

# **Marrow Transplantation from Unrelated Volunteer Donors**

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## **Introduction**

Engraftment of allogeneic hematopoietic stem cells has initially been achieved by selecting human leukocyte antigen (HLA)-identical sibling donors. Patients with hematological malignancy transplanted from related donors incompatible for only one HLA-A, B, or D/DRB1 antigen have a probability of survival similar to patients treated with HLA-identical sibling transplants.<sup>(1)</sup> In contrast, transplants from donors incompatible for two or three HLA antigens are associated with lower survival.<sup>(2)</sup> Since less than 30% of the patients in North America have an HLA-matched sibling and 3-5% have a one HLA-locus mismatched relative, for most patients in need of an allogeneic marrow transplant the only chance of finding a suitable donor is through the identification of an HLA-compatible unrelated volunteer.

Three accomplishments have allowed unrelated donor transplants to become feasible and successful: i) identification of HLA genes and their functional products; ii) development of precise and efficient HLA typing methods using DNA technology; and iii) the development of a network of registries containing more than 3.6 million HLA typed donors worldwide. To date more than 5,000 patients with hematological disorders have been transplanted using marrow from unrelated volunteers. Initial results have demonstrated that long-term survival and transplantation tolerance can be achieved, but there is a higher degree of graft-versus-host disease (GVHD) in unrelated compared to related transplants despite matching for HLA-A, B, DRB1, DQB and DPB, indicating that current assessment of histocompatibility is still incomplete.<sup>(3-4)</sup>

## **Donor Selection**

HLA antigens are cell-surface molecules encoded by class I A, B, C and class II DR, DQ, DP genes. Polymorphic HLA specificities can be typed routinely by alloantisera. Individual *specificities* defined serologically, however, do not necessarily represent a unique allele. For example, analysis of serologically-defined HLA-B27 molecules by isoelectrofocusing (IEF) gel electrophoresis and gene sequencing have revealed that there are at least eight distinct alleles, defined as B\*2702-2709, which encode a unique primary amino acid sequence that can be distinguished by T-cells.<sup>(5-6)</sup> IEF has been employed for donor selection by some transplant centers.<sup>(7)</sup> Not even IEF, however, is sufficiently sensitive to detect all HLA-A and B alleles, and DNA typing technology is likely to become routine and replace both IEF and serological typing within the next few years.

HLA-DR, DQ and DP alleles can now be identified by direct DNA typing with a high degree of precision using one of several methods. A single incompatibility for alleles distinguished by DNA typing but not by serology (for example: DR4/DRB1\*0401 vs DR4/DRB1\*0402) is associated with a significant increased risk of acute GVHD in either unrelated or related marrow transplants.<sup>(8-9)</sup> An initial study in 469 patients from Seattle found a correlation between disparity for DQB and the incidence of severe GVHD.<sup>(10)</sup>

There are, as yet, insufficient data to assess the relevance of DP mismatching to GVHD development after unrelated donor transplants.<sup>(4)</sup> Disparity for HLA class II antigens is the basis for the proliferative T cell responses that occur in the mixed lymphocyte culture (MLC) assay. The MLC assay, however, has a poor predictive value for GVHD in clinical marrow transplantation, and its use for donor selection has been abandoned.<sup>(11)</sup> Second generation functional assays for donor selection, such as limiting dilution analysis of alloreactive proliferative or cytolytic T cells, remain under development.<sup>(12)</sup>

## **Donor Registries**

Europdonor Foundation, located in the Netherlands, has organized a "Bone Marrow Donors Worldwide" directory. It includes the large majority of HLA-typed potential volunteer marrow donors in the world, from 30 registries in 26 countries - a total of more than 3.6 million donors typed for HLA-A and B, and more than one million donors also typed for DR. This directory is a useful aid for transplant physicians to focus the donor search for an individual patient in the regional or national registry where compatible donors are most likely to be found.

