality) is considerably more hazardous than ASCT (3%–5% mortality). Thus, allogeneic BMT cannot be recommended until its morbidity and mortality are reduced.[19]

Immunoablative high-dose CY therapy without stem cell rescue

There is a question as to whether these observations are merely the results of high-intensity chemoradiotherapy, or whether there is an additional role for immune reactions after HSCT. Brodsky et al.[72] found that the immunoablative doses of CY used for transplantation could induce durable, complete remission (median follow-up >10 years) without stem cell rescue in most patients with severe aplastic anemia. Based on these results, Brodsky et al.[73] investigated the efficacy of high-dose CY in various refractory severe autoimmune diseases. Eight patients were enrolled in this phase II prospective study. Their illnesses included RA with Felty syndrome (n = 2), SLE (n = 2), autoimmune hemolytic anemia (n = 1), Evans syndrome (n = 1), immune thrombocytopenia (n = 1), and chronic inflammatory demyelinating polyneuropathy (n = 1). In their protocol, CY (50 mg/kg body weight/day) was administered intravenously for 4 consecutive days, followed by G-CSF therapy (5 μg/kg/day) starting 6 days after the last dose of CY, and stopping at a neutorophil count of 10^9 cells/l. High-dose CY was well tolerated and was associated with rapid hematological recovery in all eight patients. Seven patients improved markedly (complete remission in five cases, partial remission in two cases). Continuous complete remission for 3–21 months was achieved in four patients. It was concluded that immunoablative high-dose CY therapy without stem cell rescue was able to induce complete remission in patients with refractory, severe autoimmune disease.[73] Further studies are required to assess the necessity for HSCT in nonmyeloablative conditioning protocols.

Conclusion

Finally, it is important that immunoablative high-dose chemotherapy with or without HSCT for autoimmune disease is still regarded as an experimental treatment. The application of this new procedure should be considered with caution for patients with life-threatening disease. Multicenter prospective studies are necessary to define the efficacy and safety of HSCT. Close collaboration among rheumatologists, hematologists, transplanters, immunologists, and other related specialists may offer an opportunity to beat autoimmune disease.

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