

Blood and Marrow TRANSPLANTATION

REVIEWS

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Autoimmune Diseases: When Homeland Security Fails

by John R. Wingard, MD, Editor

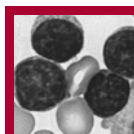
Autoimmune disease can be viewed as an insurrection by security forces charged with protecting us from lurking outside dangers. What ensues is either smoldering conflict to attrition or large-scale open warfare. Treatments have generally been disappointing. Autoimmune phenomena are sometimes consequences of both autologous and allogeneic hematopoietic cell transplantation (HCT). So, why would one consider treating autoimmune diseases with HCT?

Serendipity can fuel great initiatives. The incidental findings of concomitant autoimmune diseases improving in patients undergoing HCT for other reasons have been well documented in the literature. Animal models have amply demonstrated the potential of transplantation to correct autoimmune diseases. So, certainly there were reasons to believe that HCT is worthy for study. Now, clinical investigators have compiled an impressive array of early clinical data suggesting the potential for HCT to have an important role in the treatment of human autoimmune diseases.

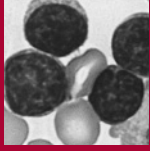
In this transcript of a symposium held at the 2004 Tandem BMT Meetings in Orlando, Florida, the current status of what we know and what is being learned in clinical trials now underway and those in the planning stages is reviewed.

Much has been learned. Rheumatologists and neurologists have set the stage by defining natural history and risk factors and developing standardized criteria for disease status and response. Transplanters have added knowledge about principles of conditioning regimens, identified treatment risk factors, and defined some of the limits of who might be helped and who cannot.

Yet much work lies ahead. And, of course, obstacles. There are other competing alternative therapies to test, many with less risky complications. What about high-dose immunosuppressive therapy without stem cells? Adjunctive studies to investigate in detail how HCT affects the dysregulated immunity are needed, to increase our understanding of pathogenesis and provide suggestions for yet further interventions. The randomized trials are ambitious and need wide support for timely completion. Only then will we know if an armed counterinsurgency will win the day.



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PRELIMINARY APPLICATION

**Be a part of a national organization
established to promote
education, research, and
medical development in the field of
blood and marrow transplantation.**

Full Membership is open to individuals holding an MD or PhD degree with demonstrated expertise in blood and marrow transplantation as evidenced by either the publication of two papers on hematopoietic stem cell transplantation-related research as recorded by curriculum vitae, or documentation of two years of experience in clinical transplantation as recorded by curriculum vitae or letter from the director of a transplant center attesting to the experience of the candidate.

Associate Membership is open to individuals with an MD or PhD degree who otherwise do not meet the criteria for full membership.

Affiliate Membership is available to allied non-MD or non-PhD professionals who have an interest in blood and marrow transplantation. This category is especially appropriate for nursing and administrative staff of bone marrow transplant centers, collection centers, and processing laboratories, and for professional staff of corporations that provide products and services to the field of blood and marrow transplantation.

In-Training Membership is open to fellows-in-training in bone marrow transplantation programs. A letter from the transplant center director attesting to the applicant's training status is required.

Included in the membership fee is a one-year subscription to *Biology of Blood and Marrow Transplantation*.

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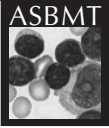
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2005 Tandem BMT Meetings Will Be Feb. 10-14 in Keystone

The combined annual meetings of ASBMT and the Center for International Blood and Marrow Transplant Research (CIBMTR, formerly IBMTR/ABMTR) will be Feb. 10-14 at the Keystone Conference Center in Keystone, Colorado.

The Tandem BMT Meetings will present the latest advances in the broad field of cellular therapy and blood and marrow transplantation, addressed in plenary sessions, concurrent sessions, workshops, poster sessions, and symposia. In addition, about 60 original abstracts will be selected for oral presentation.

The meeting deadlines are:

- Abstract submission: Oct. 18, 2004
- Early registration: Oct. 18, 2004
- Housing reservations: Jan. 3, 2005
- Pre-registration: Jan. 24, 2005

Further information, online registration and abstract submission are at the ASBMT Web site www.asbmt.org.

In addition to the five days of scientific sessions for BMT clinicians and investigators, there will be five related conferences and courses:

- BMT Pharmacists (*Feb. 9-10*)
- Clinical Research Professionals Data Management Workshops (*Feb. 9-11*)
- BMT Center Administrators (*Feb. 11-12*)
- Transplant Nurses (*Feb. 12-14*)
- BMT Center Medical Directors (*Feb. 13*)

The scientific sessions will include the following topics and speakers:

THURSDAY, FEB. 10

- Regenerating the Myocardium with Bone Marrow Cells
Armand Keating, Helmut Drexler, Emerson Perin
- Advances in TBI Delivery
Richard Tsang, Jeffrey Wong, John Pagel
- Chronic Lymphocytic Leukemia: On the Pathway to Cure
Issa Khouri, Terry Hamblin, Michael Keating
- National Marrow Donor Program
Dennis Confer

FRIDAY, FEB. 11

- Cancer Stem Cells: Implications for Therapy
John Dick, Peter Dirks, Michael Clark
- Venous Occlusive Disease and Idiopathic Pneumonia Syndrome: New Insights into Old Problems
Kenneth Cooke, Enric Carreras, Paul Richardson
- Stem Cell Biology
Peter Quesenberry, Alan Flake, Esmail Zanjani

- Pediatric Solid Tumors
Gregory Yanik, Jonathan Finlay, Kenneth Lucas
- Clinical Trials Design
Christopher Bredeson
- Non-myeloablative Allografts
Sergio Giralt, Dietger Neiderwieser
- Bloodless Transplants: Are You Utilizing Alternatives to Minimize Transfusions?
Patricia Ford, Barbara Matthews

SATURDAY, FEB. 12

- GVHD/Histocompatibility
Olle Ringden, George Sale, John Hansen
- MDS: From Biology to Stem Cell Transplantation
Pierre Fenaux, Michaela Fontenay, H. Joachim Deeg
- Tolerance: From Bench to Bedside
Megan Sykes, Harold von Boehmer, Maria-Grazia Roncarolo
- Statistical Issues and Recent Developments in Analyzing Survival Data
Mei-Jie Zhang, Neils Keiding, Jason Fine

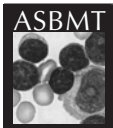
SUNDAY, FEB. 13

- Innovations in Autologous Stem Cell Transplantation
Stephen Forman, Michael Jensen, Frederick Appelbaum
- Cancer Vaccines: Do They Have a Role in the Post-Transplant Setting?
Freda Stevenson, Katharine Whartenby
- Life after Relapse: What Is the Prize?
Hans-Jochem Kolb, Julie Vose
- Animal Models for GVHD and GVL: Current Topics and Future Directions
Warren Shlomchik, Bryon Johnson

MONDAY, FEB. 14

- Immune Reconstitution after Allografts
Joseph Antin, Bruce Blazar, Georg Hollander
- Imaging in Hematopoietic Cell Transplantation
Robert Negrin, Christopher Contag, Juri Gelovani
- Hematopoietic Cell Transplantation for Non-Malignant Disorders (International Session)
Mark Litzow, Jane Apperley, Charles Peters, Mark Walters, Emanuelle Angelucci

The scientific program chair for ASBMT is Stephen Emerson, MD, PhD, University of Pennsylvania, and the co-chairs for the CIBMTR are Sergio Giralt, MD, M.D. Anderson Cancer Center, and Mark Litzow, MD, Mayo Clinic.



Stem Cell Therapy for Autoimmune Disease

Adapted from a CME symposium presented at the 2004 Tandem BMT Meeting, February 2004, Orlando, Florida, USA.

This program is supported by an unrestricted educational grant from Pfizer.



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Accreditation Statement

The Medical College of Wisconsin is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Faculty Disclosure

As an accredited sponsor, the Medical College of Wisconsin must ensure balance, independence, objectivity, and scientific rigor in all its individual or jointly sponsored educational activities. The authors who contributed to this publication have disclosed the following relationships:

Richard Burt, MD, has no relationships to disclose.

Dominique Farge, MD, has no relationships to disclose.

Athanasios Fassas, MD, has no relationships to disclose.

Alberto M. Marmont, MD, has no relationships to disclose.

Ann Traynor, MD, has no relationships to disclose.

