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Stem Cell Transplantation for Autoimmune Diseases

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Abstract

Hematopoietic stem cell transplantation is an increasingly used therapy for treatment of autoimmune diseases and severe immune-mediated disorders. We address some general concepts and principles in the development of hematopoietic stem cell transplantation in order to understand the principles and design of safe autologous and allogeneic transplant regimens for these unique diseases.

Keywords

HSCT, autologous, allogeneic, autoimmune disease, immunosuppression

Introduction

The development of hematopoietic stem cell transplantation (HSCT) for autoimmune diseases is complicated and therefore a simplified timeline of first events is shown in Table 1. HSCT in animal models of autoimmune disease predated and continues simultaneously with clinical trials. In oncology, the focus of HSCT has been to achieve a tumoricidal effect to destroy malignant cells. In distinction, the concept of HSCT for autoimmune diseases is centered around tissue regeneration from stem cells, in the case of autoimmune diseases, regeneration of the immune compartment from hematopoietic stem cells.[1,2] Immune-mediated diseases have traditionally been divided or separated within distinct subspecialties; for example, multiple sclerosis, myasthenia gravis, and chronic inflammatory demyelinating polyneuropathy are placed within the department of neurology; systemic lupus erythematosus, rheumatoid arthritis, polymyositis and scleroderma in the division of rheumatology; autoimmune bullous skin diseases such as pemphigus vulgaris in the department of dermatology; asthma and interstitial pulmonary fibrosis within the division of pulmonary diseases; and Crohn disease and autoimmune hepatitis as a part of the divisions of gastroenterology or hepatology. HSCT for autoimmune diseases traverses traditional areas of expertise and represents the first application of stem cell regenerative medicine.

Duality of the Immune System

The immune system is manifest evolutionarily by 2 immune systems, innate (natural killer cells, neutrophils, macrophages, dendritic cells) and adaptive (T and B cells). With the development of vertebrates, the immune system underwent a fundamental evolution by adding adaptive immunity to the already existing invertebrate innate immune system. Germ line receptors of innate immunity such as toll-like receptors are specific for foreign pathogens but are restricted in number. Adaptive immunity greatly amplifies the diversity of antigen-specific receptors that can be utilized by the immune system. T and B cells rearrange germ line variable (V), diversity (D), and joining (J) genes, giving rise to non–germ-line receptors with a highly diversified repertoire compared to innate immunity. While allowing for a diverse repertoire, receptors arising through random rearrangement of genes to generate receptors results in self-reactive repertoires.[3-5]

