BMT for Severe Autoimmune Diseases: An Idea Whose Time Has Come

Studies of hematopoietic stem-cell transplantation as a treatment for severe autoimmune diseases (SADS) are currently in progress. Dr. Burt thoroughly reviews the rationale for these studies. It includes: (1) preclinical studies showing that marrow transplantation is an effective therapy in animal models of autoimmune disease; (2) observations of the effect of stem-cell grafts on SADS in patients transplanted for other indications; and (3) improvements in the safety of the transplant procedure.

As shown in the author's Table 1, the primary diseases for which hematopoietic stem-cell transplantation is being considered for study include multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). While often varying in severity, autoimmune disorders may result in severe organ dysfunction, poor quality of life, and markedly shortened life expectancy in some patients. Each of these diseases predominantly affects young individuals. The goal of the initial studies is to establish whether stem-cell transplantation has an acceptable level of safety in patients with SADS and a beneficial effect on disease progression.

Selection of Autoimmune Diseases for Initial Studies

The criteria for defining such diseases as MS, RA, SLE, and SSc as autoimmune in origin have been discussed in Burt's article and elsewhere.[1] All four of these diseases are potentially severe and have limited proven therapeutic approaches, none of which is considered to be curative. Burt nicely summarizes the prognostic criteria for MS, RA, and SLE, as well as the potential criteria for selecting patients with these diseases for stem-cell transplantation. He also provides a comprehensive discussion of the evaluation of MS severity.

Less compelling cases can be made for developing studies of hematopoietic stem-cell transplantation for the other autoimmune diseases discussed in the article because of their rarity or the effectiveness of existing treatments. However, once proof-of-principle is established in the current studies of SADS, these other autoimmune diseases should be considered.

At the Fred Hutchinson Cancer Research Center, we have focused our initial studies of stem-cell transplantation for SADS on patients with severe SSc. Systemic sclerosis is a disease in which the skin, lungs, heart, gastrointestinal tract, and kidneys are major targets for progressive and often relentless fibrosis. Diffuse cutaneous SSc, the more severe form of this disease, is associated with Raynaud's phenomenon, both truncal and acral skin involvement, tendon friction rubs, an early and significant incidence of interstitial lung disease, renal failure, diffuse gastrointestinal disease, and myocardial involvement. The anticentromere antibody is usually absent in severe disease, and 40% to 60% of patients are positive for scleroderma-70 (SCL-70; specific for topoisomerase 1). Organ failure may occur early in the disease course, and mortality in the most severely affected patients is 45% by 5 years--a death rate similar to that of patients with chronic myelogenous leukemia in chronic phase.

Systemic sclerosis is a disease for which conventional immunosuppressive treatment has not been proven to prevent disease progression. Prognostic criteria that define a poor outcome are available, and patients can be selected for experimental treatment who have a poor prognosis and yet have sufficient organ function to tolerate the procedure. Although it is possible that some improvement in organ function may be seen once the autoimmune activity is ablated, it is unlikely that this will be substantial if there is extensive preexisting damage. Thus, it is desirable to perform the transplant early in the disease course.
Source of Hematopoietic Stem Cells: Autologous or Allogeneic?

**Autologous**—Although the efficacy of transplanting autologous, syngeneic, and allogeneic stem cells has been demonstrated in animal studies of autoimmune disease, these studies also have indicated that allogeneic transplantation is likely to be more effective than autologous transplantation. In the limited number of clinical cases reported to date, high-dose cytotoxic therapy followed by transplantation with unmodified autologous hematopoietic stem cells was not curative, although transient remissions were noted.[2] Recurrence of disease in these cases may have resulted from the infusion of autoreactive effector lymphocytes with the autologous graft. T-cell depletion of autografts may contribute substantially to control of the autoimmune disease, and clearly this approach needs to be investigated.

Many of the proposed or current studies involve a form of T-cell depletion by CD34+ selection. The efficiency of T-cell depletion varies depending on the type of methodology used for selection of CD34+ cells. A second depletion step may be required for highly efficient removal of T-cells from the stem-cell grafts. The use of T-cell-depleted autologous grafts after myeloablative therapy may result in a more prolonged immunodeficient state than is usually observed after autografting. Studies of immune reconstitution will be important after transplantation with T-cell-depleted autologous grafts. If a benefit is observed, it will be necessary to differentiate between (1) prolonged nonspecific suppression of the immune system and (2) modulation of a component of the immune system responsible for the autoimmune activity.

A report has been published of a patient with SSc who received high-dose cyclophosphamide (Cytoxan, Neosar) and then was infused with peripheral blood stem cells that had been CD34+-selected on a Ceprate R column and T-cell-depleted with a CD3-specific monoclonal antibody.[3] At 6 months after treatment, some clinical improvement was noted, as well as reduction in the titers of antinuclear antibody and SCL-70. This initial improvement observed in one of the first patients undergoing high-dose chemotherapy and autologous stem-cell support for SSc is encouraging, but further follow-up is required.