Continuing Medical Education Credit

The Medical College of Wisconsin designates this educational activity for a maximum of 2.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the educational activity.

Needs Assessment

This program was designed based on input from transplantation specialists regarding the evolving research in stem cell transplantation and its potential role in treating previously untreatable autoimmune diseases. A complete

literature search and a brief telephone survey were conducted to support the program design.

Program Objectives

At the conclusion of this program, participants should be able to:

- Discuss the autoimmune diseases in which stem cell therapy is currently being utilized.
- Discuss the various resources for stem cells and understand the issues related to the development of these cell lines.
- Discuss the mechanisms of tolerance and tissue regeneration.

Target Audience

This CME activity will be valuable to physicians, data managers, nurses, and pharmacists who are involved in the care of patients suffering from autoimmune diseases that may be treatable with stem cell transplantation therapy.

New Indications in Stem Cell Sources in Transplantation for Autoimmune Disease

Richard K. Burt, MD

The Division of Immunotherapy at Northwestern University has several protocols, active and pending, for autologous stem cell therapy for autoimmune diseases (Table 1) including rheumatoid arthritis, systemic lupus erythematosus (SLE), and inflammatory multiple sclerosis (MS). With MS it is difficult at times to distinguish the difference between relapsing-remitting and progressive disease and to determine when that transition occurs, so the focus is on inflammatory MS. We previously reported that this therapy was not helpful, at least in our experience, with late progressive MS, and we will no longer treat that subset of patients. Instead the focus is on treating inflammatory earlier-stage MS (inflammatory by gadolinium enhancement on magnetic resonance imaging). We have also treated systemic sclerosis (scleroderma), Crohn disease, bullous skin diseases, and vasculitis and have performed transplantation in patients with neurovascular Behcet, neurovascular Sjogren, and myasthenia gravis, including a patient with ventilatory-dependent myasthenia gravis. Multiple protocols are in development including polymyositis, sarcoidosis, asthma—that is, near fatal asthma—and alloimmunized renal disease, for which the patient cannot undergo kidney transplantation because of HLA antibodies.

Treatment Outcomes

At Northwestern, we have performed more transplantation procedures for autoimmune disease than any other single center in the world. To date autologous stem cell transplantation has been performed in more than 100 patients with different types of autoimmune diseases. It is not possible here to describe in detail the treatment outcomes for these different autoimmune diseases because they are all unique, but it is important to address the survival rates (Figure 1). The Kaplan-Meier plot of data on cumulative survival over time for these first 100 patients shows a 0% 1-year mortality rate. This outcome is very important, because in order for this procedure to be accepted by the people who normally care for these patients, the

Table 1. Advances in Autologous Stem Cell Therapy for Autoimmunity at the Northwestern Division of Immunotherapy

Active Protocols	Protocols Pending Institutional Review Board Approval
<ul style="list-style-type: none"> • Rheumatoid arthritis • Systemic lupus erythematosus • Relapsing-remitting multiple sclerosis • Scleroderma • Crohn disease • Bullous skin disease • Vasculitis • Myasthenia gravis • Chronic inflammatory demyelinating polyneuropathy 	<ul style="list-style-type: none"> • Polymyositis/dermatomyositis • Sarcoidosis • Asthma • Alloimmunized renal patients

rheumatologists, neurologists, gastroenterologists, dermatologists, and so forth, transplantation-related mortality has to be low. Even in myeloma patients, one would expect mortality of 2% or less for autologous transplantation. Data published from individual case reports or European Group for Blood and Marrow Transplantation (EBMT) registry data indicate that transplantation-related mortality can vary within the first year from 8% to 20%, and this high mortality rate has adversely impacted development in this field.

Of our 100 patients, 7 died of late disease progression; pretransplantation 3 were wheelchair-confined progressive MS patients. Patients with late progressive MS are no longer accepted as candidates for hematopoietic stem cell transplantation (HSCT) at our center. The other 4 patients who died were SLE patients. One of these patients was in a complete remission 18 months after the procedure and died of endocarditis, and the other 3 died of complications of disease relapse occurring more than 1 year after HSCT. SLE patients accepted as HSCT candidates are those who, according to the literature, have an extremely high mortality risk from their disease, so the results from our phase I/II trial are encouraging for proceeding to a randomized trial.

Our initial study of stem cell transplantation for the treatment of progressive MS was unsuccessful. We have retooled the study, making it safer and taking patients earlier in the disease, and we have focused on inflammation, using a conditioning regimen of cyclophosphamide and Campath, without CD34 selection. Figure 2 shows Expanded Disability Status Scale (EDSS) scores for the first 3 patients (the higher the number, the worse their disability) [1]. Marked improvements in the EDSS were evident in these patients. The first 10 patients had no infections; 8 never even had a fever during the procedure. The patients were discharged around day 8 or 9, and 3 did not even require a transfusion. The procedure was extremely well tolerated, and the patients had sustained and in some cases continuing improvement in neurologic disability. When a modified, nonmyeloablative, safer regimen is used, HSCT for MS is very promising for the right subset of patients (early stage, inflammatory disease).

We also performed the first stem cell transplantation treatment for pemphigus. This case was the first stem cell transplantation patient sent to us by a dermatology department, a very severe case of pemphigus foliaceus that covered all of the patient's body. Eighteen

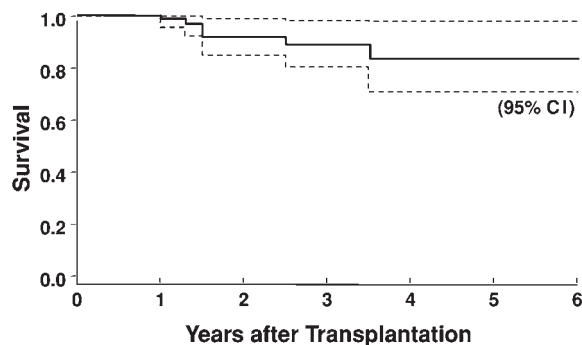


Figure 1. Northwestern University experience: probability of survival in 103 patients with autoimmune disease who underwent autologous hematopoietic stem cell transplantation.

- 10 patients
- No infections
- 8 No fevers
- 3 No transfusions
- Discharge day 8-9

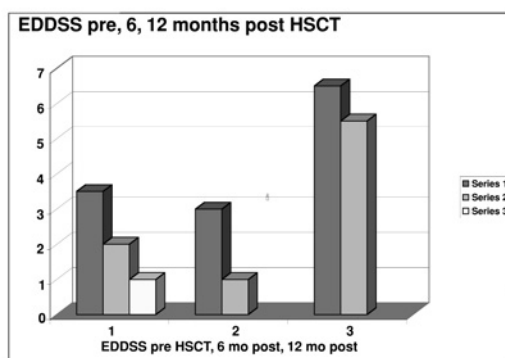


Figure 2. Autologous hematopoietic stem cell transplantation (HSCT) with cytoxan/campath conditioning for relapsing multiple sclerosis. EDSS indicates Expanded Disability Status Scale.

months after stem cell transplantation the patient was in complete remission.

Treatment Rationale for Autologous Transplantation

Our treatment rationale for autologous stem cell therapy is summarized in Table 2. There are different approaches to autologous transplantation for autoimmune disease, particularly in regard to myeloablative or nonmyeloablative conditioning. From our own experience, an important factor in the low treatment-related mortality from autologous stem cell transplantation in these 100 patients is the selection of patients with inflammatory disease and the use of a nonmyeloablative but intense immune suppressive regimen. Wherever possible, as a general rule, we focus on dose-escalating agents that work as a conventional therapy.

Conditioning regimens should avoid agents that damage already injured tissues. Unlike malignancies, for which signs of tissue injury such as organ dysfunction, elevated creatinine, elevated transaminase, low ejection fraction, pulmonary function abnormalities, and low DLCO are contraindications for transplantation, for autoimmune diseases, organ dysfunction is often the indication for transplantation. For instance, if a patient has disease-related pulmonary fibrosis, regimen design should avoid agents such as bleomycin, which could cause pulmonary fibrosis, or radiation, which could cause further fibrosis. The conditioning regimen should minimize agents that could damage tissue stem cell compart-

ments, because virtually every organ appears to have its own stem cell compartment. Unfortunately, the dose-limiting toxicity for most tissue stem cells, such as neural, pulmonary, and liver stem cells, is unknown, but myeloablative regimens are by definition fatal to marrow stem cells and may damage other tissue-specific stem cell compartments.