Table 1. Timeline in the Development of HSCT for Autoimmune Diseases

Year	Author/reference	Comment
1977	Baldwin JL. *Arthritis Rheum.* 1977;20:1043-1048.	First case report of remission of autoimmune disease in patients undergoing HSCT for another reason
1979	Morton JI, Siegel BV. *Transplantation.* 1979;27:133-134.	First report of reversal of autoimmune syndrome in animals (NZB mice) by allogeneic bone marrow transplantation
1983	Pestronk A. *Ann Neurol.* 1983;14:235-241.	First report of animals cured of myasthenia gravis in EAMG model by syngeneic bone marrow transplant
1985	Ikehara S, Good RA. *Proc Natl Acad Sci U S A.* 1985;82:2483-2487.	First report that allogeneic bone marrow transplant cures SLE-like disease in murine MRL/lpr model
1985	Ikehara S, Good RA. *Proc Natl Acad Sci U S A.* 1985;82:7743-7747.	First report that allogeneic bone marrow transplant prevents diabetes in NOD mouse model
1989	van Bekkum DW. *Proc Natl Acad Sci U S A.* 1989;86:10090-10094.	First report that syngeneic bone marrow transplantation cures arthritis in animal model of adjuvant-induced arthritis
1992	Karussis DM, Slavin S. *J Neuroimmunol.* 1992;39:201-210.	First report that syngeneic bone marrow transplantation cures MS-like disease in experimental autoimmune encephalomyelitis animal model
1993	Marmont AM. *Lupus.* 1993;2:151-156.	First editorial suggesting that HSCT should be used as treatment for SLE
1995	Burt RK. *Bone Marrow Transplant.* 1995;16:1-6.	First editorial suggesting that HSCT should be used as treatment for MS
1995	Committee Chair: Alan Tyndall.	EBMT and EULAR establish a working committee on stem cell transplant for autoimmune diseases for Europe and Asia
1995	Committee Chair: Richard Burt.	IBMTR and ABMTR establish a working committee on stem cell transplant for autoimmune diseases for the Americas
1997	Fassas A. *Bone Marrow Transplant.* 1997;20:631-638.	First report of HSCT for MS
1997	Marmont AM. *Lupus.* 1997;6:545-548.	First report of autologous HSCT for SLE
1997	Burt RK. *N Engl J Med.* 1997;337:1777-1778.	First report of autologous HSCT for SLE in America
1997	Joske DJ. *Lancet.* 1997;350:337.	First report of autologous HSCT for RA
1997	Tyndall A. *Lancet.* 1997;349:254.	First report of autologous HSCT for scleroderma
1998	Burt RK. *Bone Marrow Transplant.* 1998;21:537-541.	First report of autologous HSCT for multiple sclerosis in America
1999	Wulffraat N. *Lancet.* 1999;353:550-553.	First report of autologous HSCT for juvenile chronic arthritis
1999	Burt RK. *Arthritis Rheum.* 1999;42:2281-2285.	First report of autologous HSCT for RA in America
1999	Contract principal investigators: Burt RK, Burns WH, Sullivan K.	NIH awards 3 contracts to develop phase III trials of HSCT for autoimmune diseases
2000	Slavin S. *Exp Hematol.* 2000;28:853-857.	First clinical evidence of allogeneic GVA effect
2001	Principal investigator: Snowden J.	EBMT/EULAR opens phase III trial of autologous HSCT for RA
2001	Principal investigator: van Laar J.	EBMT/EULAR opens phase III trial of autologous HSCT for scleroderma
2002	Burt RK. *Blood.* 2003;101:2064-2066.	First report of autologous HSCT for Crohn disease
2004	Burt RK. *Arthritis Rheum.* 2004. In press.	First report of allogeneic HSCT for the indication of rheumatoid arthritis

HSCT=hematopoietic stem cell transplantation; NZB=New Zealand black; EAMG=experimental autoimmune myasthenia gravis; SLE=systemic lupus erythematosus; MRL/lpr=Murphy Roth laboratory lymphoproliferative; NOD=nonobese diabetic; MS=multiple sclerosis; EBMT=European Bone Marrow Transplant Registry; EULAR=European League Against Rheumatism; IBMTR=International Bone Marrow Transplantation Registry; ABMTR=Autologous Blood and Marrow Transplant Registry; RA=rheumatoid arthritis; NIH=National Institutes of Health; GVA=graft versus autoimmunity.

During thymic maturation, T cells with receptors that bind to self-epitopes with either high or no affinity undergo deletion (apoptosis) while T cells with receptor repertoires that recognize self with moderate avidity are positively selected.[4,6-8] Therefore, one duality of the immune system is that autoreactive T cells are physiologic while autoimmune disease is pathologic. Autoimmunity is normal but autoimmune disease is abnormal.[8] This is distinct from oncology where all malignant cells are considered pathologic. Depending upon the signals, T cell tolerance may be maintained or broken outside of the thymus through interaction with antigen-presenting (macrophages or dendritic) cells of the innate immune system. For adaptive immunity it is, therefore, as much the context in which the antigen is presented as the cell itself that determines tolerance or immunity.

In cancer, every tumor cell is pathologic, and treatment is designed to destroy every tumor cell. In contrast, autoimmune cells are physiologic. A second duality of autoimmune disease is that treatment must preserve or regenerate that which it is designed to destroy. HSCT for autoimmune disease is the art of resetting and regenerating this immune system.[1,2] Unlike cancer, autoimmune diseases may go into spontaneous remissions. HSCT of autoimmune disease requires, like all forms of immune suppression, the art of balance. Conditioning regimens must be designed to justify the risk-benefit ratio for each disease and patient cohort.