The National Marrow Donor Program (NMDP) of the United States of America contains more than 2 million donors typed for HLA-A and B, and more than 750,000 also typed for DR. The racial origin of NMDP donors is approximately 80% Caucasian, 7% African American, 5% Asian, 7% Hispanic, and 1.5% Native American. The NMDP network includes 105 donor centers, 111 marrow collection centers and 76 transplant centers, located in 40 different states and 10 countries. Several registries have recently begun operation in Asia. The desirable goal in the future will be to establish a computerized network that would allow simultaneous access to national registries worldwide.

## **Donor Search**

At least one HLA-A, B matched donor is found in the NMDP for 97% of patients. The probability of finding an HLA-A, B, DR match at the initial search has increased from 10% in 1987 to 64% in 1995. The probability for white, Hispanic, Asian-Pacific, and black patients was 71%, 62%, 45% and 24%, respectively. An additional 15% of patients eventually find a match after requesting DR typing of HLA-A and B matched donors. NMDP has provided HLA matched unrelated donor marrow for more than 4,500 transplants, approaching 1,000 during the last year.

Confirmatory HLA typing of patient and donor must be performed by a laboratory associated with the transplant center. The time interval from the initiation of the search to the date of transplant has varied according to patient's HLA type and diagnosis, and currently averages 4 to 5 months. This long search time has been a concern, especially for patients with severe marrow failure or acute leukemia. A substantial amount of this waiting is due to obtaining donors blood samples for additional typing. With more complete typing of registry donors the duration of the donor search is expected to decrease.

## Results of Unrelated Donor Transplants

### *Engraftment*

The probability of achieving sustained engraftment in unrelated donor marrow transplants is reported to vary from 80% to 99%.<sup>(13-14)</sup> The risk of graft failure depends primarily on the patient's underlying disease, donor HLA mismatching, the intensity of the immunosuppressive conditioning regimen utilized, marrow cell dose, and by removal of T cells from the marrow inoculum. Other factors associated with an increased risk of graft failure after HLA-incompatible transplants are the presence of a positive patient anti-donor HLA lymphocytotoxic crossmatch, and the use of less intensive immunosuppression after transplantation. In a study from the NMDP, the overall incidence of graft failure was approximately 14% and reached 20% in patients who received T cell depleted grafts.<sup>(13)</sup> In a Seattle study of non-T depleted transplants in patients conditioned with whole body irradiation, graft failure occurred in 18 of 312 (6%) patients with CML and one of 152 (0.7%) patients with acute leukemia (15, and unpublished). Mismatching for HLA-A, B or C defined by sequencing of exon 2 and 3 was associated with an increased risk of graft failure and accounted for almost all cases of graft failure.<sup>(15)</sup> A regimen of busulfan 16 mg/kg/day for four days followed by cyclophosphamide 120 mg/kg/day for two days proved sufficiently immunosuppressive to allow sustained engraftment in 26 of 27 patients with leukemia at Ohio University,<sup>(16)</sup> and 17 of 18 patients with myelodysplasia in Seattle.<sup>(17)</sup> There was no favorable effect of recombinant human GM-CSF on engraftment and transplant-related morbidity in a controlled trial conducted in Seattle.<sup>(18)</sup> In contrast, transplantation of a higher marrow cell dose was associated with faster recovery of neutrophils, lymphocytes and platelets and better survival in patients with acute leukemia (19, and unpublished).

### *Acute GVHD*

Despite immunosuppression with cyclosporine and methotrexate, the incidence of acute grades II-IV GVHD was significantly higher in HLA matched unrelated transplants (79%) than in HLA matched sibling transplants (35%).<sup>(3)</sup> In patients less than 36 years of age, the probability of grades II-IV acute GVHD was 95% in 42 transplants incompatible for a one locus minor mismatch at HLA-A, B, or D/DRB1 compared to 78% in 70 HLA-A, B, D/DRB1 matched unrelated donor transplants ( $p < 0.05$ ).<sup>(14)</sup> No effect of patient and donor age, use of supportive therapy with GM-CSF, IV immunoglobulins or nursing in a protected environment using a laminar air flow room could be shown on GVHD in the Seattle series.<sup>(20)</sup> The use of female donors with a history of pregnancy as opposed to nulliparous females or male donors was associated with a significant increase in the risk of acute GVHD.<sup>(20)</sup> Compliance with the prescribed doses of cyclosporine and methotrexate is important in optimizing the prevention of GVHD.<sup>(20)</sup>