An important aspect of our autologous transplantation procedure is the use of nonmyeloablative regimens. This strategy is based on the supposition that this disease process is not a predetermined stem cell defect but is environmentally induced and will not recur from the stem cell; thus the immune system can be reset or regenerated to function normally. In fact the goal is not to destroy the stem cell compartment but rather to maximize immune suppression. Nonmyeloablative agents include fludarabine or cyclophosphamide or antibodies to immune cells, such as the antithymocyte globulins, campath, or rituximab (Rituxan), which will not damage the stem cell compartment.

Kashyap et al [2] reported a retrospective study of 263 patients in the EBMT registry. They found 4-fold higher mortality from myeloablative regimens, that is, regimens with busulfan or total body irradiation, compared to nonmyeloablative regimens, with no evidence of improved efficacy in terms of disease remission. There are limitations to non-disease-specific, non-protocol-specific retrospective data, and so it might be good timing for my colleagues here from the EBMT

to work with the International Bone Marrow Transplantation Registry (IBMTR)—they now have well over 600 patients in EBMT, in our own center there are more than 100 patients, and there are approximately 100 more patients in the IBMTR registry who received transplants for autoimmune disease—to again compare treatment-related mortality between myeloablative and nonmyeloablative regimens.

Allogeneic Transplantation

With the experience gained in autologous HSC treatment for autoimmune diseases, we are moving forward to evaluate allogeneic transplantation. Just as our approach in autologous transplantation is to use nonmyeloablative conditioning, our approach in allogeneic transplantation is to induce mixed chimerism by a nonmyeloablative regimen, because with proper regimen design mixed chimerism may be generated without graft-versus-host disease (GVHD). Table 3 lists the regimens that are already approved for allotransplantation at our institution and protocols that are pending approval. For amyotrophic lateral sclerosis (ALS) (Lou Gehrig's disease) we are waiting on the results of our animal work with superoxide dismutase mutant ALS mice, to support preclinical data for a clinical trial.

A report on our results for allogeneic stem cell transplantation for rheumatoid arthritis has been accepted in *Arthritis and Rheumatism*. Briefly, eligible patients either failed an autologous transplantation or failed to respond to tumor necrosis factor inhibitors and methotrexate or leflunomide, with failure being defined as 12 or more swollen joints or 20 or more involved joints. The treatment goal was mixed chimerism without GVHD. To achieve that goal with a nonmyeloablative stem cell approach, we used a regimen cyclophosphamide 150 mg/kg, Campath-1H 20 mg, fludarabine 125 mg/m², and megadoses of CD34-enriched cells, up to 10⁷ CD34⁺ cells/kg if possible, from an HLA-matched rheumatoid factor-negative donor.

Table 2. Rationale of Autologous Stem Cell Therapy based on Experience from 103 Patients at 1 Center

- Select inflammatory disease
- Dose escalate agents that work as conventional therapy
- Avoid agents that damage already injured tissue
- Avoid agents that damage stem cell compartments
- Use nonmyeloablative regimens
- Each disease is unique in eligibility and complications
- Focused team important: experience counts

Table 3. Advances in Allogeneic Stem Cell Therapy for Autoimmunity at the Northwestern Division of Immunotherapy

Active Protocols	Protocols Pending Institutional Review Board Approval
<ul style="list-style-type: none"> • Rheumatoid arthritis • Scleroderma • Renal/hematopoietic stem cells • Intestinal/hematopoietic stem cells 	<ul style="list-style-type: none"> • Systemic lupus erythematosus • Idiopathic pulmonary fibrosis • Amyotrophic lateral sclerosis • Liver/hematopoietic stem cells

In our first patient, donor chimerism steadily increased. Myeloid CD33 chimerism stayed steady at approximately 70% to 80%, but T-cell donor chimerism progressively improved over time and rheumatoid factor decreased and

became negative for the first time in this patient's history. At this time the patient is in a complete and sustained remission, has never had GVHD, and has had no infections except *Clostridium difficile* diarrhea.

The European Randomized HSCT Trial for Scleroderma

Dominique Farge, MD, JM van Laar, Alan Tyndall, on behalf of the EBMT/EULAR Autoimmune Disease Stem Cell Transplant Project

Although the exact pathogenesis of scleroderma is still unknown, during the past 10 years enough experimental and clinical data have been gathered to support the fact that the scheme proposed by Furst (Figure 1), which was still hypothetical when originally published, is progressively proving to be true. Whatever the original stimulus, antigen stimulation by an external stimulus or genetic susceptibility or both, scleroderma is an autoimmune disease that is characterized by predominant T-cell activation with production of autoantibodies and cytokine release. Resulting disease onset is due to diffuse microvascular injury and endothelial lesions that contribute to activation of macrophages, mast cells, and fibroblasts and increased production of collagen. All these factors ultimately lead to diffuse sclerosis within the skin and internal organs, which is responsible for end-stage organ disease. Another important finding of the past 10 years, achieved through prospective follow-up of several large clinical cohorts of systemic scleroderma (SSc) patients, is that whenever heart, lung, and renal involvement is present within the first 3 to 5 years after the diagnosis, prognostic survival is down to between 35% and 45% at 3 to 5 years later [2-4].

Cyclophosphamide Treatment of Scleroderma

Although no treatment has yet proven to be consistently effective in scleroderma, data

acquired in the past 10 years have shown that cyclophosphamide, an alkylating agent that inhibits B- and T-cell function, can be used. Because of poor absorption of the oral form, intravenous bolus in monthly pulses is the best form of cyclophosphamide administration, and has been shown to induce significant decreases in skin scores and improvement in lung function, although these results have been achieved on small numbers of patients (n = 14-28) in a few open phase I/II studies [5-7].

Autologous Bone Marrow Transplantation to Treat Scleroderma

In 1996, European groups, under the auspices of the European Group for Blood and

References

1. Burt RK, Cohen BA, Russell E, et al. Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of intense immune suppression to prevent disease progression in patients with high disability scores. *Blood*. 2003;102:2373-2378.
2. Kashyap A, Passweg J, Tyndall A. Autologous hematopoietic stem cell transplant conditioning regimens for the treatment of severe autoimmune diseases. In Dicke KA, Keating A, eds. *Autologous Blood and Marrow Transplantation, Proceedings of the 10th International Symposium, Dallas, Texas*. Charlottesville, Va: Carden Jennings. 2001;219-225.

Marrow Transplantation (EBMT) and the European League against Rheumatism (EULAR), began the use of autologous peripheral blood stem cell (PBSC) or bone marrow transplantation to treat scleroderma in several phase I/II studies. The initial results in 2001 [8] indicated that these procedures seem to be effective. For the first time in this disease, a significant fall in skin scores was shown in two thirds of the patients 3 and 6 months after the procedure, but the transplantation-related mortality (TRM) of 17% was far too high initially, and that was unacceptable. The high mortality rate was directly linked to the underestimation of organ involvement during pre-transplantation evaluation. So in our original

SSc PATHOGENESIS ? AUTOIMMUNE DISEASE

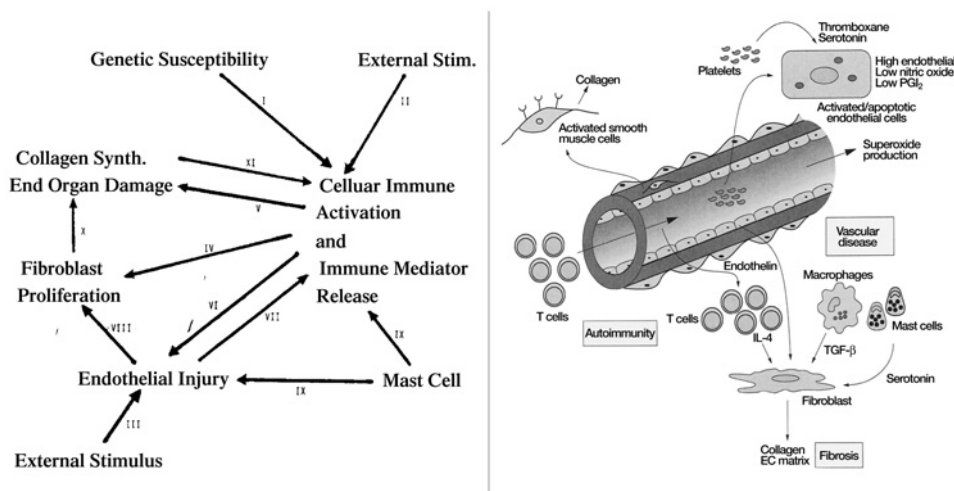


Figure 1. Proposed mechanisms of scleroderma pathogenesis. Left, Reprinted with permission from Furst DE. Rational therapy in the treatment of systemic sclerosis. *Curr Opin Rheumatol*. 2000;12:540-544. Right, reprinted with permission from Sule SD, Wigley FM. Treatment of scleroderma: an update. *Expert Opin Investig Drugs*. 2003;12:471-482.

