Bone marrow transplantation using unrelated donors for haematological malignancies

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Bone marrow transplantation from unrelated donors is increasingly used to treat haematological malignancies. There are almost 4 million volunteer donors now available. Therefore, it is possible to find an HLA-A, -B and -DR-identical donor for around 70% of the patients. The major obstacles to unrelated bone marrow transplantsations have been rejection, severe acute graft-versus-host disease (GVHD) and prolonged immune recovery leading to frequent infections and a high transplant-related mortality. However, with improved tissue typing using DNA techniques, immunosuppression using T-cell depletion in vitro or in vivo, the frequency of acute GVHD is acceptable and the results approach those obtained with HLA-identical siblings. For patients with chronic myeloid leukaemia, the worldwide 3-year survival is around 40%. Other indications for bone marrow transplantation with unrelated marrow include acute leukaemia and myelodysplastic syndromes with high-risk features. Unrelated cord blood cells and unrelated peripheral blood progenitor cells will be increasingly used as alternative haematopoietic stem cell sources to bone marrow. Improved immunosuppression, more accurate tissue typing, growth factors and better management of infections is expected to improve outcome using unrelated haematopoietic stem cells for transplantation in the near future.

**Keywords:** unrelated bone marrow transplantation; leukaemia; HLA-system; graft-versus-host disease; immunosuppression.

**INTRODUCTION**

Bone marrow transplantation (BMT) from genotypic HLA-identical sibling donors has for many years been a well established therapy for treating patients with a variety of haematologic malignancies [1-4]. Indications include: first, complete remission in patients with acute myeloid leukaemia (AML) and patients with acute lymphoblastic leukaemia (ALL) with high-risk criteria. High-risk criteria include age below 1 year or above 20 years, chromosomal abnormalities, >100 x 10⁹/l WBC at diagnosis, CNS involvement, T-cell phenotype and not achieving remission within six weeks of chemotherapy [5,6]. Acute leukaemia in early relapse, second or later remission are also indications for HLA-identical sibling BMT. Chronic myeloid leukaemia (CML) is an indication for HLA-identical sibling BMT, since BMT is the only way to cure this disease today. End-stage leukaemia, such as relapse of acute leukaemia and CML in blast crisis, may be cured by BMT although long-term survival is 10% or less [3,4]. Myelodysplastic syndrome (MDS) is also an indication for BMT, but multiple myeloma is controversial. Lymphomas are treated with autografts because of the lower transplant-related mortality (TRM), but in advanced stages or in patients with bone marrow involvement, BMT may be considered [7].

However, only one third of the patients have an HLA-identical sibling. Therefore, HLA-matched unrelated volunteer donors (MUD), sometimes abbreviated VUD (volunteer unrelated donors), are increasingly used to provide allogeneic bone marrow. The first reported transplant using an
unrelated donor was performed in a child with ALL in second remission in 1981 [8]. However, since then, large registries with volunteer donors have been established all over the world. The first registry was the Anthony Nolan Registry in Great Britain, which has around 150,000 donors. The largest registry is the American National Marrow Donor Program (NMDP) with around 2.5 million volunteer donors. Worldwide there are now more than 3.5 million volunteer donors. With this donor pool now available, it is possible to find an HLA-A, -B and -DR-identical donor for around 70% of the caucasian patients who lack an HLA-identical sibling. If a one HLA-antigen mismatch is accepted, the possibility of finding a donor is increased to above 80%. This review will deal with the outcome and indications for MUD transplantation in patients with haematological malignancies. There are several obstacles to MUD BMT versus BMT using HLA-identical sibling donors [9–18]. These obstacles are because the donors are not as well HLA-matched in the unrelated situation, which may pave the way for rejection, graft-versus-host disease (GVHD), prolonged immune reconstitution and infections.

HLA-typing

The reported experience of MUD transplantation has mostly involved the use of donor/recipient pairs matched by serologic tissue typing for HLA-A, -B and -DR together with mixed lymphocyte cultures (MLC). HLA class I typing may be defined by a more discriminating technique than conventional serology, the one-dimensional isoelectric focusing of HLA class I molecules [19]. In more recent years, HLA class II antigens have been determined using molecular-typing techniques. Initially, the restriction fragment-length polymorphism (RFLP) method was used with the help of cDNA probes to determine DRB, DQA and DQB alleles [20]. In more recent years, the PCR method using sequence specific primer pairs (PCR-SSP) has been used to define the DR B1-B5, DQA1, DQB1 and DP B1 alleles [21,22]. Using the sequence-specific oligonucleotide probe hybridization (SSOP), it became apparent that many donors who appeared HLA-identical serologically, were disparate at the molecular level at these alleles [20]. By matching recipients and donors by genomic typing for HLA class II antigens, it seems that the incidence of acute GVHD and the outcome has improved, compared to MUD transplantation using serological typing only [16,23,24]. When HLA-A, -B or -DR typing was defined by serologic analysis, there seemed to be no major difference regarding the risk for severe acute GVHD (grades III-IV) in recipients of identical or one antigen mismatched bone marrow [25]. In contrast, a study by Beatty et al. showed a 36% probability of grades III-IV acute GVHD in recipients of HLA-A, -B and -DR identical grafts from unrelated donors compared to 51% in donor/recipient pairs with ‘minor’ HLA disparity [26].

A study in children showed an increased TRM in recipients of HLA-mismatched marrow: 51% compared to 24% in those receiving HLA-identical bone marrow (p = 0.04) [27]. The probability of grades II-IV acute GVHD was 83% in HLA-matched and 98% in HLA-mismatched children (p = 0.0009). HLA-DRB1 alleles were defined by hybridization of PCR-amplified DNA with sequence-specific oligonucleotide probes. Incompatibility for a single HLA locus was allowed if there was a HLA-A or -B disparity within a cross reactive group, or if there was HLA-Dw or DRB1 disparity within the same DR type.

In a study by Petersdorf et al. HLA-DPβ1 disparity was analysed using sequence-specific oligonucleotide hybridization [28]. The patients were matched for HLA-A, -B, -DRB and -DQB and different for HLA-DPB1 alleles with the donors. With no DPB incompatibility, one DPB mismatch or two DPB mismatches, the probability of grades II-IV acute GVHD was 0.69, 0.83 and 0.72 in the three groups, respectively. Therefore, HLA-DP disparity may not play a major role for the outcome in MUD transplantation.

Molecular typing of DRB1 alleles can allow more accurate donor-recipient matching and thereby improve clinical outcome after marrow transplantation. In another study by Petersdorf et al. from Seattle, DRB1 alleles were typed by sequence-specific oligonucleotide probe hybridization [29]. The probability of moderate-to-severe acute GVHD was 48% for 305 matched and 70% for 59 mismatched patients. TRM was 39% and 51% in the two groups, respectively (p = 0.04). Using HLA-A, -B and -DR-identical unrelated donors, where the patients were genotypically typed and matched for HLA-DR, we reported an incidence of grades II-IV acute GVHD of 15% [16].

A report from NMDP showed that serologic HLA-mismatch was associated with a decreased leukaemia-free survival [25]. The Minnesota group reported that recipients matched serologically at HLA-A, -B and -DR, compared to patients with a minor serological mismatch, had the same survival in patients below 18 years of age [30]. However, in adult recipients, those with serologically matched donors had a significantly better 3-year survival, 50% compared to 10% in recipients of mismatched bone marrow (p < 0.01). With more precise DNA molecular matching, compared to serologic matching only, matching is improved. However, with more specifically defined matching, it will be more difficult to find a completely matched donor for each recipient.