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Stem Cell Transplantation in Thalassemia

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ABSTRACT The beneficial results of stem cell transplantation from HLA identical family members for patients with severe thalassemia are clear. Class I patients have a very high probability of cure with a very low early and late morbidity and mortality. Delay of transplantation until the patient is in a risk category beyond class I substantially reduces the probability of transplant success and jeopardizes the reversibility of liver and cardiac damage. It is reasonable to suggest that patients with β-thalassemia who have HLA-identical donors should be transplanted as soon as possible. Umbilical cord blood (UCB) has been shown to be capable of reconstituting the bone marrow of the patient with thalassemia after myeloablated pre-conditioning treatment. The major advantage of UCB over other sources of stem cells is the ability to cross HLA barriers, and there is evidence of less GVHD. The use of related – donor UCB stem cells with HLA mismatches at one to three antigens needs to be considered. It would be worth while to do a prospective study to evaluate the role of UCB stem cell transplantation in the treatment of the thalassemias and hemoglobinopathies.

Aggressive transfusion and iron chelation therapies have improved the quality of life in thalassemia. However, hyper transfusion and iron chelation are expensive in developing countries and also require life-long management. Hematopoietic stem cell transplantation (HSCT) has become an accepted method of therapy for the treatment of thalassemia. The first successful bone marrow transplant (BMT) in thalassemic patient was reported in 1982 (Third International Symposium 1997). Till date more than 1000 patients have been transplanted around the world.

The risks associated with allogeneic bone marrow transplant (BMT) are substantial as the patient may become severely immunocompromised or if the transplant is rejected, the patient may have bone marrow aplasia and / or recurrence of disease. The transplanted inoculum contains competent donor lymphoid cells that are able to respond immunologically and reject the recipient (a syndrome referred to as graft-versus-host disease, GvHD).

At present, the only established means that can prevent or at least limit the severity of GvHD is matching the stem cell donor and recipient for the major human leukocyte antigens (HLA). Today, it is accepted in the medical practice to search early for an HLA-compatible family member that could eventually serve as a HST donor. This information can aid the physician greatly in selection of both the initial therapy and decisions on long-term management of the patient. Alternatively, if a compatible family member cannot be identified, referral of the patient to a transplant center that might identity an HLA-matched unrelated donor offers a future alternative.

Because of the enormous diversity and polymorphism of the HLA system parents and siblings of the patient's immediate family should be typed for both HLA-A, B, and C locus (Class I) antigens and HLA –DR locus (Class II) antigens. In the past, it was considered mandatory that the donor and recipient be a perfect HLA genotypic match; however, there is growing evidence suggesting that a sibling, parent, or unrelated individual with a single major HLA-A, B, or DR mismatch can be a suitable HSCT donor without necessarily conferring an increased risk for severe GvHD.

In order to evaluate the full extent of HLA compatibility, an extended battery of tissue typing reagents must be used to identify the HLA class I antigens (currently over 60 can be defined by serology). In contrast, for differentiation of HLA class II antigens, DNA-based typing procedures must be utilized (since neither the 200+ polymorphic HLA-DR antigens or homozygosity can be adequately defined by standard HLA-DR serology). Interestingly, these high resolution DNA typing methods have been shown to better

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predict GvHD and transplant outcome as compared to other methods like mixed lymphocyte culture assay etc.

HLA-A, B, and C locus antigens are determined by a complement-dependent lymphocytotoxicity assay with a minimum of 144 to 216 different HLA alloantisera and monoclonal antibodies. These reagents, collectively, can identify over 60 different HLA antigens. HLA-DR alloantigens are defined using DNA-based procedures. Currently, more than 200 HLA-DRB1 alleles or groups of alleles can be identified. For molecular typing genomic DNA is first isolated and then amplified by the polymerase chain reaction (PCR) using several pairs of oligonucleotide primers.

It is highly desirable to evaluate all first degree blood relatives of the patient's family, including parents, at the same time so that direct comparisons of the data can be performed. It is absolutely essential to identify the racial background of the family and the relationship of each member in relation to the patient. With this information, HLA genotyping results (with HLA haplotype assignments) can be provided to the clinician, together with a narrative interpretation of the extent of HLA compatibility.

The immune response against HLA molecules can cause two types of problems after a bone marrow transplant. When the immune system of the recipient responds against HLA molecules of the donor, rejection can occur. When this happens, the normal marrow from the donor is destroyed. Recent studies have shown that HLA-A, HLA-B, and HLA-C molecules of the donor are more likely to cause rejection than HLA-DR or HLA-DQ molecules. When immune cells of the donor respond against HLA molecules of the recipient, graft-versus-host disease (GvHD) can occur. When this happens, the skin, liver, stomach and intestines of the recipient are injured. Recent studies have shown that HLA-DR and HLA-DQ molecules of the recipient are more likely to cause GvHD that of HLA-A, HLA-B, and HLA-C molecules. The role of HLA-DP molecules in marrow transplantation is not yet known.

The best way to prevent rejection and GVHD is to ensure that the donor and recipient have the same types of HLA molecules. Because there are so many different kind of HLA molecules, and because each kind of HLA molecule can have many different types, the chance that any two unrelated people will have the same combination of HLA types is very low. This problem is being solved by establishing registries containing large numbers of volunteers who have had HLA typing by blood tests and who have agreed to be available as a marrow donor if they have the same type of HLA molecules as someone who needs a transplant. A patient's chance of finding a donor who has the same combination of HLA types is greatly increased by having a large number of people in the registry. Even with registries containing millions of donors, however, some patients are not able to find a donor who is perfectly matched for all HLA molecules. In this situation, transplantation must be done with a donor whose HLA molecules are not all the same as those of the recipient, even though this increases the chance of rejection or GvHD after the transplantation.