Inclusion criteria

- ≤ 4 yrs + Rodnan ≥ 15
- + Heart: conduct/rythm/pericardial
- + Lung (DLCO, FVC < 80%)
- + Kidney: HBP, protu, MAT

- ≤ 2 yrs + Rodnan ≥ 20
- + ESR > 25 mm or Hb < 11 g/dL

Exclusion criteria

- PHT > 50 mm Hg
- DLCO < 40% predicted
- Creat cl < 40 mL/min
- LVEF < 45%, uncontrolled arrhythmia, tamponade
- Infection, cancer
- Previous CY (> 5 g)

Figure 2. Updated inclusion and exclusion criteria for the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (www.astistrial.com) for patients aged 16-60 years (65 biological) with diffuse systemic scleroderma. PHT indicates pulmonary hypertension; DLCO, carbon monoxide diffusing capacity; FVC, forced vital capacity; Creat cl, creatinine clearance; HBP, high blood pressure; protu, proteinuria; MAT, thrombotic microangiopathy; LVEF, left ventricular ejection fraction; ESR, erythrocyte sedimentation rate; CY, cyclophosphamide.

report, we underlined the importance of careful pretransplantation evaluation of heart and lung function and of the use of selective criteria for excluding patients with (a) pulmonary hypertension with pulmonary artery pressure above 50 mm Hg or a carbon monoxide diffusing capacity (DLCO) below 40%, and (b) with an ejection fraction below 50% according to cardiac echography or MUGA (multigated equilibrium radionuclide angiography). We also suggested avoiding the use of cyclophosphamide in these scleroderma patients with significant severe cardiac involvement because of enhanced risk of cyclophosphamide cardiotoxicity in this context [9]. This emphasis on better screening appears to have been important. When we now analyze the extended follow-up of the patients included in the original report plus those included in the protocols since then, the results emphasize the importance of better pretransplantation evaluation and screening. The transplantation-related mortality was down to 8.5%, whatever the priming or conditioning regimen used (usually it was cyclophosphamide alone plus granulocyte colony-stimulating factor for PBSC priming and cyclophosphamide 200 mg/kg total dose for conditioning) [10]. The TRM was as low as 5.4%, a result related to the use of exclusion criteria to select good candidates for this procedure and the inclusion of patients who are not too late in the disease process. However, we also learned with extended follow-up of these patients that disease-progression-related deaths account for 14% (n = 8/57) of the overall observed mortality, and that disease progression may occur in approximately one third of all patients after the procedure. Among 57 patients treated with autologous PBSC or BM transplantation, there

was a significant fall in skin scores at 1 year (n = 30 patients) and at up to 2 years (n = 20 patients) and 3 years (n = 16 patients), respectively, after the procedure. To our knowledge such a result has never been shown in scleroderma data prior to this study. This significant fall in skin scores was associated at 3 years with a slight reincrease, although it is still significantly below 25% compared to inclusion data. This significant benefit was associated with stabilized lung function as indicated by no further deterioration in vital capacity or DLCO. Therefore the projected 5-year survival rate of these patients could be calculated at 72%, which is much higher than the observed survival for nontreated patients with SSc disease of the same severity.

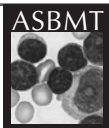
The risk of disease progression after the transplantation procedure, which was calculated at 48% at 5 years, must be better understood. In the French ISAMAIR phase I/II study [11], we analyzed the type of immune reconstitution within the first 9 months after the procedure, considering the observed clinical response. Reconstitution was retrospectively analyzed in 2 groups of patients according to whether they showed sustained major or partial responses (n = 4 patients) or whether after 9 months they needed the reintroduction of some type of immunosuppression due to no response or relapse (n = 3 patients). We found that patients who relapsed or did poorly after the graft were undergoing faster reconstitution than the patients with sustained clinical responses. Before PBSC transplantation, the absolute numbers of CD19⁺, CD3⁺, CD3⁺CD4⁺, CD3⁺CD8⁺, CD4⁺CD45RO⁺, and CD4⁺CD45RA⁺ were all normal in both groups. CD3⁺ remained low thereafter, but in those with clinical response the CD3⁺ T-cell

defect was sustained with an opposite trend and faster CD4⁺ immune reconstitution profile in those with relapse or no response. The B-cell number was below normal until 9 months in patients with clinical response and back to normal at 3 months in those with no response or relapse. CD4⁺CD45RO⁺ profiles were similar and the CD4⁺CD45RA⁺ reconstitution profile was faster in patients with relapse or no response. These results will have to be confirmed on a larger scale.

Autologous Stem Cell Transplantation International Scleroderma Trial

The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, www.astistrial.com, has been ongoing for the past 15 months in Europe, with 30 patients included to date in 2 arms. The aim of the study is to evaluate the potential clinical benefit of high-dose immunoablation and autologous stem cell transplantation versus standard pulse-therapy by 12 monthly infusions of cyclophosphamide (the control arm) with respect to survival and prevention of major organ, heart, lung, or kidney failure (referred to as event-free survival, which is considered the primary endpoint). Safety and impact on skin thickening, visceral involvement, functional status, and quality of life will also be analyzed. Patients in the transplantation group receive a mobilization regimen consisting of cyclophosphamide 2 g/m² on 2 consecutive days to avoid cyclophosphamide toxicity, plus granulocyte colony-stimulating factor 10 µg/kg per day for 5 days or more when necessary. Leukaphereses are performed with the goal of obtaining at least 5×10^6 CD34⁺ cells per kg body weight, with a minimum of 2×10^6 CD34⁺ cells/kg after effective T-cell depletion. Conditioning is to be initiated as soon as possible after recovery, preferably within 6 weeks after successful harvest. Because T-cell depletion was considered important in the design of this protocol, the conditioning regimen consists of cyclophosphamide 50 mg/kg per day intravenously for 4 consecutive days (total 200 mg/kg) and rabbit antithymocyte globulin at a total dose of 7.5 mg/kg on 3 days. The number of CD34 cells to be reinfused should be 2×10^6 /kg on day 0.

The first 30 patients were selected with original, stricter inclusion criteria. Recent safety analysis of the first 20 patients by the safety committee, which includes 2 Europeans



and 1 North American, enabled us to enlarge our inclusion criteria because there was no increased mortality in one arm compared to the other. Therefore we extended our inclusion criteria to patients with recent onset of the disease with a Rodnan skin score above 20 and signs of an increased inflammatory state compared to the original criteria, which were restricted to severe disease of less than 4 years duration with a Rodnan skin score above 15 and heart, lung, or kidney involvement. The exclusion criteria that were developed based on the results of the EBMT/ EULAR trial [10] are also extremely important (Figure 2).

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The European Randomized HSCT Trial for Multiple Sclerosis

Athanasios Fassas, MD

Multiple sclerosis (MS) is not an uncommon disease, and it is a seriously disabling one. MS does not compromise life expectancy; patients do not die of MS but of unrelated causes. But MS does cause serious psychological and social problems, and the suicide incidence is much higher among MS patients. MS is regarded as a T-cell-mediated autoimmune disease that destroys myelin around axons. Another effect of the disease, the importance of which was previously underestimated, is secondary neuronal degeneration. This effect is now regarded as pivotal and is known to have important therapeutic implications, because it may start very early in the course of the disease and go on irrespective of the existence of inflammation. Characteristics of MS pathogenesis are outlined in Table 1.