Rationale for Autologous Conditioning Regimen

Animal Models

Numerous animal autoimmune diseases may be induced by environmental influences. For example, nonspecific stimulation with complete Freunds adjuvant (CFA; emulsified heat-killed mycobacterium) induces adjuvant arthritis (AA), a model of rheumatoid arthritis, while either proteolipid protein (PLP) or myelin basic protein (MBP) combined with CFA induces experimental autoimmune encephalomyelitis, a model of multiple sclerosis.[9-13] In these environmental or immunization induced diseases, autologous HSCT induces disease remission. The mechanism of disease remission is presumed secondary to immune regeneration, that is, thymic regeneration of naive (virgin) T cells from stem cells. Similar results of HSCT remission of induced autoimmune diseases were observed in experiments performed by laboratories in the Netherlands,[9,11] Jerusalem,[14] and Chicago.[10,13]

Spontaneous-onset animal autoimmune diseases like type 1 diabetes in nonobese diabetic (NOD) mice or a lupus-like disease in either MRL/lpr or NZW/NZB mice require an allogeneic hematopoietic stem cell source from a non–disease-prone strain to be cured. These observations were confirmed in both Japan and America.[15-18] In these highly inbred mice, the disease is a stem cell defect. MRL/lpr lupus-like disease arises from a defect in *fas*, an apoptosis-inducing gene, while in NZW/NZB mice the disease is polygenetic.[15,16,19]

Autologous HSCT

For autologous HSCT, the goal of the conditioning regimen is immune suppression. How intense the immune-suppressive regimen should be is unclear and the intensity of the regimen required for durable disease remission may vary by disease. In the only paper comparing outcome of myeloablative (total body irradiation [TBI] or busulfan) regimens to less intense regimens, the mortality of TBI or busulfan-based regimens was significantly greater (4 times higher) than less intense regimens without improvement in disease-free survival. This study of 263 patients undergoing HSCT for autoimmune disease did not separate co-founding variables such as patient age, type of autoimmune disease, prior therapies, or disease severity.[20] While further registry studies analyzing outcome between myeloablative and nonmyeloablative regimens are needed, currently there is no data to support the more intense myeloablative regimens containing either TBI or busulfan compared to less intense nonmyeloablative regimens containing agents such as cyclophosphamide (Cytoxan; Bristol-Myers Squibb), fludarabine (Fludara; Berlex), or antibodies such as antithymocyte globulin (ATG), rituximab (Rituxan; Genetech), or alemtuzumab (Campath; Ilex).

After autologous HSCT, the immune system is regenerated from the same hematopoietic stem cell compartment as existed prior to HSCT. The concept of autologous HSCT presumes that the autoimmune disease is environmentally induced and not a genetic stem cell defect. While the goal of autologous HSCT is intense immune suppression, myeloablation is an unwanted side effect. Following a nonmyeloablative regimen, hematopoietic stem cells are not essential for survival but are generally infused to shorten the duration of regimen-related cytopenias. Therefore, it seems reasonable to design autologous HSCT conditioning regimens to maximize immune suppression without myeloablation using combinations of agents such as cyclophosphamide, fludarabine, ATG, rituximab, and alemtuzumab.[1,2]

Visceral organ dysfunction is generally a contraindication for HSCT in patients with malignancy. In contrast, impairment of visceral organ function is often the indication for HSCT of patients with autoimmune disease. Organ impairment should be considered in development of disease-specific conditioning regimens. Drugs such as cytosine arabinoside (ara-C) and fludarabine have dose-dependent central nervous system (CNS) toxicities that are increased in patients with renal insufficiency due to impaired clearance. Agents that cause pulmonary fibrosis such as TBI, busulfan (Myleran; GlaxoSmithKline), or bleomycin (Blenoxane; Bristol-Myers Squibb) could exacerbate disease-related pulmonary fibrosis in patients with scleroderma or mixed connective tissue diseases.[21] Cardiovascular stress from infection-related fever or aggressive hydration that is often given with cyclophosphamide may cause cardiopulmonary arrest in patients with scleroderma-related pulmonary artery hypertension.[22] In patients with myasthenia gravis, numerous medications including antibiotics may cause respiratory failure (myasthenic crisis).[23] In patients with multiple sclerosis, fever from any cause including drug-related from conditioning agents such as ATG may cause exacerbation of symptoms and neurologic deterioration.[24] For patients with Crohn disease, which causes gastrointestinal inflammation and ulceration, conditioning regimen drugs that cause mucositis should be avoided. The conditioning regimen should be designed to avoid adding further insult to already damaged organs.

