Autologous Hematopoietic Stem Cell Transplantation for Severe Autoimmune Disease with Special Reference to Rheumatoid Arthritis

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ABSTRACT. In 1996 an international collaboration began to explore the use of immunoablation and stem cell rescue in the treatment of severe autoimmune disease. Around 500 patients have been so treated according to consensus guidelines, the majority being registered in the combined European League Against Rheumatism and European Group for Blood and Marrow Transplantation (EULAR/EBMT) data registry. Results in terms of toxicity and benefit are different in the different autoimmune diseases, e.g., for rheumatoid arthritis (RA) a low transplant related mortality (TRM) of one patient out of 43 but high relapse rate (around two-thirds), whereas for systemic sclerosis (SSc) a higher TRM (12%) but less relapse. More aggressive immunoablative regimes were associated with more procedure related toxicity, but so far a clear therapeutic advantage has not been demonstrated. An overall actuarial TRM of 9% was observed. Randomized, prospective controlled phase III trials have begun in SSc and will soon commence in RA and multiple sclerosis. More phase I and II data are required for systemic lupus erythematosus and juvenile idiopathic arthritis. (J Rheumatol 2001;28 Suppl 64:5–7)

Key Indexing Terms:
STEM CELL TRANSPLANT
BONE MARROW TRANSPLANT
AUTOIMMUNE DISEASE
RHEUMATOID ARTHRITIS

As of May 2001 the combined European Group for Blood and Marrow Transplantation and European League Against Rheumatism (EBMT/EULAR) Data Base contains 350 registrations from 78 centers in 22 countries relating to patients who have received a hemopoietic stem cell transplant (HSCT) as primary treatment of an autoimmune disease.

Autoimmune diseases. The number of cases and types of autoimmune diseases transplanted are as follows: multiple sclerosis (MS) 102, systemic sclerosis (SSc) 70, rheumatoid arthritis (RA) 43, juvenile idiopathic arthritis (JIA) 35, systemic lupus erythematosus (SLE) 25, idiopathic thrombocytopenic purpura 9, cryoglobulinemia 4, and other rarer disorders including myositis, vasculitis, Behçet's disease and myasthenia gravis.

The number of such transplants each year is shown in Figure 1. The reduced number recorded in 2000 probably reflects a more cautious patient selection, based on the emerging data concerning benefit/risk ratio of this procedure for autoimmune diseases.

Most patients received autologous peripherally mobilized hemopoietic stem cells (HSC), with only 7 allogeneic HSCT, mostly for hematologic autoimmune diseases. Mobilization refers to the giving of cyclophosphamide and/or granulocyte colony stimulating factor (G-CSF) to drive the HSC from the marrow into the blood for harvest via leukapheresis. Conditioning (chemotherapy to ablate the marrow and theoretically the autoreactive immune cells) was via one of 4 basic regimens: cyclophosphamide (Cy) 200 mg/kg body weight, busulfan (Bu)/Cy, Cy 120 mg/kg plus radiation, or BEAM quadruple chemotherapy (carmustine, etoposide, cytosine arabinoside, and melphalan). Antithymocyte globulin (ATG) or antilymphocyte globulin was added in some centers as was T cell depletion, according to a consensus statement[1].

Overall, an actuarially calculated procedure related mortality of 8–10% was seen[2], with significant between-disease variation. In SSc this was 12% in the first 65 registered patients, while in RA only one transplant related death occurred in a patient receiving busulfan and Cy as conditioning. Although the regimens varied in intensity, there is so far no clear-cut advantage regarding remission induction or maintenance between protocols. A tendency toward more complications was seen with the more severe regimens. Median followup is 12 months (range 3–55).

A positive clinical response has been recorded in about two-thirds of patients, ranging from drug-free complete remission to partial response with relapse. A detailed analysis is under way in the different autoimmune disease subgroups — in SSc 70% of patients achieved > 25% improvement in skin score[3] and in MS 78% of secondary progressive disease had a 3 year progression-free survival (EBMT/EULAR Data Base).

Concerning RA, data on 50 patients from 11 centers show

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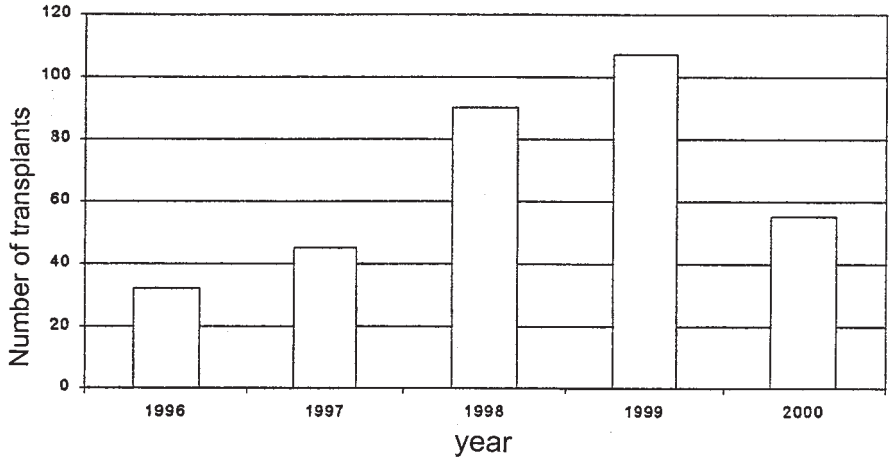