The aim of MS treatment is to halt disease progression. Therapeutic drugs include steroids for acute attacks, interferon and glatiramer acetate (Copaxone) for relapsing/remitting MS, and mitoxantrone for rapidly progressing relapsing/remitting MS and secondary progressive MS. Cyclophosphamide is not very widely used, but it is used in acute attacks in which there is a lot of brain inflammation. The problem is that results are not very good with these drugs. They are not very

effective, especially in patients with chronic progressive, primary progressive, and secondary progressive MS and in those patients who have an extremely progressive form of the disease, the Marburg or malignant form. These types of MS are usually unresponsive to these drug treatments.

Experimental Model of Transplantation for MS

Transplantation as a treatment for MS was introduced in the early 1990s in the experimental setting to treat experimental autoimmune encephalomyelitis (EAE), which is the animal model of MS [1-3]. The remission rate was found to be high (approximately 100%), but the relapse rate was also high (approximately 30%) and depended on the intensity of the conditioning and T-cell depletion of the graft. In mouse and rat animal models, less intense conditioning regimens without T-cell depletion of the graft were followed by more relapses. Thus T-cell depletion was determined to be necessary to avoid frequent relapses. Another finding for EAE was that long-term tolerance can be established, but if transplantation is performed late then there is no therapeutic result. This time-sensitivity is understandable because the changes late in the disease are of the degenerative form and not the inflammatory form.

Clinical Results

A comprehensive analysis of the first 83 MS patients treated with transplantation was pub-

lished in 2002 [4]. The most prominent effect observed was almost complete suppression of inflammation in the brain, an objective criterion of response that can be observed with magnetic resonance imaging (MRI). Clinically MS is a very difficult disease in which to prove the efficacy of an investigational agent or therapy. However, it seems that transplantation delays progression, especially in secondary progressive MS and in young patients with low disability scores, whereas patients with high disability scores and possibly those who also receive total body irradiation as a conditioning regimen do not fare well. There is an associated transplantation-related mortality that goes from 1.5% up to 5%, especially if the patients are not very well selected or are elderly with high disability scores and if intense regimens are employed with extensive T-cell depletion. An invariable and important finding in all

Table 1. Multiple Sclerosis Pathogenesis

• Common	1.2/1000
• Disabling	50% Unable to walk by 15 y
• Incurable	Psychological and social issues
• Autoimmune, T-cell mediated inflammation	
Focal demyelination—plaques	
Reversible disability	
• Axonal—neuronal degeneration	
Secondary	
Axonal injury in plaques	
Early	
Brain atrophy; gliosis	
Irreversible disability	

Table 2. Autologous Stem Cell Transplantation International Multiple Sclerosis (ASTIMS) Trial Description

- Prospective, comparative, multicenter, single-blinded, randomized trial comparing autologous stem cell transplantation to mitoxantrone in severe MS (secondary progressive or relapsed remitting) unresponsive to traditional therapies
- Primary aim: Reduction of progression of disability for up to 3 years
- Secondary aims: Compare clinical course, magnetic resonance imaging activity, lab parameters, safety, and mortality

studies was that brain atrophy continued. Brain atrophy reflects axonal degeneration, neuronal degeneration, and irreversible disability. But this finding can be explained by the fact that practically all these patients were patients with longstanding disease whose pathogenic feature was neurodegenerative rather than inflammatory.

Which MS patients are the best candidates for transplantation? Young patients with rapidly progressing disease who still have low Expanded Disability Status Scale (EDSS) scores with inflammatory changes in the central nervous system. We still do not know what is the best regimen or whether or not grafts should be T-cell depleted *ex vivo*. The intensity of conditioning seems to play an important role, not only for transplantation mortality, as was already shown by Kashyap et al in 2001 [5] and again in the recent analysis of the 473 patients in the European Cooperative Group for Bone Marrow Transplantation (EMBT) megafile [4], but also because conditioning intensity is associated with sustained response in disease progression, so there is a need for an intense conditioning regimen in the clinical setting just as there was in the experimental setting. There is no definite answer regarding *ex vivo* graft manipulation. In the analysis, the results were the same whether or not the grafts were T-cell depleted. There may be more toxicity with T-cell depletion. Apart from that, there is an Australian randomized trial in rheumatoid arthritis that shows no benefit of T-cell depletion with CD34 selection in these patients [6].

ASTIMS Trial

The Autologous Stem Cell Transplantation International MS (ASTIMS) trial is a prospective, comparative, single-blinded, randomized trial comparing transplantation to mitoxantrone in treating cases of severe, secondary-progressive, and relapsing-remitting MS for which traditional therapy (interferon, glati-

ramer acetate) has failed, or for which a good response was not obtained with mitoxantrone, provided that mitoxantrone had not been received for a dose greater than 700 mg/m² (Table 2). The primary aim of the study, reduction of progression of disability at 3 years, is clinical, and the secondary aims include MRI activity, laboratory parameters, safety, and decreased mortality.

An ethical problem may exist because patients are randomized into one arm with 5% mortality and the other with 0% mortality. But we still consider the randomization to be ethical because mitoxantrone, although it is a good drug, has limited activity, can be used only once in a lifetime, and has a less beneficial impact on MRI and parameters than does transplantation. On the other hand, we believe mortality can be reduced with transplantation if patients are properly selected, and finally, we must determine whether transplantation is superior or not, because we cannot go on using a treatment that is not superior and is known to be dangerous. The only way this can be determined is through a randomized trial.

Patients will be included in the trial if they are younger than 50 years and have no medical contraindication for transplantation (Table 3). From the neurological standpoint they must have progressing disease, with progression indicated by an EDSS score increase of at least 1 point during the year preceding enrollment. They must also have active disease visible on MRI as at least 1 gadolinium-enhancing lesion. Without positive MRI evidence, they must have more severe disease progression, indicated by an increase of more than 1 EDSS step over the previous year.

The treatments used for the control arm will be mitoxantrone 20 mg intravenously every month for 6 months and methylprednisone 1 g. For the transplantation arm, the conditioning

Table 3. Patient Selection: Autologous Stem Cell Transplantation International Multiple Sclerosis (ASTIMS) Trial

- Hematological aspects
 - Age < 50 y
 - No organ diseases, pregnancy, breastfeeding
 - No mental dysfunction
 - No previous irradiation (total body irradiation, total lymphoid irradiation)
- Neurological aspects
 - Secondary progressive and relapsing-remitting MS with documented clinical worsening during the last year despite treatment
 - Active disease visible on magnetic resonance imaging scans

regimen will be the BEAM regimen (BCNU 300 mg/m² day -6, etoposide 200 mg/m² day -5 to day -2, araC 200 mg/m² day -1, melphalan 140 mg/m² day -1, cell infusion day 0), rabbit antithymocyte globulin at 7 mg/kg on days +1 and +2, and methylprednisolone 5 mg/kg on days -1, +1, and +2. Mobilization will be achieved with cyclophosphamide at 4 g/m² plus granulocyte colony-stimulating factor from day +5 on. Lymphocyte purging is not proposed because it increases toxicity, causes viral reactivation and increased risk of Epstein-Barr virus lymphoma, and has thus far shown no clear benefit.

The ASTIMS study will be coordinated by 3 committees, an executive committee to deal with practical problems and run the study, a steering committee to follow the study and propose improvements and amendments, and an external safety committee composed of investigators who are not involved with the study but will be kept informed by the chair of the trial and may propose the termination of the study if toxicity exceeds 5%, treatment-related mortality exceeds 5%, or clinical progression exceeds 30%.

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Is There Any Evidence of a Graft-versus-Autoimmunity Effect in Allogeneic Transplantation?

Alberto Marmont, MD

Allogeneic stem cell transplantation (SCT) may be considered to treat patients with extremely severe autoimmune diseases (SADs), not only diseases that are nonresponsive to conventional immunosuppressive therapy but also, in some cases, those for which treatment with autologous stem cell transplantation (SCT) has already failed [1]. As has been widely demonstrated in hematologic and also in some nonhematologic malignancies, conditioning treatment, whether myeloablative or not, is considered a platform for the subsequent graft-versus-malignancy effect operated by the donor's immune system. The vital question is whether this effect has also been seen in autoimmune diseases, and if so, can it be used in the admittedly rare, life-threatening SADs for which allogeneic SCT may be considered?