Just as bone marrow contains stem cells to regenerate blood and immune compartments, other organs have tissue-specific stem cell compartments involved in repair and regeneration. Tissue-specific stem cells are found in virtually every organ including skin, liver, muscle, gastrointestinal tract, lung, kidney, and CNS. Depending on the type of autoimmune disease, many of these organ systems may be impaired. The conditioning regimen should avoid agents that may damage tissue-specific stem cell compartments. Little is available on organ-specific stem cell drug sensitivity. However, blood stem cells are sensitive to even relatively low doses of radiation, and neural stem cell repair of the CNS in animal models is impaired by doses of TBI (10 cGy) used in HSCT protocols.[10,25] The extent to which damaged organs can repair or remodel remains unclear. Whether fibrosis, especially in diseases such as systemic sclerosis or interstitial pulmonary fibrosis, can reverse is also unknown.[21,26] However, conditioning regimens should be designed to minimize injury to tissue-specific progenitor cells.

Mortality varies by disease and subsets of patients at risk of significant morbidity or mortality can generally be identified. However, autoimmune diseases generally have a better prognosis than malignancies; and autoimmune diseases unlike

malignancies may go into spontaneous remission. Therefore, conditioning regimens for autoimmune diseases, compared to malignancies should have a greater emphasis on safety. In summary, for autologous HSCT, the rationale behind the conditioning regimen is to: 1) dose escalate agents that work as conventional therapy, 2) maximize immune suppression without myeloablation, 3) avoid conditioning regimen agents that cause injury to already disease affected and damaged tissues, 4) avoid injury to tissue-specific stem cell compartments that may be important for tissue repair, and 5) design regimens that are justified for the risk of the disease being treated.

Allogeneic HSCT for Autoimmune Diseases

Unlike autologous HSCT in which the goal is to suppress and restart the immune system from autologous stem cells, the goal of an allogeneic HSCT is to change the genetic predisposition to disease by changing the stem cell compartment. It is not clear whether a full chimera in which all hematopoietic stem cells are reconstituted from the donor or mixed chimerism with coexistence of both donor and recipient hematopoiesis and immune cells is sufficient to control disease. In animal models, either full donor chimerism or mixed chimerism is sufficient to induce remission and prevent relapse of autoimmune diseases.[15,16] Therefore, unlike malignancies where mixed chimerism, in contrast to full chimerism, is associated with a high rate of malignancy relapse, mixed chimerism may be beneficial in autoimmune diseases.

Full donor chimerism in malignancies has been complicated by a high rate of graft-versus-host disease (GVHD), an immune-mediated disease in which allogeneic donor lymphocytes are directed against the host. However, if the protocol is properly designed, mixed chimerism may be induced without significant risk of GVHD. Due to the risk and complications of allogeneic HSCT compared to the disease itself, until methods to eliminate GVHD with full donor chimerism are proven, the current goal of allogeneic HSCT in autoimmune diseases is to induce mixed chimerism.

Mixed chimerism may be induced without GVHD by an intense immune suppressive but nonmyeloablative regimen combined with a lymphocyte depleted donor graft.[27] The donor graft may be depleted of lymphocytes ex vivo by stem cell (CD34) enrichment or in vivo by infusion of a potent lymphocyte depleting antibody such as alemtuzumab.[22,28] The principles behind the selection of the conditioning agents for induction of allogeneic mixed chimerism are otherwise similar to those for autologous HSCT. The conditioning regimen is selected to avoid agents such as TBI that cause recipient myeloablation, damage to tissue specific stem cell compartments, or injury to already damaged organs.

Northwestern University Experience in HSCT for Autoimmune Diseases

Autologous HSCT

The first autologous HSCT for multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, relapsing polychondritis, Sjögren disease, and Behçets in the United States, and the world's first autologous HSCT for Crohn disease, pemphigus vulgaris, and myasthenia gravis were performed at Northwestern University in Chicago. Each disease is different and unique in terms of eligibility, toxicities, risk of infection, and instruments to measure outcome. Some of these diseases are briefly summarized below.

Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated demyelinating disease manifest as acute relapses with gadolinium-enhancing lesions on MRI, and an axonal degenerative disease manifest as slow progressive disability often without enhancing lesions.[29,30] Initial HSCT protocols were, for ethical reasons, focused on patients with nonrelapsing progressive disease and severe neurologic disability (requiring bilateral support, a cane, walker, or wheelchair).[31-34] The Kurtzke extended disability status scale (EDSS) is one of several instruments to measure MS-related neurologic disability. The EDSS varies by half-point increments from 0 (normal) to 10 (death due to neurologic disability). Mild disability is defined as EDSS <4.0, moderate disability is 4.0–6.0, and severe disability is >6.0. At an EDSS of 4.0, patients are able to ambulate without difficulty. At an EDSS of 6.0, support is required to ambulate, while at an EDSS of 7.0, patients can only ambulate for a few steps.[35] In this initial phase I study, patients with progressive MS and an EDSS ≥6.0 continued to have progressive neurologic decline following HSCT. Patients with less disability (EDSS <6.0) have not progressed although continued long-term follow-up and more patients are necessary to confirm a change in the natural history of disease progression.[31,36]

From this initial study, we concluded that HSCT should be performed earlier in disease before significant disability and in patients with continued inflammatory disease manifest by acute relapses and preferably by gadolinium enhancement on MRI[37] despite treatment with interferon. Although this subgroup of patients may over several years develop significant and irreversible neurologic impairment, a relatively nontoxic and well tolerated conditioning regimen is required since the 10-year survival of this subset of patients is similar to the general population. The conditioning regimen chosen is cyclophosphamide (50 mg/kg on days -5, -4, -3, -2) and the antilymphocyte antibody alemtuzumab (20 mg on day -2). This is based on efficacy of both drugs in suppressing active inflammatory disease in MS as well as the established safety of similar doses of cyclophosphamide and antilymphocyte antibodies in over 70 patients undergoing HSCT for rheumatoid arthritis.[38] Since alemtuzumab has a long half-life and can effectively purge the graft in vivo, no CD34+ selection or manipulation of the autologous graft is performed prior to infusion.

We have previously reported that granulocyte colony-stimulating factor (G-CSF) given during mobilization can cause an acute exacerbation of MS and that disease flare can be prevented by mobilizing with combined cyclophosphamide and G-CSF. Cyclophosphamide 2.0 g/m^2 is followed 72 hours later by daily G-CSF with stem collection from the peripheral blood upon leukocyte rebound, usually day 10 after cyclophosphamide.[22]

Candidates are selected for an EDSS of 2.0 to 5.5 and failure of at least 6 months of interferon. Failure being defined as gadolinium-enhancing lesion(s) on MRI or acute relapses within the prior 12 months. Therefore, unlike the earlier study that selected patients for progressive neurologic deterioration with severe disability, this study selects patients for active relapses with mild to moderate disability. Late progressive MS is not amenable to immune suppression while relapsing disease responds clinically to traditional immune suppressive therapies. Similarly, in HSCT for late progressive disease, improvement in neurologic dysfunction assessed by EDSS did not occur.[31] In contrast, from the initial results of HSCT in active relapsing disease, the EDSS is clinically improving (unpublished data, Burt et al).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a clinically heterogeneous disease with manifestations that may affect predominately one or combinations of organ systems and varies between patients. Some patients have predominately a single system affected, such as nephritis, serositis, pneumonitis, cerebritis, vasculitis, antiphospholipid antibody syndrome with venous and vascular thrombi, arthralgias, myalgias, cutaneous symptoms (rash, livedo reticularis, ulcerations), or immune-mediated cytopenias. The common theme is T and B cell hyperreactivity to environmental stimuli.[39-41]

One of the most effective therapies for SLE is intravenous (IV) cyclophosphamide (500–1,000 mg/m^2 monthly for 6 months then every 3 months for 18 months). Patients who fail this therapy with active visceral disease have at least a 20% and 35% mortality within 2 and 5 years, respectively, and are candidates for HSCT. Mobilization is with cyclophosphamide 2.0 g/m^2 and G-CSF beginning 72 hours later. The conditioning regimen is 200 mg/kg cyclophosphamide and 90 mg/kg equine ATG. This regimen is based on dose escalation of perhaps the most effective lupus medication, IV cyclophosphamide. The mobilized cells are CD34(+) enriched.[42,43]