Some of the other protocols outlined in Table 1 of the Burt article are giving high-dose cyclophosphamide for immunosuppression, as well as antithymocyte globulin for in vivo T-cell depletion. Although myelosuppressive, high-dose cyclophosphamide may not require support with autologous peripheral blood stem cells.[4-6] High-dose cyclophosphamide without the infusion of autologous stem cells may be more effective since it poses no risk of infusing autoreactive effector lymphocytes. Even though this approach fails to test the hypothesis that myeloablative and immunosuppressive therapy of sufficient intensity to require stem-cell support may be beneficial in the management of SADS, it is reasonable to explore the efficacy of high-dose cyclophosphamide in the hope that more aggressive approaches may not be necessary.

The European Group for Blood and Marrow Transplantation and the European League Against Rheumatism recently recommended that only studies of autologous transplantation should be conducted initially because of the high mortality associated with allogeneic transplantation. However, as Burt notes, patients treated with autologous grafts still have an expected mortality of 1% to 10%. There is also a risk of a myelodysplastic syndrome developing after myeloablative therapy and autologous transplantation.[7] Patients who have already received extensive alkylating agent therapy prior to transplantation are at increased risk of this complication. The risk may be lower in patients receiving treatment with high-dose cyclophosphamide alone.

**Allogeneic**—Allogeneic or syngeneic hematopoietic stem-cell transplantation may be more effective than autologous transplantation because allogeneic or syngeneic grafts are not contaminated by autoreactive effector lymphocytes that may perpetuate the disease. Moreover, the graft-vs-host effect associated with the infusion of allogeneic donor lymphocytes may suppress host lymphopoiesis, including the production of autoreactive effector lymphocytes. A major impediment to the use of allogeneic stem-cell transplantation is the potential for significant morbidity and high mortality. However, mortality has decreased significantly after allogeneic transplantation as supportive care has improved.[8,9] Survival at 3 years after transplantation of allogeneic grafts from HLA-matched siblings is greater than 90% for patients with aplastic anemia and greater than 80% to 85% for patients with chronic myelogenous leukemia in chronic phase.[10,11]

In general, patients have been considered for allogeneic marrow transplantation if there are data showing poor survival with conventional treatment and if there is a reasonable expectation that the disease can be cured. Preservation of critical organ (eg, central nervous system) function may be an equally compelling indication for transplant. Patients should not be considered for allogeneic transplantation if they have markedly advanced disease with significant organ dysfunction, which...
might unduly increase the risk of transplant-related complications. Transplantation early in the disease course improves outcome in several diseases for which transplantation is indicated. Intuitively, this would also appear to be true for those patients with SADS who are being considered for marrow transplantation since organ dysfunction may increase the risk of toxicity from the conditioning regimen and also compromise the administration of prophylaxis for graft-vs-host disease (GVHD).

Approaches are being investigated to minimize the risk of transplant-related mortality from the myeloablative therapy necessary to establish an allogeneic graft or from complications related to GVHD. The establishment of substantial mixed hematopoietic chimerism in a large outbred dog model can be achieved after low-dose cytotoxic therapy without prolonged periods of pancytopenia.[12] A state of donor-host allogeneic tolerance has been noted in these dogs, which are mixed chimeras.

If this preclinical study proves to be predictive of what can be achieved in humans, mixed chimeric states might be induced in patients with minimal risks from the transplant procedure. The induction of mixed hematopoietic chimerism alone may provide some relief from the autoimmune disease. If not, it will be the first step in establishing full donor chimerism by infusion of donor lymphocytes, potentially eradicating autoreactive host lymphocytes.

Conclusions
Current management of many SADS is suboptimal in preventing progression and loss of organ function or life in some patients. Studies of hematopoietic stem-cell transplantation after myeloablative therapy or high-dose cyclophosphamide represent an exciting step that holds promise for the treatment of poor-prognosis patients with SADS.

Substantial improvements have occurred in the supportive care of patients after both autologous and allogeneic transplantation. However, there may be unanticipated problems in patients with SADS that could increase the risk of the procedure. To expedite the accrual of patients and the completion of studies, investigations of hematopoietic stem-cell transplantation in SADS should be carefully performed in a limited number of centers by multidisciplinary teams, until the safety and efficacy of this procedure are proven. These multidisciplinary teams should include experts in the autoimmune disease under study and a transplant team with a high degree of experience.

References:
9. Chao NJ, Schmidt GM, Niland JC, et al: Cyclosporine, methotrexate, and prednisone compared with


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