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Allogeneic stem cell transplantation for autoimmune diseases: nonmyeloablative conditioning regimens

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Summary:

Hematopoietic stem cell transplantation (HSCT) for autoimmune diseases have been, because of safety reasons, overwhelmingly autologous. Results are, in general, encouraging with improvement in quality of life, a remission of up to several years, and perhaps in some diseases improved survival. This indicates that further study of autologous HSCT especially under phase III design is warranted. However, the ultimate goal of HSCT is cure of otherwise incurable autoimmune diseases. For this reason, allogeneic HSCT in carefully selected high-risk patients with autoimmune diseases using strategies to minimize both regimen-related toxicity and graft-versus-host disease (GVHD) is ongoing at Northwestern University and will be reviewed briefly.
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There have been several case reports that have documented remission of coexistent autoimmune diseases following allogeneic hematopoietic stem cell transplantation (HSCT) for hematological malignancy or aplastic anemia that are reviewed in the paper by Nash in this supplement. HLA-matched allogenic HSCT may cure an autoimmune disorder by transferring numerous non-HLA autoimmune disease-resistant genes to the donor. Alternatively, the donor's lymphocytes could also eliminate residual host hematopoietic and immune cells resulting in true chimerism, a phenomena in autoimmune diseases that has been termed graft *vs* autoimmunity (GVA).[1–2]

Mixed chimerism

In cancer, mixed chimerism is associated with the persistence of malignant clones and disease relapse. However, the concept of mixed chimerism may be beneficial in ameliorating autoimmune disorders. Mixed chimerism, that is, both recipient and donor hematopoiesis, induces remission of diabetes and lupus-like autoimmune diseases in animal models.[3–8] A clinical, phase I trial under US FDA IND is ongoing to determine if mixed chimerism gives durable remissions of rheumatoid arthritis. Approximately one-half of patients with rheumatoid arthritis stop working within 10 years, and 90% will stop within 30 years. Lost earnings are substantial. According to one estimate, 6.5 billion dollars are lost annually. Those patients with the most severe rheumatoid arthritis, involving greater than 20 joints, and/or the greatest limitation of daily activities are at the greatest risk for increased mortality, approximately 40–60% within 5 years.[9–11] While these patients do not die from active synovitis *per se*, they die of complications from disability, immune suppression, immobilization, infections, cardiovascular disease, renal failure, cervical myelopathy, and hip fractures.[11]

Owing to the older age of rheumatoid arthritis patients a nonmyeloablative stem cell transplant (NST) regimen, is used to minimize regimen-related toxicity (RRT). Again due to older age, in order to minimize the risk of graft-versus-host disease (GVHD), the donor graft is lymphocyte depleted. The goal of this approach is stable mixed chimerism. Candidates must have severe and refractory rheumatoid arthritis despite infliximab, methotrexate, and leflunomide defined as more than 12 swollen and 20 involved joints (Table 1). A rheumatoid factor negative HLA-matched sibling must be available as donor. The conditioning regimen is fludarabine (125 mg/m^2), cyclophosphamide (150 mg/kg), and CAMPATH (20 mg). The donor graft is CD34$^+$ selected (Isolex, Baxter) with a goal of >10 million CD34$^+$ cells/kg.

A 52-year-old woman, who failed a prior autologous HSCT 4 years earlier and subsequently failed infliximab, methotrexate, leflunomide, prednisone, and oral cytoxan, underwent NST with 8 million CD34$^+$ donor cells/kg. Engraftment occurred on day 11. She has been platelet and RBC transfusion independent since day 14. At day 30, hematopoiesis is 98% donor without GVHD or infections. Rheumatoid symptoms have resolved. Tender and swollen joint count are zero and morning stiffness has disappeared. Ongoing infection prohylaxis includes oral cytovene, vorconazole, and aerosolized pentamidine. GVHD and graft rejection prohylaxis is subtherapeutic low-dose mycophenolate mofetil (500 mg oral bid). While still early