This phase I/II study was remarkably successful in inducing remission in previously refractory disease.[42-44] Appropriate supportive care guidelines are important for these patients who have multiple organ dysfunction to prevent transplant-related complications. Patients with nephritis rapidly develop refractory volume overload and pulmonary edema. IV mesna (Mesnex; Baxter) and continuous bladder irrigation is employed instead of hyperhydration during cyclophosphamide conditioning. SLE patients, due to disease-related Th2 skewing and T cell receptor repertoire restriction as well as chronic high-dose corticosteroid and other immune suppressive medications, are unusually prone to infections that mimic active lupus. Bacterial peritonitis mimics SLE serositis, central nervous system viral and fungal infections mimic lupus cerebritis, and bacteremia can be misdiagnosed as lupus-related fever. Therefore, surveillance cultures for infections, and aggressive antiviral, fungal, and bacterial prophylaxis throughout HSCT, independent of fever, is prudent. SLE patients with antiphospholipid antibodies are prone to arterial and venous thrombi[45] and should remain on either prophylactic or therapeutic dalteparin sodium or enoxaparin sodium throughout HSCT. After HSCT, these patients generally require a slow taper over 6–12 months of corticosteroids. These patients have often been on long-term high-dose corticosteroids and rapid steroid taper may not only precipitate adrenal insufficiency but a withdrawal syndrome of joint pain, muscle aches, anxiety, and nervousness.

To date, 42 patients with SLE have undergone autologous HSCT at Northwestern University. The majority of patients enter drug-free remissions for up to several years (unpublished data, Burt et al). We are currently reviewing and summarizing outcomes to determine if any modifications are warranted for development of randomized trials.

Crohn Disease

Crohn disease is a Th1-skewed delayed type of hypersensitivity that may involve any region of the gastrointestinal tract. Whether inflammation is initiated and directed against exogenous antigens such as gastrointestinal bacteria or against a gut-specific autoantigen is unknown. Crohn disease is complicated by chronic abdominal pain often leading to narcotic addiction, diarrhea, repeated surgeries, colostomy or ileostomy, weight loss, fistulae, abcesses, abdominal obstruction, nausea, vomiting, and failure to thrive. Repeated surgery results in short gut syndrome and chronic total parenteral nutrition (TPN).[46]

We have performed 12 HSCTs for patients with a Crohn Disease Activity Index (CDAI) >250 (active disease) despite treatment with tumor necrosis factor (TNF)-inhibitor (infliximab [Remicade; Centocor]) therapy. The same regimen with CD34(+) selection used for SLE is utilized, because it has been well tolerated without mucositis. Clinical symptoms such as diarrhea and abdominal pain generally resolve before hospital discharge. All patients have entered remission (CDAI <150). Small bowel radiographs and colonoscopy gradually improve over 2 years. Narrowing of the large bowel has reversed, while of 2 patients with small bowel narrowing, 1 required posttransplant surgery for obstruction, although histology revealed no evidence of active Crohn disease (unpublished data, Burt et al).

Systemic Sclerosis

Systemic sclerosis also known as scleroderma is a vasculopathy, perhaps immune-mediated, but of unknown etiology. One suggested etiology is an autoimmune process directed against unknown self antigen(s). Another hypothesis is that scleroderma is an alloimmune response due to child or parent lymphocytes that cross transplacentally, survive dormant, and years to decades later become active and cause an allogeneic graft-versus-host disease.[47-49] Mortality for scleroderma with high cutaneous skin scores (Rodnan score >14) and/or visceral organ involvement is approximately 12% per year.[50,51] There is no known effective therapy for scleroderma, although IV cyclophosphamide appears to improve early pulmonary manifestations.[52] Using cyclophosphamide at 200 mg/kg and rab-

bit ATG at 7.5 mg/kg without CD34(+) selection or manipulation of the graft, we have seen marked improvement in skin scores and quality of life, and improvement in pulmonary function parameters by 1 year. Post-HSCT improvement of skin begins prior to transplant hospital discharge and seems to continue gradually beyond 1 year after treatment. The most common cause of death in scleroderma is cardiovascular and patients with pulmonary artery hypertension cannot tolerate cardiac stress from any cause (fever, infection, anemia, or hyperhydration).[53] For this reason, patients with systemic pulmonary artery pressures >40 mm Hg are excluded as candidates. In addition, during HSCT, IV mesna and continuous bladder irrigation is used instead of hyperhydration during cyclophosphamide conditioning.

