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Special report

The promise of hematopoietic stem cell transplantation for autoimmune diseases

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Summary:

Hematopoietic stem cell transplantation (HSCT) is being increasingly utilized for the treatment of a whole spectrum of severe autoimmune diseases refractory to conventional therapy. Although allogeneic HSCT has been followed by durable complete remission in a restricted number of patients with coincidental disease, the autologous procedure is generally preferred because of its lesser toxicity. Most autoimmune diseases are the consequence of a multistep process, mainly originating from the interplay of genetic, environmental, and hormonal factors. It has been postulated that if immunosuppressive regimens can eliminate or effectively reduce the level of autoreactive T and B cells, then regeneration of *de novo* immunity even in the autologous setting may bypass the initial breakdown of self-tolerance and ensure prolonged disease remission. As mentioned in a recent review of this field, protocol design including conditioning regimen, patient selection, stem cell source and final outcome are likely to be disease-specific. The following is a summary of the 2002 International Bone Marrow Transplantation Registry/ American Society of Blood and Bone Marrow Transplantation (IBMTR/ASBMT) satellite symposium in Orlando, Florida on 24 February 2002 on 'Expanding the Promise of Hematopoietic Stem Cell Transplantation in Autoimmune Diseases'.
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Systemic lupus erythematosus (*Ann Traynor, Northwestern University, Chicago, IL*)

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with variable and multisystem involvement and easily identified autoantibodies, such as antinuclear antibodies (ANAs) and antidouble stranded DNA (anti-ds DNA). The introduction, in the 1980s, of monthly intravenous cyclophosphamide (500–1000 mg/m^2) had a significant impact on SLE-related morbidity and mortality. Nevertheless, overall lupus-related mortality is 1% per year and high-risk patients have a 5-year mortality of 35%. The next major advance in treating lupus may have occurred when cyclophosphamide was dose escalated to highly immune-suppressive transplant doses of 200 mg/kg and combined with antithymocyte globulin (ATG) and hematopoietic stem cell reinfusion, beginning in 1996.[1–3]

Patients were selected for active disease refractory to monthly intravenous cyclophosphamide. Ongoing visceral organ dysfunction, provided it was secondary to active SLE, was an indication for hematopoietic stem cell transplantation (HSCT). Therefore, patients were generally heavily pretreated, corticosteroid-dependent for years, Cushingoid, and severely ill. Some patients required supplemental oxygen while others were on dialysis at the time of entry.

At Northwestern University, a total of 18 patients have been treated and 12 are beyond 1 year following HSCT. No patient died as a consequence of transplantation. Since candidates were highly immune-suppressed prior to study entry, aggressive antimicrobial prophylaxis, including lipid amphotericin formulations, were undertaken during periods of neutropenia regardless of fever. Treatment-related complications were initially higher in patients with nephritis predominately caused by electrolyte disturbances, fluid shifts, and volume overload leading to pulmonary edema and intubation. Subsequently, for patients with nephritis, early initiation of dialysis or ultrafiltration to maintain dry weight prevented pulmonary edema and intubation. Somewhat surprisingly, patients without nephritis who were oxygen-dependent either because of pulmonary interstitial fibrosis or pulmonary hemorrhage had few transplant-related complications.

Following HSCT, patients gradually improved and were slowly weaned off corticosteroids. By 12–18 months after HSCT, patients are corticosteroid free, often for the first time since disease onset that occurred years or a decade or more earlier.[3] Of the 18 patients undergoing HSCT, only two have had a clinical relapse of active disease occurring at 3 and 4 years, respectively. This phase I/II trial, which began 5 years ago, has provided the data and impetus for a

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randomized phase III trial of HSCT *vs* pulse cyclophosphamide in patients with less severe disease at the time of entry.[4]

Crohn's disease (*Robert Craig, Northwestern University, Chicago, IL*)

Although immunologic derangements have been described in Crohn's disease, it is still not perfectly clear that Crohn's disease is an autoimmune disease. Nevertheless, it is clear that immunologic processes are engaged in the pathophysiology of this disease, whether or not autoimmunity is the underlying process.