Figure 1. Data on the number of hematopoietic stem cell transplants in patients with autoimmune diseases from the EBMT/EULAR database, 1996 to 2000. No cases were reported prior to 1996. The reduction in cases in 2000 probably reflects more restricted patient selection.

that around half were mobilized with G-CSF and Cy, and half with G-CSF alone. There were some mild to moderate disease flares noted with G-CSF mobilization alone, easily controlled.

Most were conditioned with Cy 200 mg/kg body weight, in 3 ATG was added, 2 others received Bu/Cy, and one fludarabine and ATG. No deaths occurred in the Cy-only regimens.

Although analysis is incomplete, of the 39 evaluable cases, 13 were registered as "better," one stable, and in 18 initial improvement was followed by relapse over a median followup of 10 months (Figure 2). In the majority of these relapses an adequate response to simple disease modifying antirheumatic drugs (DMARD) (e.g., methotrexate, cyclosporin A, or leflunomide) was subsequently observed. These patients by definition had failed conventional DMARD treatment pretransplant.

Consensus has been reached concerning core data collection pre- and post-HSCT in RA, as well as in SSc, MS, JIA, and SLE. This has been an International Bone Marrow Transplantation Registry (IBMTR) and EBMT effort. In addition, inclusion and exclusion criteria guidelines for RA include:

1. Failed 2 conventional DMARD, including methotrexate
2. Failed any combination of DMARD
3. Failed anti-tumor necrosis factor-α therapy for at least 3 months
4. Between 2 and 10 years' disease duration
5. No major organ failure
6. Progressive, erosive disease
7. A potential functional status to ensure an adequate quality of life if inflammation controlled

Analysis of the international experience is currently underway, with the aim of collective publication. Issues such as

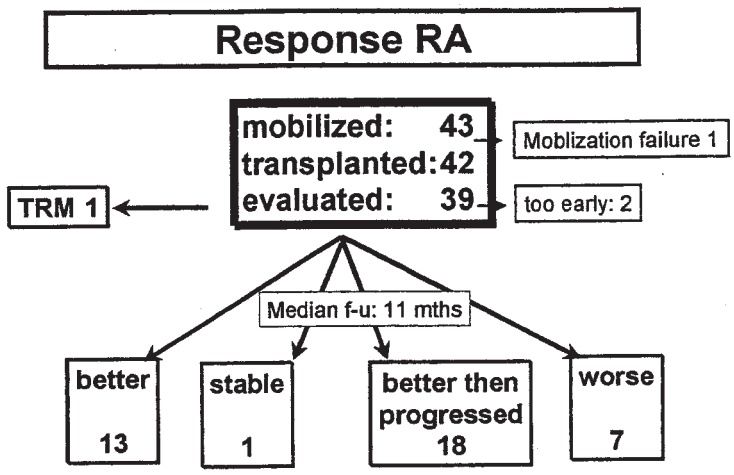

Figure 2. Outcome of hematopoietic stem cell transplant in RA. Transplant related mortality (TRM) (infection) occurred in one patient receiving combined busulfan and cyclophosphamide conditioning. In patients who initially improved then relapsed, most responded to drugs that had been ineffective pretransplant.

need for T cell depletion are not resolved, with data from Australia showing no clear advantage (J. Biggs, personal communication).

At a meeting in Basel in October 2000 consensus was reached concerning a randomized, prospective, controlled phase III trial[4]. This protocol consists of mobilization with Cy 4 g/m^2 and G-CSF, followed by harvesting and storage in all. Randomization will then occur between HSCT (Cy 200 mg/kg body weight, unmanipulated graft) and continued "best available" management. The primary endpoint is number of patients who, at 6 months, respond to medications to which they were previously resistant, i.e., number achieving a moderate to good EULAR or American College of Rheumatology 20% response. Patients in the mobilization-only arm who fail to respond satisfactorily will be able to switch to HSCT after 6 months.

The study, called the Autologous Stemcell Transplantation International Rheumatoid Arthritis (ASTIRA) Trial, is being conducted under the leadership of Sarah Bingham and Paul Emery in Leeds.

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