SOURCES OF STEM CELLS

Majority of stem cell transplantations in thalassemias were performed by using HLA-compatible sibling donor bone marrow. In recent years, the source of stem cells have been extended to include peripheral blood stem cell (PBSC) and cord blood stem cells (CBSC) for transplantation. Since the first successful transplantation of CBSC in a patient with Fanconi's anemia (Gluckman et al. 1989), more than 600 cord bloods have been used as a source of hemotopoietic stem cells for transplantation to treat a variety of malignant and nonmalignant hematologic disorders. (Gluckman et al. 1989; Gluckman et al. 1997; Rubinstein et al. 1998; Kelly et al. 1997).

PROGNOSTIC FACTORS FOR OUTCOME AFTER BMT

The risk of BMT using an HLA-identical sibling donor could be predicted according to the presence or absence of only three criteria: hepatomegaly, evidence of portal fibrosis in the liver on biopsy, and inadequate iron chelation therapy (Lucarelli et al. 1990). Patients with none of these risk factors can be categorized as class I, with one or two of these risk factors as class II, and with all the three risk factors as class III. When such type of analysis was performed in a large series of patients it was seen that disease-free survival was 94%, 77% and 53% in class I, II and III, respectively (Lucarelli et al. 1990).

CONDITIONING REGIMENS

Most BMT centers use a combination of busulfan and cyclophosphamide for the conditioning regimen, with cyclosporine +/- short course methotrexate as graft-versus host disease (GVHD) prophylaxis. The most widely used regimen is a total dose of 14 mg/kg of cyclophosphsmide over the next 4 days (Lucarelli et al. 1990; Galimberti et al. 1997). This regimen is the most appropriate for patients with class I and II disease. For those higher risk patients in class III (particularly for patients >17 years), a lower dose of cylocphosphamide (120 – 160 mg/kg) is recommended in order to reduce transplant related mortality (Lucarelli et al. 1996), although this is likely to be at the expense of an increased chance of graft rejection. On the other hand, to overcome the risk of graft rejection in poor-risk class III patients, some centers use either 16 mg/kg or 600 mg/m2 of busulfan especially in children with markedly expanded abnormal erythropoiesis (Lucarelli et al. 1996; Issargrisil et al. 1997). The addition of antilymphocyte globulin (ALG) / antithymocyte globulin (ATG) or Campath to the pre-BMT preparative regimen effectively have reduced the rate of graft rejection in many trials (Galimberti et al. 1997; Krishnamorrthy et al. 1999; Souillet et al. 1995; Roberts et al. 1995).

LONG-TERM CONSEQUENCES

For thalassemic patients who have undergone BMT and acquired normal hematologic status post transplant, the term "exthalassemic after transplant" has been proposed by Lucarelli (Lucarelli et al. 1996). The long-term consequences in these ex-thalassemics include both the complications associated with the underlying disease and those that arise from the allogeneic stem cell transplantation. Virtually all "ex-thalassemic" patients have moderate-severe iron overload (Li et al. 1997). In order to prevent progressive cardiac and hepatic damages in patients who maintain high levels of iron overload, it is now recommended that these "exthalassemic" patients should have their total iron burden reduced towards normal levels by regular venesection or desferrioxamine administration. The effect of BMT on growth and development in "ex-thalassemics", particularly on fertility, is still not clear. Thalassemic children transplanted early in the history of their disease (<8 years) regain a normal growth rate after BMT, while older children and children in class III, especially those who developed chronic GvHD, often have severely impaired growth (Lucarelli et al. 1990). There are evidences that gonadal function of some patients who have undergone BMT for thalassemia is impaired, but it is not clear how much of this effect is a result of previous iron overload or a consequence of the preparatory regimen (Giardini et al 1995). Indeed, successful pregnancy following BMT for thalassemic, as well as following BMT got other hematological disorders using busulfan/ cylophosphamide conditioning, has been reported, and no increase in congenital anomalies of the resultant offspring has yet been seen (De Sanctis et al. 1991; Borgna-Pignatti et al. 1996).

CONCLUSION

The beneficial results of stem cell transplantation from HLA identical family members for patients with severe thalassemia are clear. Class I patients have a very high probability of cure with a very low early and late morbidity and mortality. Delay of transplantation until the patient is in a risk category beyond class I substantially reduces the probability of transplant success and jeopardizes the reversibility of liver and cardiac damage. It is reasonable to suggest that patients with β-thalassemia who have HLA-identical donors should be transplanted as soon as possible. Umbilical cord blood (UCB) has been shown to be capable of reconstituting the bone marrow of the patient with thalassemia after myeloablated pre-conditioning treatment. The major advantage of UCB over other sources of stem cells is the ability to cross HLA barriers, and there is evidence of less GVHD. The use of related –donor UCB stem cells with HLA mismatches at one to three antigens needs to be considered. It would be worth while to do a prospective study to evaluate the role of UCB stem cell transplantation in the treatment of the thalassemias and hemoglobinopathies.

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