Substitution of prednisone for methotrexate has been followed by an unacceptably high incidence of severe acute and chronic GVHD in unrelated transplants.<sup>(21)</sup> An attempt to improve GVHD prevention by adding prednisone to cyclosporine and methotrexate was associated with a decreased incidence of acute GVHD but lower 100 day survival because of high incidence of opportunistic infections in unrelated transplants at Vanderbilt.<sup>(22)</sup> In contrast, the triple regimen achieved better control of GVHD and a two-

year survival of 80% in 17 unrelated recipients with CML in chronic phase or ALL in first remission treated at City of Hope.<sup>(23)</sup>

An analysis of the combined results from NMDP-affiliated marrow transplant centers demonstrated a reduction in the incidence and severity of acute and chronic GVHD in patients receiving T cell depleted marrow prepared with a variety of T cell depletion techniques; however, there was no significant effect on overall disease-free survival.<sup>(13)</sup> As previously reported for HLA identical sibling transplants, use of T cell depletion was associated with an increased risk of graft failure. New immunosuppressive agents have to be investigated for GVHD prevention.

### ***Chronic GVHD***

Clinical extensive chronic GVHD occurred in 77% of 146 patients, alive in remission a minimum of 100 days from an unrelated donor transplant.<sup>(20)</sup> Overall, 25-30% of patients died with complications of chronic extensive GVHD during immunosuppressive therapy. In surviving patients, the median time to successful withdrawal of immunosuppressive therapy was 18 months, while 26% of patients continued to require some degree of immunosuppression 5-8 years after transplant. At one year after transplantation, 25% of patients had a Karnofsky performance status below 80%, but at four years fewer than 5% of patients had a score below 80%. The most prevalent causes of permanent disability were cataracts, osteoporosis, avascular bone necrosis, scleroderma and chronic obstructive pulmonary disease.

### ***Opportunistic Infections***

Immune reconstitution is severely impaired by acute and chronic GVHD and by prolonged immunosuppressive treatment. Patients are subjected to opportunistic infections, predominantly from aspergillus and CMV. The incidence of disseminated aspergillus infection including sinusitis, pneumonia and cerebral abscesses is 15%, with more than 90% mortality.<sup>(20)</sup> There has been no significant improvement in the prevention or treatment of aspergillus infection within the last eight years. CMV seropositive patients have a much greater risk of CMV disease and CMV associated mortality after transplantation compared to CMV seronegative patients. The risk of disease is slightly increased in seronegative transplant recipients of seropositive marrow grafts but not to the same extent as seen in seropositive recipients. Controlled trials have shown that ganciclovir can prevent CMV disease in recipients of allogeneic marrow transplants including transplants from unrelated donors.<sup>(20,24)</sup> Prevention of CMV disease has been the major and perhaps only improvement occurring in the supportive therapy given to unrelated transplant recipients since 1985.

### ***Relapse after Transplantation***

The probability of relapse after transplantation depends predominantly on the diagnosis and the stage of the disease at time of transplant. It appears that relapse is lower in patients transplanted from an unrelated donor compared to patients transplanted from an HLA identical sibling.<sup>(3)</sup> This trend is particularly apparent in patients transplanted for CML in chronic phase. Data from Seattle indicate that the probability of relapse is on the order of 7% following unrelated transplants compared to 18% following HLA identical

sibling transplants. A report from Milwaukee, where a regimen of T cell depletion is used, indicated a relapse probability of 5% in unrelated transplants compared to 50% in HLA matched sibling transplants using the same regimen.<sup>(25)</sup> There also appears to be further reduction in the probability of relapse in HLA incompatible compared to HLA compatible unrelated donor transplants for acute leukemia (14, 19 and unpublished).

