The 9th Conference on Health Care of the Chinese in North America

Bone Marrow Transplant and HLA Typing in the Asian Population

Auayporn Nademanee, MD, Associate Clinical Director, Department of Hematology/BMT, City of Hope National Medical Center

---

Abstract

Introduction

Bone marrow transplantation (BMT) has become the treatment of choice for patients with hematologic malignancies, and bone marrow failure. However, only 30% of the patients have an human leukocyte antigen (HLA) matched sibling and <5 have a HLA matched or one antigen mismatched relative. Therefore, the only chance of finding a suitable donor for >60% of the patients in need of an allogeneic BMT is through the identification of an HLA matched unrelated volunteer donor.

Four accomplishments have made unrelated donor transplants feasible and successful: 1) the identification of HLA genes and their functional products, 2) the development of precise and efficient HLA typing methods using DNA technology, 3) the development of a network of volunteer donors registries, containing more than 2.8 million HLA-typed donors worldwide, and 4) the clinical efficacy of unrelated donor transplants. Since the inception of NMDP and other National networks in 1987, more than 6000 patients with acute and chronic leukemias, lymphoma, myelodysplastic syndrome, aplastic anemia, multiple myeloma, congenital inborn errors of metabolism, and immunodeficiency syndromes have been transplanted using marrow from unrelated volunteer donors.

Histocompatibility

HLA antigens are cell-surface molecules that are encoded by a series of closely linked genes mapping located on human chromosome 6. There are two distinct types of HLA genes: class I HLA A, B, C genes; and class II HLA DR, DQ, DP genes. Two characteristics of HLA genes that make them of special importance in transplantation are their high degree of polymorphism and the strong immune reactions that their products can evoke in other individuals. HLA molecules bind and present antigenic peptides to T lymphocytes, a determinant step in the initiation of immune response. T cells from one individual react vigorously to mismatched HLA molecules on the surface of antigen-presenting cells from another individual in what is known as an allogeneic reaction. When non-HLA identical related donors are used, the risk of acute graft-versus-host disease (GVHD) is increased, but no significant decrement in survival is seen if only one HLA allele is mismatched. However, increasing the degree of incompatibility for HLA not only increases the risk of GVHD, but also increases the risk of graft rejection, resulting,, in a lower rate of patient survival.

Typing of HLA Antigens

Serology. The standard method for HLA typing is based on serology, utilizing a complement-dependent micro cytotoxicity assay and panels of selected alloantisera containing HLA antibodies. These antisera, which are highly selected for HLA specificity, are usually obtained from multiparous women immunized to HLA through pregnancy. More, recently; monoclonal antibodies specific for a variety of HLA class I and II antigens have been developed. However, due to HLA polymorphism and recent evidences suggesting that serologic methods are not adequate for identifying all HLA antigens revelant to marrow transplant, molecular typing or DNA typing are now being widely used.

Molecular Typing. Hybridization of sequence-specific oligonucleotide probes (SSOP) to polymerase chain reaction (PCR)amplified DNA has proved to be a powerful method for identifying polymorphism of both class I and class II loci. Typing with panels of SSOP can reveal specific alleles indistinguishable by serological typing; for example, at least 11 unique DR4 alleles have been identified by SSOP/PCR typing. Class II typing by PCR and SSOP is not only feasible, but may be highly advantageous because of its sensitivity and efficiency, and its ability to precisely define individual HLA alleles. Application of molecular typing to class I HLA-A, -B, and -C genes, however, is not as well developed as class II typing. Recent studies have shown that a single incompatibility for alleles distinguished by SSOP but not by serology (for example, DR4/DRB1 *0401 vs DR4/DRB1*402) is associated with a significantly increased risk of acute GVHD in either unrelated or related marrow transplants.

Racial Distribution of NMDP Donors

For individual patients the probability of identifying HLA-A, -B and DRBI matched donors can range widely, from near certainty for some patients even if the registry has only 10,000 donors, to less than a 50% chance for some patients even with a registry of over a million donors. Moreover, the chance to find donors may be better for more homogeneous racial groups. For example, using data from the 8th International Histocompatibility Workshop, a Japanese registry would need only 50,000 donors to provide the average Japanese patient an 80% chance for finding at least one donor, versus 1,000,000 and 400,000 for European and North American Caucasians, respectively. In addition, if registries containing predominantly one racial group are searched for a patient of another racial group, the odds of finding a donor dramatically decrease. This underscores the need to build wide ethnic and racial diversity in donor pools around the world, and develop mechanisms to allow cross-searching of registries on an international basis.

As of July 1997, there are 156,033 Asian/Pacific Islander registered with the NMDP, which represent 7% of all the donor pool. According to U.S. Census Bureau statistics, this representation (donors per million of population by race) exceeds that of Caucasians, however, it is necessary for each race to be significantly overrepresented in the NMDP registry in order to provide comparable opportunity of matching for non-Caucasian races.