Evidence for a Graft-versus-Autoimmunity Effect

The evidence for a graft-versus-autoimmunity (GVA) effect comes from solid experimental experience and from some observational clinical studies (Table), including the demonstrated influence of GVHD in maintaining remission of SAD in coincidental diseases and the effect of donor lymphocyte infusions (DLI) in patients who have undergone allogeneic bone marrow transplantation for primary SADs. Landmark experiments in NOD mice have shown that nonlethal conditioning will not affect diabetes per se, but that

Evidence of a Graft-versus-Autoimmunity Effect in Allogeneic Transplantation.

Experimental

Landmark experiments in NOD mice

Regression of insulinitis following allogeneic stem cell transplantation

Clinical

Metaanalysis of 30 coincidental disease patients following allogeneic stem cell transplantation

Case reports in single coincidental disease patients

Primary autoimmune disease and graft-versus-host disease

Donor leukocyte infusion induced complete remission after relapse following allogeneic stem cell transplantation for primary hematologic autoimmune disease

the addition of donor marrow will not only prevent diabetes but will also cause regression of ongoing autoimmune insulinitis.

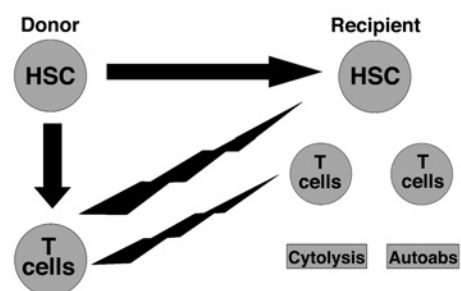
Evidence is much more meager in humans, and may be considered as level IV-V. In a retrospective analysis of 30 coincidental disease patients (coincidental meaning patients with autoimmune disease who have developed a hematologic malignancy requiring allotransplantation), those who had acute and/or chronic GVHD did not suffer relapse of their SAD, whereas relapses did occur in patients who were free of GVHD [2]. The difference was significant. In another retrospective analysis of 7 transplantation patients with psoriasis and leukemia, complete chimerism was followed by GVHD and long-term resolution of psoriasis (unpublished data).

In 3 patients, DLI were used to treat primary autoimmune disease that had relapsed after reduced-intensity conditioning (10 mg thiotepa and 100 mg cyclophosphamide/kg) and allotransplantation. All of these patients had very severe autoimmune hematologic disease; the first case was thrombocytopenia following Evans disease [3], the second relapsing pure red cell aplasia [4], and the third relapsing pure white cell aplasia (unpublished data). After a first remission, posttransplantation rejection and relapse occurred simultaneously. Complete chimerism and complete remission were achieved following a series of gradually incremental DLI.

Possible Mechanisms of GVA

If the GVA effect were to be further confirmed in clinical settings, what might be its mechanism? Two pathways may be theoretically envisaged, the first through a direct attack of donor T-cells on autoimmune clones and the second by the substitution of the recipient's immune system by the donor's (Figure). Will this prove to be all it takes to eradicate autoimmunity? With these procedures we are suppressing a delinquent immune system, but we are neglecting the reverse side of the coin, that the culprit is the autoantigenic drive. The latter's relevance has been elegantly demonstrated recently in thyroid autoimmunity, where thyroid ablation is followed by extinction of antithyroid antibodies [5]. Perhaps this mechanism is the reason why allo-SCT appears to be curative in hematologic autoimmunity, in which marrow/blood antigens and autoimmune clones are both removed.

A MODEL FOR GVA



A model of the graft-versus-autoimmunity (GVA) effect. HSC indicates hematopoietic stem cell; Autoabs, autoantibodies.

Conclusions

Allotransplantation for very severe refractory autoimmune disease is feasible and possibly curative. Nonmyeloablative technique is indicated to reduce transplantation-related mortality and morbidity and provide a platform for immunotherapy. The cases presented here give an idea of what is possible. A graded DLI approach is also indicated. DLI is effective for suppressing relapse and eradicating autoimmune clones. There is an increasing evidence for a GVA effect. Whether this effect is separable from GVHD remains to be determined.

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American Randomized Trial for Systemic Lupus Erythematosus

Ann Traynor, MD

We are beginning a multicenter National Institutes of Health–sponsored trial of hematopoietic stem cell transplantation (HSCT) treatment of systemic lupus erythematosus (SLE). This trial will involve a number of rheumatology and transplantation centers across the United States. The data that support our beginning a multicenter trial at this juncture are the result of stem cell transplantation procedures for lupus performed for more than 7 years predominantly at Northwestern University but also at selected other sites. At these centers over the course of the last 7 years, approximately 50 transplantations for severe refractory SLE have been performed without any transplantation-related mortality, and approximately 70% of those critically affected individuals have achieved sustained freedom from active disease, defined as lupus not requiring any treatment, including immune suppressive treatment. Single-arm data suggest that this procedure is safe and beneficial, with benefit being very carefully monitored prospectively by improvement in organ function.

Pulmonary Function

The organs critically affected by SLE, the lung, the brain, and the kidney, are affected to a greater extent and in a broader population of SLE patients than is often realized. The prospective monitoring of these organs in SLE-HSCT is not done to ensure that the individual has adequate pulmonary, renal, or cardiac function to safely undergo transplantation, but rather to have baseline data on the degree of organ system dysfunction prior to the transplantation procedure in order to accurately monitor the effect of the HSCT on diseased organ systems.

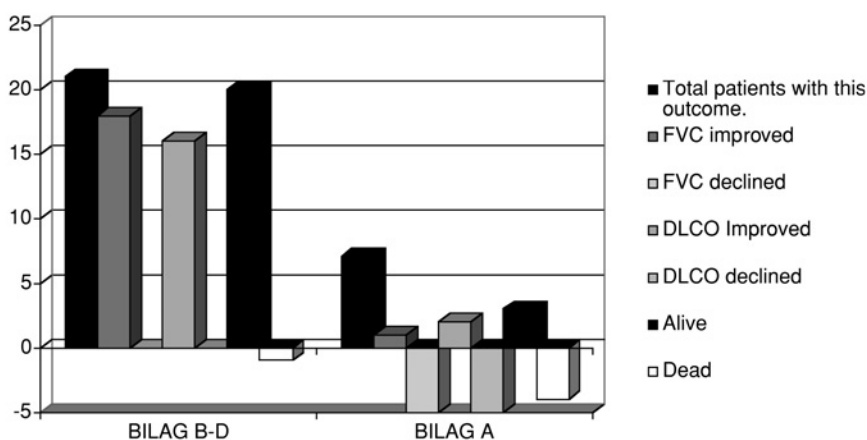
A number of patients underwent transplantation with a forced vital capacity significantly below what would normally be considered safe or reasonable for a transplantation candidate. Among these patients, who have now been followed for more than 7 years, a clear pattern is emerging. So far 7 of the approximately 40 patients treated at Northwestern and at the University of

Massachusetts did not obtain sustained remission from lupus post-HSCT, as indicated by a prolonged period free of any immune suppression. As a rule, at 1 year post-HSCT these individuals also failed to show significantly improved forced vital capacity and diffusion capacity of the lung. A deficit in pulmonary function at the outset of treatment by no means predicts the likelihood of remission or improvement in lung function. Patients with profound deficits in pulmonary function have experienced normalization and little toxicity from HSCT. In other words, individuals presenting with complaints of neurologic disease or renal disease often have had a diffusion capacity for carbon monoxide (DLCO) adjusted below 50% that was unknown to the patient or referring physician.

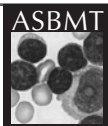
Improvement of DLCO values at 1 year post-HSCT turned out to be a very important predictor of long-term outcome. Only 1 of the 7 individuals who failed to achieve sustained freedom from SLE activity showed any improvement in forced vital capacity or DLCO. The other 6 did not, and some declined significantly. Four of the 7 patients who failed to gain sustained remission from SLE have since died, and the other 3 remain under treatment. In contrast, among those patients who experienced significant improvement in pulmonary

function, as the large majority of the transplantation patients did, all have sustained that improvement. There has been only 1 late death and no early deaths among the 20 patients who experienced sustained remission from SLE. In each of these patients, pulmonary function markedly improved, or stabilized if it had been normal pre-HSCT.