### *Survival*

Survival is better in patients with CML, those transplanted at an earlier stage of malignancy, younger patients, patients with negative CMV serology, patients who received the prescribed dose of MTX and CSA in weeks 2-5 after transplantation, and patients with donors HLA matched for HLA-A, B and DRB1.<sup>(20)</sup> CML is the most common indication for unrelated donor transplantation. In a report of 333 transplants for CML from Seattle, the probability of 3-year disease-free survival was 74% for patients less than 50 years of age, in chronic phase within the first year from diagnosis, transplanted from a matched donor; 56% for patients less than 50, in chronic phase more than 3 years from diagnosis, transplanted from a matched donor; and 40% for patients less than 50, in chronic phase more than 3 years from diagnosis, transplanted from an HLA-mismatched donor.<sup>(26)</sup> The probability of survival was 39% for patients in accelerated phase, 35% for patients in second chronic phase, and 6% for patients in blast phase. Results of unrelated transplants reported by different centers have been variable: Two-year disease-free survival for CML in chronic phase was 52% among 27 patients treated in Milwaukee, 42% among 46 patients treated at Hammersmith Hospital in London, 37% among 115 patients reported by the NMDP, and approximately 30% in transplants communicated by the International Bone Marrow Transplant Registry.<sup>(7,25,27)</sup> The factors accounting for these apparent differences are unknown.

NMDP has reported on the outcome of unrelated donor transplantation in patients with acute leukemia.<sup>(13)</sup> The probability of disease-free survival at 1.5 years was 45% in 58 patients transplanted in first or second remission and 19% in 98 patients with more advanced disease. Through June 1994, 174 patients with primary acute leukemia have received an unrelated donor transplant in Seattle. Three year disease-free survival showed a correlation with the stage of disease at the time of transplantation, and was 55% for 11 patients in first remission, 31% for 35 patients in second remission, 26% for 20 patients in third remission and 12% for 94 patients in relapse.<sup>(19)</sup> Patients transplanted with "early" relapse, whose marrow blasts were < 30%, had a survival of 27%, better than patients with more "advanced" relapse.

The length of time required to find an unrelated donor and schedule a transplant still limits the success of this approach. To overcome this limitation, an unrelated donor search should begin as soon as possible. Patients with high-risk AML (for example, deletions of parts of chromosomes 5, 7, or 11), Ph1-positive ALL, or biphenotypic leukemia should begin a donor search at the time of initial diagnosis; if a donor is found, patients should proceed to transplantation as early as possible in the event of primary induction failure or in first remission. Patients with "standard" risk leukemia should be considered candidates for an unrelated donor transplant at the time of first relapse. Delaying the unrelated donor search in these cases will compromise treatment outcome.

A joint report from five centers demonstrated a 28% survival rate in 40 unrelated transplants for severe aplastic anemia,<sup>(28)</sup> and similar results were reported by NMDP.<sup>(13)</sup> Most patients died of early infections and graft failure, indicating the need to transplant patients just after they failed intensive immunosuppressive treatment, but still early in the course of the disease before they become infected or sensitized to alloantigens by multiple transfusions.

An initial report from NMDP has described results in unrelated donor transplants in 41 patients with a variety of congenital diseases including immunodeficiency syndromes.<sup>(13)</sup> The probability of survival was 52% at two years. Better results with 83% survival at two years were reported by the Minneapolis transplant team in patients with congenital immunodeficiency disorders.<sup>(29)</sup>

## **Conclusion**

Use of an unrelated donor has become standard practice for those patients who need an allogeneic marrow transplant but lack HLA compatible relatives. Unrelated donor transplants have become feasible in more than 40% of patients without a family donor and have allowed long-term disease-free survival in 15-70% of patients with a variety of hematological disorders. When compared to HLA-matched sibling transplants, unrelated donor transplants are associated with an increase in the incidence of graft failure and GVHD. Such increase may be due to disparities for undetected HLA determinants or non-HLA histocompatibility antigens. Because of the complexity and extensive polymorphism of the HLA system, HLA-identical unrelated donors will not be found for many patients, and a certain degree of HLA disparity between donors and recipients will be inevitable. The ultimate goal of research in this field is to improve safety and efficacy of unrelated marrow transplantation and simplify the procedure to allow disseminating its application from a few highly specialized centers to marrow transplant units worldwide.

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