Unrelated Donor Marrow Transplants

Unrelated donor marrow transplant has become an effective therapy for patients with hematologic malignancies, bone marrow failure and inherited immune and metabolic disorders, who have no matched sibling donors. Chronic myelogenous leukemia (CML) is the most common disease treated by unrelated donor marrow transplant, followed by acute leukemia, myelodysplasia and severe aplastic anemia. The outcome of unrelated BMT depends on several factors including: diagnosis and stage of disease, time from diagnosis to BMT, age of recipient, age of donor, the degree of HLA matching, prior exposure to cytomegalovirus (CMV seropositive), ganciclovir prophylaxis and fungal prophylaxis. In general, improved outcomes are associated with shorter disease duration, younger age of both recipient and donor, 6/6 antigens match by molecular typing and CMV seronegative recipient.

Engraftment

One of the mechanisms for failure of unrelated donor grafts is immunological rejection of donor hematopoietic cells by recipient T cells that recognize incompatible HLA determinants. Several factors increase the risk of graft failure, including sensitization of the recipient against donor antigens from a previous pregnancy or transfusion, HLA mismatching of the donor, using of less intense preparative regimen before transplant, suboptimal post-transplant immunosuppressive therapy, and depletion of T lymphocytes from marrow grafts. The incidence of graft failure was about 3% for patients receiving HLA matched unrelated transplant after conditioning with total body irradiation and cyclophosphamide, and after post-transplant immunosuppressive therapy with cyclosporine and methotrexate. However, the incidence of graft failure reached 20% in patients who received T-cell depleted marrow grafts.

Acute GVHD

Clinical GVHD results from an immune reaction of mature donor T lymphocytes against HLA determinants of the recipients. This reaction is directed toward normal tissues including skin, gastrointestinal mucosa and hepatic biliary tract. The use of T-cell depleted marrow transplants has been shown to reduce the incidence of acute GVHD, but also increased the risk of graft failure and relapse of malignancy. The incidence of moderate to severe acute GVHD was significantly higher in HLAmatched unrelated BMT than in HLAmatched sibling transplants (79% vs. 35%). Matching donor/recipient pairs at HLA DRB 1 by molecular typing has also been shown to reduce the incidence of moderate to severe acute GVHD (48% vs. 70%), and decrease the risk of transplant-related mortality. Therefore, matching donor/recipient pairs for DRB1 alleles decreases the risk of acute GVHD and improves survival after unrelated donor BMT. Recent studies also suggest that matching for HLA-C may also decrease the risk of graft rejection as well as the incidence of acute GVHD. The impact of molecularly matching for class I HLA-A and B loci is being investigated.

Chronic GVHD

Chronic GVHD is the principal cause of morbidity and nonrelapse mortality for patients reaching day 100 after allogeneic transplant. Chronic G'VHD may involve skin, oral mucosa, eyes, liver, gastrointestinal tract, and lungs, features resembling scleroderma, biliary cirrhosis, and bronchiolitis obliterans. Chronic GVHD occurs in 35% to 70% of patients after unrelated donor BMT, with mortality rates ranging from 25% to 70%, depending on the associated risk factors. Permanent disability may be caused by complications of GVHD, such as scleroderma and chronic obstructive lung disease or by side effects of immunosuppressive therapy, such as cataract formation, severe avascular necrosis and immune deficiency state.

Opportunistic Infections

Repopulation by mature T cells and recovery of immunoglobulin production is extremely slow after unrelated donor BMT. Prolonged immunosuppressive therapy, which is commonly required in recipients of unrelated BMT, causes further impairment of immune reconstitution. Glucocorticoid therapy and immunodeficiency predispose patients to opportunistic infections, predominantly with fungal and CMV. Ganciclovir prophylaxis has been shown to reduce the incidence of CMV infection and CMV related morbidity and mortality in seropositive recipients of marrow transplants from unrelated donors. Disseminated Aspergillus infection remains problematic and is associated with >90% mortality in unrelated transplants. Other opportunistic infection are also more common in unrelated transplants.

Conclusion

Unrelated donor marrow transplants have become standard treatment for patients who need allogeneic marrow transplant, but lack an HLA-compatible family member. The major obstacle to successful unrelated BMT is the high incidence of acute and chronic GVHD. Using a molecularly matched donor/recipient pair may further reduce the incidence of GVHD and improve outcome of unrelated marrow transplants. Clinical studies aiming at new approaches to GVHD prevention and treatment are being investigated. Continued efforts directed toward increasing the probability of a donor by expanding the size and genetic heterogeneity of donor registries, decreasing the search time by implementing more efficient strategies for donor typing, selecting better donors and candidates for BMT will make unrelated marrow transplants safer and more successful.