The significance of pulmonary function is shown in the Figure. On the left are those individuals who gained sustained remission in their lupus activity and achieved a prolonged status of British Isles Lupus Assessment Group disease activity index (BILAG) B through D. BILAG A patients, on the right, had a firm indication for treatment in the posttransplantation period. Of the initial 28 patients with prolonged follow-up, 21 had sustained freedom from any indication for immune suppression, and these 21 cases included individuals whose forced vital capacity improved and individuals whose DLCO improved or stabilized. In contrast, patients who did not have a sustained period of freedom from lupus had a very high risk of death. Among these patients, 1 patient showed a slight improvement in forced vital capacity whereas 6 showed a decline in forced vital capacity. There were 2 patients who had a transient improvement in diffusional capacity



Correlation of change in pulmonary function test results with sustained freedom from active systemic lupus erythematosus, or lack thereof, among 22 patients 15 to 77 months post-hematopoietic stem cell transplantation. Patients on the left gained sustained remission in their lupus activity and achieved a prolonged status of British Isles Lupus Assessment Group disease activity index (BILAG) B through D. Patients on the right were BILAG A status and had a firm indication for treatment in the posttransplantation period. FVC indicates forced vital capacity; DLCO, carbon monoxide diffusion capacity.



Phase III Multicenter Lupus Erythematosis Trial Study Design*

Treatment Arm	Control Arm
<ul style="list-style-type: none"> • CTX/G-CSF/autologous CD34⁺ hematopoietic stem cell mobilization • Transplantation regimen of CTX/ATG and G-CSF with Mesna and 3-way bladder irrigation • Follow subjects for 30 mo after treatment initiation 	<ul style="list-style-type: none"> • Cyclophosphamide 500-1000 mg/m² intravenously, monthly × 6 mo followed by: • Cyclophosphamide IV every 3 mo × 12 mo for a total of 11 pulses over 18 mo

*CTX indicates cytoxan; G-CSF, granulocyte colony-stimulating factor; ATG, antithymocyte globulin.

as opposed to 5 patients who had a decline. At the time of this report, 3 of these 7 who did not experience sustained freedom from lupus were alive, and 4 of 7 had died.

Kidney Function

The kidney is a complex organ, and we are still performing the subgroup analysis of long-term outcome relative to the chronicity/acuity of disease and the stability of the entering creatinine clearance. The vast majority of patients who had abnormal renal function, defined as less than 80 mL/min creatinine clearance, at the time of entry into this procedure have experienced marked and sustained improvements in their creatinine clearance. There were 2 patients who entered the study with impaired renal function, who went on to develop chronic renal failure (CRF) and dialysis dependence several years posttransplantation in spite of no active nephritis and no other signs of active SLE. Both of these patients have subsequently undergone organ transplantation 3 years post-HSCT and remain free of SLE activity. One patient with multisystem lupus who underwent HSCT failed to gain remission from SLE. He became dialysis dependent from active nephritis 18 months post-HSCT. This patient's lupus remained active for 5 years post-HSCT, and he received chemotherapy and glucocorticoids

on and off for those 5 years. He is now free of SLE symptoms and will undergo kidney transplantation this year. Two patients underwent HSCT for SLE after having been on dialysis for 2 years. Before undergoing HSCT each of these patients was unable to qualify to receive a donated kidney because of persistent active disease of other organ systems. One of these patients received a kidney a year post-HSCT for SLE and at the time of this report was doing well with no evidence of disease. The second patient never met criteria for remission post-HSCT. She remained on dialysis and experienced severe central nervous system and hemolytic symptoms leading to death 1 year post-HSCT. In all other patients improved renal function has occurred post-HSCT. Only a prospective comparison can tell us whether a less intensive regimen could have benefited the 2 patients who gradually experienced CRF posttransplantation. Both of these patients had received cyclophosphamide and mycophenolate prior to HSCT.

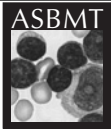
Neurocognitive Function

The most exciting aspect of this work, which is now prepublication, is the recovery of neurocognitive function. Improvement in neurocognitive function, like improvement in forced vital capacity, probably speaks for long-term survival in lupus. The majority of lupus

patients who undergo neurocognitive function testing show a particular pattern of neurocognitive deficits related to frontal amygdala and hippocampal dysfunction, memory and verbal loss, and loss of executive function. In the first 6 months to a year that we have had formal posttransplantation testing for these individuals, they have shown improvement in each of the areas of deficit. The majority of these patients, who have now been followed for 5 to 7 years, continue to show sustained and/or increased cognitive function in the posttransplantation period. We hope these data will become stronger with more prolonged follow-up testing in a larger number of patients.

Phase III Multicenter Trial

The study design as it currently exists for the phase III multicenter trial (Table) will involve an investigational arm incorporating a preparative regimen for the transplantation arm consisting of cyclophosphamide mobilization followed by cyclophosphamide/antithymocyte globulin and Mesna with 3-way bladder irrigation. The control arm will also be investigational in the sense that there is no proven treatment for refractory SLE. These individuals may be treated with 6 months of consecutive cytoxan followed by quarterly cytoxan for 1 year or a therapy more appropriate for their disease manifestations. Eligibility is for patients aged between 16 and 60 years whose disease meets 4 of 11 American College of Rheumatology criteria for the diagnosis of lupus, with at least 1 organ system indicating persistence of BILAG A or an indication for treatment. Categories include mucocutaneous disease, myositis, immune cytopenias, visceral and nonvisceral disease, or lupus nephritis, and in each instance the patient must have failed the specified standard treatment for that organ system.



Journal Watch

A scan of recent medical literature identified these articles of special importance in the science and clinical application of blood and marrow transplantation.

Blood and Marrow
TRANSPLANTATION

REVIEWS

Corradini P, Ladetto M, Zallio F, et al: Long-term follow-up of indolent lymphoma patients treated with high-dose sequential chemotherapy and autografting: evidence that durable molecular and clinical remission frequently can be attained only in follicular subtypes. *J Clin Oncol.* 2004;22:1460-1468.

The strategy of high-dose chemotherapy followed by stem-cell autografting has been relatively little used in patients with indolent forms of non-Hodgkin's lymphoma (NHL), such as small lymphocytic (SLL), follicular (FCL), and mantle-cell lymphoma (MCL). However, studies of molecular monitoring for minimal residual disease suggest possible benefits of intensified cytoreduction for indolent NHL. Long-term molecular and clinical outcomes of patients with indolent NHL treated with an intensified high-dose chemotherapy regimen were evaluated.

The study included 70 patients with indolent NHL: 40 with FCL, 16 with MCL, and 14 with SLL. All received intensified high-dose chemotherapy followed by autografting with peripheral blood progenitor cells. This regimen was given as first-line therapy in 61 of 70 patients, and as second-line therapy in the rest. Molecular follow-up was performed using a polymerase chain reaction (PCR) strategy, including the lymphoma-specific Bcl-1, Bcl-2, and immunoglobulin gene rearrangements. Eighty-six percent of patients had a molecular marker identified in diagnostic tissue specimens. At a median follow-up of 75 months, molecular and clinical outcomes were analyzed and prognostic factors evaluated.

Among patients with FCL, 54% had one or more collections of PCR-negative cells, compared to just 25% of patients with either MCL or SLL. Molecular remission was achieved after transplantation in 70% of patients with FCL, compared to 12.5% of those with SLL or MCL.

Patients who achieved durable molecular remission had a relapse rate of 8%, compared with 88% for patients not attaining molecular remission. At last follow-up, 20 of 26 patients with FCL were long-term survivors with no evidence of clinical or molecular disease, compared to only 6 of 30 patients with SLL or MCL.

For patients with FCL, a strategy of intensive chemotherapy and autografting is associated with good molecular and clinical responses, including a high rate of long-term, disease-free survival. In contrast, patients with other subtypes of indolent NHL have a lower molecular response rate, associated with a higher risk of relapse. For patients undergoing

autologous transplantation, achievement of a negative PCR is a strong predictor of prolonged disease-free survival.

Gluckman E, Rocha V, Arcese W, et al: Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. *Exp Hematol.* 2004;32:397-407.

Unrelated cord blood transplantation (UCBT) has provided a new alternative for treatment of hematologic malignancies. Survival appears similar to that of bone marrow transplantation; engraftment is delayed but graft vs host disease is reduced. Further outcome improvements might be possible by steps to optimize selection of cord blood donors—eg, based on graft cell content and human leukocyte antigen (HLA) disparities. The effects of these and other donor-related factors on the outcomes of UCBT were analyzed.

The study included 550 UCBTs reported to the Eurocord Registry of the European Blood and Marrow Transplant Group. The characteristics of cord blood units were analyzed as predictors of clinical outcomes in univariate and multivariate analyses, including center and time period effects.