Treatments for Crohn's disease include: local anti-inflammatory agents such as 5-aminosalicylic acid (5-ASA) products, broad immune suppression such as corticosteroids, cytokine suppression such as the antibody to TNFα, and antibiotics such as ciprofloxacin and metronidazole that might work by decreasing the putative antigen exposure. Any of these treatments for Crohn's disease or any autoimmune disease are designed to suppress inflammation until a spontaneous remission ensues.

Crohn's disease has serious morbidity including fistulae, abscesses, eye manifestations, skin illnesses, arthritis, hepatobiliary complications, the need for recurrent surgery, severe abdominal pain with drug addiction, and eventually a short bowel syndrome after multiple operations requiring home parenteral nutrition. There is little in the literature available on mortality data related to Crohn's disease, but a large series by Farmer *et al*[5] showed a 6% mortality attributed to Crohn's disease. The mortality rate in selected patients, such as those we shall be studying, is probably higher, in the range of 10%. The subjects eligible for HSCT are patients with severe Crohn's disease defined as a Crohn's disease activity index (CDAI) between 250 and 400 (remission <100).[6] Each patient has to have failed high-dose corticosteroids, 5-ASA, metronidazole, azathioprine, and infliximab. In addition, each disease must be severe enough to be considered for surgical excision.

At Northwestern University, two patients with severe Crohn's disease (CDAI >250) refractory to TNFα inhibitors have undergone autologous HSCT. Patients' stem cells were mobilized by administration of cyclophosphamide 2 g/m^2 intravenously and G-CSF. The conditioning regimen was cyclophosphanide (200 mg/kg) and ATG, similar to the regimen used for HSCT of SLE. Each had continuous disease for 6 and 10 years, respectively. Following HSCT both patients are in remission (CDAI <100) and asymptomatic.

Multiple sclerosis (*Richard Burt, Northwestern University, Chicago, Ill*)

There are several types of multiple sclerosis (MS). Relapsing remitting disease (RRMS) has acute relapses with or without residual neurologic deficits between relapses. Progressive disease is characterized by insidious and gradual neurologic deterioration whether or not acute relapses are present. Secondary progressive MS (SPMS) is disease with a progressive course after an initial relapsing remitting presentation. Primary progressive MS (PPMS) is progressive disease from onset. Most cases of MS, approximately 85%, begin as RRMS and over 15 and 30 years, 50 and 85%, respectively, become secondary progressive.

In RRMS, relapses are associated with signs of active inflammation on MRI and are thought to be autoimmune-mediated. In SPMS and PPMS, the insidious accumulation of persistent neurological impairment is thought to be related to axonal degeneration. Therefore, MS appears to be both an immune-mediated demyelinating as well as an axonal degenerative disease.[7–9] It is unknown whether immune-mediated demyelination predisposes to axonal degeneration or if axonal injury is at least partially independent of demyelination. Not surprisingly, RRMS is more responsive to immune-suppressive therapies than either primary or secondary progressive disease. Experimental autoimmune encephalomyelitis, an animal model of MS, may be cured if HSCT is performed early after onset but not if performed in animals with chronic disease.[10] It, therefore, seems that therapies such as HSCT that are aimed at the immune-mediated pathogenesis would be most effective in RRMS.

Instead of treating patients with relapsing disease, initial phase I safety trials were designed to enroll patients with progressive disease and high disability scores. In the Northwestern/Milwaukee trial, 28 patients have undergone HSCT with no significant transplant-related morbidity or mortality.[11–13] The regimen used was cyclophosphamide (120 mg/kg) and total body irradiation (TBI) (1200 cGy divided 120 cGy BID with 50% lung shielding) and CD34$^+$ and selection of the graft. Except for two cases of dermatomal zoster, no late opportunistic infections have occurred. The longest post-transplant follow-up is 5 and 1/2 years with 20 patients beyond 1 year. However, other centers that combined CD34$^+$ selection with more aggressive regimens such as cyclophosphamide/TBI/ATG or busulfan/cyclophosphamide/ATG have reported lethal opportunistic infections.[14,15] These phase I trials, therefore, indicate caution in combining aggressive immune-suppressive regimens with lymphocyte-depleted grafts.