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Table 1 Eligibility of patients with rheumatoid arthritis for allogeneic NST

1. Less than age 60 at time of pretransplant evaluation
2. An established clinical diagnosis of rheumatoid arthritis by American College of Rheumatology criteria
3. Patients must have failed an autologous hematopoietic transplant or have failed to respond to either methotrexate or leflunomide in combination with a TNF inhibitor. Failure is defined as at least 12 swollen joints and either 20 involved joints or inability to answer at least 70% of HAQ questions with 'no difficulty' despite 2 or more months of treatment
4. Patient must have a healthy HLA-matched sibling donor at the A, B, C, and DR loci
5. Donor must be rheumatoid factor negative

post-NST, these data suggest that further investigation of NST in rheumatoid arthritis is warranted.

Complete donor chimerism

An unmanipulated graft, while complicated by GVHD, is likely to result in complete donor chimerism. The high disease-related mortality of scleroderma could justify the risk of some treatment-related GVHD. As a rule of thumb, mortality for diffuse cutaneous scleroderma with visceral involvement is 12% per year or 60% in 5 years.[12–15] Diffuse cutaneous disease and visceral involvement has an overall 10-year survival rate of 35–68%. Factors associated with high mortality are proteinuria, a high ESR, a low diffusion capacity, abnormal EKG, presence of arrhythmia, abnormal urine sediment, leukocytosis, thrombocytosis, anemia, high serum-soluble IL-2 receptor level, abnormal cardiopulmonary findings on examination, and diffuse skin disease with high Rodnan skin score. As a result of the paucity of treatment options and lack of significant efficacy of conventional treatment, patients with these adverse prognostic factors who have a matched sibling are candidates for an allogeneic HSCT at Northwestern University (Table 2).

Peripheral blood stem cells (PBSC) are mobilized for a targeted CD34 positive cell count greater than 5×10^6/kg. The allograft is not T-cell depleted or manipulated. The conditioning regimen is cyclophosphamide (200 mg/kg) and Campath-1H. Campath-1H is used because it has been reported to significantly reduce the risk of GVHD in both matched sibling and unrelated HSCT for malignancies.[16] Since the severity of GVHD increases with age, GVHD-associated complications are further minimized by limiting eligibility to patients less than 45 years old. Corticosteroids may precipitate renal crisis in patients with scleroderma. Therefore, cyclosporin which is rapidly tapered off and mycophenolate mofetil are used for GVHD prophylaxis. The pretransplant creatinine must be less than 2.0 mg/dl to avoid further exacerbating renal injury from cyclosporin. Patients with scleroderma-related pulmonary involvement develop pulmonary artery hypertension (PAH) and are at high risk for cardiovascular complications. PAH is, therefore, a contraindication to NST. Chimerism is monitored by PCR for variable number tandem repeats. The first scleroderma patient has just been enrolled on this allogeneic nonmyeloablative study.

Table 2 Eligibility of patients with systemic sclerosis for allogeneic NST

1. Age <45 years at the time of pretransplant evaluation
2. An established diagnosis of scleroderma and two or more of the following:
(a) Diffuse cutaneous scleroderma with involvement proximal to the elbow or knee and a Rodnan score of >14
(b) DLCO $<80\%$ of predicted or decrease in lung function (TLC, DLCO or FEV_1) of 10% or more over 12 months
(c) Active alveolitis on bronchoalveolar lavage
(d) Pulmonary fibrosis or alveolitis on CT scan or CXR
(e) Elevated ESR $\geqslant 25$ mm/h
(f) Proteinuria (greater than trace on dipstick)
(g) Urine blood on dipstick or sediment
(h) Abnormal EKG (nonspecific ST-T wave abonormalities, low QRS voltage, or ventricular hypertrophy)
3. Estimated systolic pulmonary arterial pressure must be <40 mmHg by doppler echocardiography or measurement by pulmonary arterial catheter
4. Serum creatinine <2.0 mg/dl
5. Patient must have a healthy HLA-matched sibling donor at the A, B, C, and DR loci

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