Approximately two-thirds of the patients were children aged 15 years or younger; most patients had acute myeloid or acute lymphoblastic leukemia. More than 80% had intermediate or advanced disease at the time of UCBT. The 60-day cumulative incidence (CI) of neutrophil recovery was 74.0%, with a 19.1% CI of grade III or higher acute graft vs host disease. Overall survival at 12 months was 40.8%, with a 25.9% CI of chronic graft vs host disease.

Number of HLA disparities had a significant influence on outcome, as was nucleated cell dose before freezing. Both of these factors, along with use of granulocyte colony-stimulating factor, were associated with the CIs of neutrophil and platelet recovery. Patients whose transplants were characterized by coexisting HLA class I and II disparities and a high CD34 cell dose had elevated rates of grade III to IV graft vs host disease. A higher number of HLA disparities was associated with a lower CI of relapse, consistent with a graft vs leukemia or graft vs tumor effect in HLA-mismatched UCBTs.

At 3 years, overall survival was 34.4%. The chances of survival were affected by patient age, sex, and disease status, but not by cell dose or number and type of HLA disparities.

This registry study finds that cell content and HLA may be useful in selecting cord blood units for transplantation. The chances of engraftment are greater for units with a higher number of cells and a lower num-

ber of HLA disparities. Cord blood units with a higher number of HLA disparities are associated with a higher rate of severe acute graft vs host disease but a lower risk of relapse.

Milpied N, Deconnick E, Gaillard F, et al: Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. *N Engl J Med.* 2004;350:1287-1295.

Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is the standard initial treatment for adult disseminated aggressive lymphoma. Several trials have reported good outcomes in patients receiving high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation, although this approach has yet to be directly compared with CHOP. A randomized, controlled trial of CHOP vs high-dose chemotherapy with autologous stem cell support for initial treatment of disseminated aggressive lymphoma is reported.

The study included 207 consecutive patients, aged 15 to 60 years, with previously untreated, disseminated aggressive lymphoma. All had no more than two adverse prognostic factors, based on the age-adjusted International Prognostic Index. Of these, 197 were randomized to receive initial treatment with eight courses of CHOP or with high-dose chemotherapy plus autologous stem cell support. The patients were followed up for a median of 4 years.

Treatment completion rate was 78%: 72% in the CHOP group and 85% in the high-dose therapy group. Estimated 5-year event-free survival was 37% among patients receiving CHOP, compared with 55% for those receiving high-dose chemotherapy with stem cell support. For patients at "high intermediate" risk of death, 5-year survival was 44% with CHOP vs 74% with high-dose therapy. For low- or low intermediate-risk patients, event-free survival was similar between groups.

Overall 5-year survival was similar between groups—56% with CHOP and 71% with high-dose therapy—likely reflecting the effectiveness of salvage therapy. For CHOP nonresponders, 5-year survival was just 26%.

For adults with disseminated aggressive lymphoma and no more than two adverse prognostic factors, high-dose chemotherapy with stem cell support provides better event-free survival than CHOP therapy. The authors believe that CHOP should no longer be considered the standard for initial therapy of disseminated aggressive lymphoma in adults.

Stem Cell Therapy for Autoimmune Disease

CME Assessment Test

- Which of the following is true regarding SCT treatment for autoimmune diseases?
 - This treatment has been shown to be effective in patients with inflammatory early-stage MS but may not be helpful in patients with late progressive MS.
 - Development of these treatments has been adversely impacted by data indicating that transplantation-related mortality within the first year may be as high as 8% to 20%.
 - SLE patients accepted as HSCT candidates are those who have an extremely high mortality risk from the disease.
 - All of the above.
- Which of the following is true regarding autologous transplantation treatment for autoimmune diseases?
 - Organ dysfunction, which would be a contraindication for transplantation in patients being treated for malignancies, is often the indication for autologous transplantation.
 - Patients with inflammatory autoimmune disease are not good candidates for autologous transplantation.
 - The goal of autologous transplantation in these patients is to destroy the stem cell compartment but minimize immune suppression, so nonmyeloablative regimens are not indicated.
 - All of the above.
- Which of the following occurred in initial trials of autologous bone marrow transplantation treatment for scleroderma?
 - The results of these trials had no effect on criteria used to select candidates for transplantation treatment.
 - The transplantation-related mortality was acceptably low.
 - A high mortality rate was directly linked to the underestimation of organ involvement during pretransplantation evaluation.
 - All of the above.
- Which of the following is true regarding autologous bone marrow transplantation treatment for scleroderma?
 - Patients with pulmonary hypertension with pulmonary artery pressure above 50 mm Hg or a DLCO below 40% are not good candidates for transplantation treatment.
 - Patients with an ejection fraction below 50% on cardiac echography or on MUGA are not good candidates for transplantation treatment.
 - Disease progression may occur in approximately one third of all patients after the transplantation procedure.
 - All of the above.
- Which of the following is true regarding experimental development of transplantation treatment of MS?
 - According to animal studies, the timing of transplantation is not important.
 - In the animal model, both remission and relapse rates were low.
 - In the first MS patients treated with transplantation, the most prominent effect, observed with MRI, was almost complete suppression of brain inflammation.
 - All of the above.
- Which of the following is true of transplantation treatment of MS?
 - Transplantation seems to delay disease progression, especially in patients with secondary MS and in young patients with low disability scores.
 - Brain atrophy reflecting axonal degeneration, neuronal degradation, and irreversible disability was found to continue in all studies.
 - The ASTIMS trial will compare transplantation to mitoxantrone in treating cases of severe, secondary-progressive, and relapsing-remitting MS for which traditional therapy has failed.
 - All of the above.
- Which of the following is true regarding HSCT treatment of SLE?
 - At transplantation centers over the last 7 years, approximately 70% of the critically affected SLE patients who have undergone HSCT have achieved sustained freedom from active disease.
 - Some SLE-HSCT patients have been followed for 5 to 7 years and have continued to show sustained and/or increased cognitive function in the post-transplantation period.
 - In SLE-HSCT candidates, prospective monitoring of the organs critically affected by SLE, the lung, the brain, and the kidney, is not done to ensure that the individual has adequate function to safely undergo transplantation, but rather to assess the degree of organ system dysfunction in order to accurately monitor the effect of the HSCT on diseased organ systems.
 - All of the above.
- Which of the following is true regarding pulmonary function in SLE patients undergoing HSCT treatment?
 - Improvement of DLCO at 1 year post-HSCT has been found to be an important predictor of long-term outcome.
 - SLE patients with forced vital capacity significantly below what would normally be considered safe or reasonable for a transplantation have never been selected to undergo HSCT for SLE.
 - A deficit in pulmonary function in SLE patients at the outset of HSCT treatment is a strong predictor of low probability for remission or improvement in lung function.
 - All of the above.
- Which of the following is true regarding evidence for a graft-versus-autoimmunity effect in allogeneic SCT used to treat patients with extremely severe autoimmune diseases (SADs)?
 - Allogeneic SCT cannot be used to treat SAD patients for which treatment with autologous SCT has already failed.
 - Complete chimerism and complete remission have been achieved following a series of gradually incremental DLI in patients with very severe primary autoimmune disease that had relapsed after reduced intensity conditioning and allotransplantation.
 - In an analysis of 30 patients with autoimmune disease who developed a hematological malignancy requiring allotransplantation, relapses of SAD occurred in patients who had acute and/or chronic GVHD, whereas relapses did not occur in patients who were free of GVHD.
 - All of the above.
- Which of the following is a possible mechanism of the graft-versus autoimmunity effect?
 - A direct attack of donor T-cells on autoimmune clones.
 - Substitution of the recipient's immune system by the donor's.
 - A and B.
 - None of the above.

CME Assessment Test Answer Sheet

Release Date: August 29, 2004

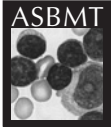
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Instructions

(1) Read the articles in the supplement carefully. (2) Circle the correct response to each question on the Answer Sheet. (3) Complete the evaluation Form. (4) To receive CME credit, fax the completed Answer Sheet and Evaluation Form to the MCW CME office (414-456-6623) or mail to the Office of Continuing Education, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. No processing fee is required.

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| 2. | A | B | C | D | 6. | A | B | C | D | 9. | A | B | C | D |
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