Allogeneic HSCT

As mentioned earlier, the objective of allogeneic HSCT in autoimmune diseases is to induce donor recipient mixed chimerism while avoiding GVHD using allogeneic HLA-matched donor HSCT. It is hoped that similar to animal models of autoimmune disease, mixed chimerism presumably by changing genetic susceptibility, will result in prolonged disease remission. While several protocols are in development (Table 2), allogeneic HSCT studies are currently open for rheumatoid arthritis and scleroderma.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory synovial disease with subsequent cartilage and joint destruction. Patients with a large number of involved joints or significant restriction of activities of daily living are at high risk for death with 40–60% mortality over 5 years.[54-56] Patients with these manifestations despite TNF and methotrexate/leflunomide therapy are candidates for allogeneic HSCT. In order to obtain mixed chimerism without GVHD, patients are treated with a nonmyeloablative transplant (NST) regimen and CD34(+) enriched (lymphocyte depleted) megadose (>10^7 CD34[+] cells/kg) donor hematopoietic stem cells. The conditioning regimen is fludarabine 125 mg/m^2, cyclophosphamide 150 mg/kg, and alemtuzumab 20 mg. One patient has been treated. At 14 months post HSCT, the patient is a stable mixed chimera (both donor and host myeloid [CD33] and T [CD3] cells), in a complete remission, and rheumatoid factor negative. The patient is off all immune-suppressive or modulating therapy, and has had no GVHD or infections.[27]

Scleroderma

Patients with scleroderma have a disease that is clinically similar to chronic GVHD.[49] It is, therefore, important to avoid GVHD which could exacerbate and be clinically indistinguishable from scleroderma. Again, in order to obtain mixed chimerism without GVHD, patients are treated with an NST regimen of cyclophosphamide (200 mg/kg) and alemtuzumab (90 mg) followed by an unselected HLA-matched sibling peripheral blood stem cells transplantation. alemtuzumab is a potent in vivo purging agent that not only eliminates donor T cells but also antigen-presenting cells (B cells and dendritic cells) markedly decreasing the risk of GVHD even for unmanipulated grafts. One patient has been treated and is a stable mixed chimera with gradually improving skin scores over 6 months. She has had no GVHD or infections (unpublished data, Oyama et al).

Future Direction of Stem Cell Transplantation for Autoimmune Diseases

New autologous disease specific protocols are ongoing or being developed for a number of autoimmune disorders (Table 2). Autologous HSCT phase III studies are being developed for diseases completing phase I/II protocols. While autologous HSCT is giving impressive short-term results in previously refractory diseases, a long-term cure remains uncertain and allogeneic HSCT protocols are already open or being developed (Table 2). The focus in protocol development for autoimmune diseases must be on patient safety. Although more

Table 2. Northwestern University HSCT Protocols for Immune-Mediated Diseases

Autologous HSCT		Allogeneic HSCT	
Current protocols	**Protocols in development**	**Current protocols**	**Protocols in development**
Multiple sclerosis	Asthma	Rheumatoid arthritis	Systemic lupus erythematosus
Systemic lupus erythematosus	Polymyositis	Systemic sclerosis	Idiopathic pulmonary fibrosis
Rheumatoid arthritis	Sarcoidosis	Combined renal/HSC	Amyotrophic lateral sclerosis
Systemic sclerosis (scleroderma)	Alloimmunized kidney transplant candidates	Combined intestinal/HSC	Combined liver/HSCT
Myasthenia gravis			
Crohn disease			
Chronic inflammatory demyelinating polyneuropathy			
Pemphigus vulgaris and pemphigus foliaceus			
Wegener's vasculitis			
Behçets (neurovascular)			
Sjögrens (pulmonary or neurovascular)			

HSC=hematopoietic stem cell; HSCT=HSC transplantation.

data is needed, current studies suggest less morbidity and mortality from nonmyeloablative autologous regimens. In order to decrease the toxicity of allogeneic HSCT, phase I studies are combining nonmyeloablative regimens with methods of eliminating GVHD through lymphocyte depletion of the donor graft, either by CD34(+) selection or in vivo alemtuzumab. The goal of these allogeneic regimens is to determine the effect of mixed chimerism on autoimmune diseases.

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