Fever in patients with MS may cause neurologic deterioration,[16] called psuedoexacerbation and should be minimized by avoiding drugs that may cause fever and early prophylactic antimicrobial coverage to prevent infection-related fevers. Engraftment may also be associated with a rash, fever and increased fatigue, termed engraftment syndrome, which resolves spontaneously or with corticosteroids.[16] These phase I studies have provided the ground work for phase II/III trials targeting patients with relapsing disease and lower disability scores. Due to concern over the effect, if any, of radiation on damaged neurons, neuronal and oligodendrocyte, regeneration and radiation-induced late malignancies, future Northwestern University HSCT trials will utilize a non-TBI regimen of cyclophosphamide +/– ATG.

Stem cell therapy for severe autoimmune diseases: future directions (*Alberto Marmont, Centro Trapianti di Midollo Osseo, Azienda Ospedaliera S. Martino, Genoa, Italy*)

There are now three new aggressive approaches for the treatment of severe autoimmune diseases of the refractory (relapsing) life-threatening subtype. High-dose cyclophosphamide with no stem cell rescue has been attended by encouraging results in the Johns Hopkins single center experience.[17] However, intense immunosuppression is most generally followed by the infusion of hematopoietic stem and progenitor cells included in the CD34 selected compartment. Autologous HSCT, which originated from animal experiments,[10,18] is being utilized worldwide because of the procedure's greater safety, although transplant-related mortality (TRM) in registry data has been higher (8.6%) than initially anticipated (1–3%).[19] However some centers, including Northwestern University that has transplanted more than 70 autoimmune patients, have had no TRM. Possible reasons for center differences in TRM include: diseases transplanted, selection or exclusion criteria, and intensity of immune-suppressive preparative regimens when combined with $CD34^+$ selection of the graft.

It is still uncertain whether the mechanism of action is essentially immunosuppressive, or whether lymphoid reconstitution following mobilization plus conditioning may ensure the emergence of a tolerant immune system *vis-à-vis* the same autoantigens that had caused the autoimmune process.[1,20] Be that as it may, clinical results are encouraging and even dramatic in properly selected patients. Some of the best results are being obtained in SLE, juvenile idiopathic arthritis, Crohn's disease, and in active MS, where the abrogation of all gadolinium-enhancing lesions has been reported on serial post-transplant MRIs.[21] Complete remissions have been reported following syngeneic transplants in cases of severe rheumatoid arthritis[22] and, quite recently, of chronic refractory (splenectomized) autoimmune thrombocytopenic purpura.[23] A prolonged follow-up of these cases might offer information on the role of autoantigenic rechallenge. From the initial phase I/II clinical studies, randomized phase III trials are currently evolving in Europe, including in scleroderma, the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, in MS, the ASTIMS trial and in rheumatoid arthritis, the ASTIRA trial. In America, phase III studies funded by the National Institutes of Health for MS, SLE, and scleroderma are in development.[4,24]

Nonmyeloablative allogeneic HLA-matched transplants are being discussed not only because of their limiting effects on conditioning regimen-related mortality but also because a graft-versus-autoimmunity (GVA) effect has been suggested in experimental autoimmune diseases and may also be present in humans.[25,26] This is reminiscent of an allogeneic graft-versus-leukemia (GVL) effect. There are now two documented case reports of nonmyeloablative allogeneic transplants for Evans syndrome in which complete clinical and immunologic remissions appeared following graft-versus-host disease (GVHD), in one case elicited by donor lymphocyte infusions (DLI).[27,28]

Separating GVH from GVA appears as hard to achieve as GVH from GVL. Superimposing GVH to a patient with a severe autoimmune disease is not a good proposition for the patient, but to harness GVA in order to eradicate the last autoimmune lymphoid clones would seem a reasonable objective in the not-too-distant future. Will this be all that it takes to cure autoimmune diseases, which are a combination of pathogenic immune autoreactivity and multiple (auto) antigenic challenges? The answer to this fundamental question will be found only by a continuous and hopefully fruitful cooperation between basic and clinical investigators.

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