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Allogeneic stem cell transplantation for thalassemia major in India

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ABSTRACT

Allogeneic stem cell transplantation (allo-SCT) is the only currently available curative treatment for thalassemia major. Since it was first done in 1981, several thousand patients have benefited from it and it is now possible to offer this treatment in different parts of the world with good results. With better risk stratification and supportive care, the results of allo-SCT are now very good even in high risk patients who have significant iron overload related organ dysfunction. The improvements have mainly been in the conditioning strategies with less toxic myeloablation and management of the complications of SCT. However, several challenges remain. Transplant related complications still cause significant morbidity and mortality. There is data to show that the results of transplantation as best if done in well transfused and chelated patients <7 years of age. As only a third of the patients will have a matched related donor, there is need for investigating SCT with alternative donors. Experience with SCT for thalassemia major from matched unrelated donors or haplo-identical donors is still limited but needs further exploration. Adequate management needs to be provided post-SCT for all pre-existing complications particularly iron chelation to prevent further organ dysfunction. Systematic follow-up is needed to measure long term outcomes. The biggest challenges in India are the cost of this treatment and access to centres capable of providing this treatment. With greater support from the government, health insurance and philanthropic programs, there has been a rapid increase in the number of SCTs for thalassemia major in India. The number centres providing this treatment are also increasing making this curative treatment more widely available in India.

1. Introduction

Recent advances in gene therapy for hemoglobinopathies could potentially be a paradigm change in the management of these disorders. Currently however, an allogeneic stem cell transplant (allo-SCT) remains the only curative option for the majority of patients with β thalassemia major. The use of allo-SCT is rapidly increasing in India and other developing countries and is hence the most widely available and accessible curative therapeutic strategy for this condition. The central concept revolves around the ability to replace the hematopoietic stem cells (HSC) from a donor to a recipient resulting in a new donor derived hematopoietic system in the recipient. Significant advances over the last two decades have resulted in a steady improvement in clinical outcomes for patients with this disorder undergoing such a procedure. Currently in patients with good risk features it is reasonable to anticipate a greater than 90% chance of a successful transplant outcome [1]. Even among those with high risk features, success rates are approaching 80%. These improvements have resulted from use of better risk stratified conditioning regimen and more effective supportive care [1,2].

With thalassemia being a significant public health problem in the country, there is great need for effective transplant programs. Absence of suitable donors, cost of treatment and lack of enough centers capable of offering this therapy are major challenges preventing wider use of this therapy. With increase in the donor pool by the use of matched unrelated donors, cord blood stem cells and haplo-identical donors, more patients can access this curative therapy. Experience with alternate donor transplants for

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thalassemia major is gradually increasing and their results are also getting better. However, more experience is required with these transplants before they can be considered standard of care. Better understanding of graft characteristics and immune re-constitution post-transplant has the potential to identify interventions to further improve the short and long term clinical outcomes. There is limited data on the role of splenectomy prior to transplant or optimal post-transplant chelation and care of these patients. These are some of the issues that will be briefly addressed in this review along with a description of the situation with HSCT for thalassemia in India.

2. Risk of graft rejection and regimen related toxicity (RRT) in high risk populations

Risk stratification of patients with β thalassemia major undergoing a myelo-ablative allogeneic (SCT) classifies them into three risk groups (Pesaro Class I, II and III) based on liver size (>2 cm), presence of liver fibrosis and inadequate iron chelation [3,4]. Patients with none of the above risk factors are classified as Class I, those with one or two of these risk factors are Class II while those patients who have all three adverse risk factors are classified as Class III. Patients in Class I and II our considered to be low risk and have an excellent long term outcome following an allogeneic SCT [3,4]. Class III patients on the other hand are considered high risk and have inferior outcomes following a SCT. However, in a population with poor medical treatment prior to SCT, the above risk stratification is limited by its failure to recognize [2] the significant heterogeneity among patients in Class III. The Pesaro risk stratification [3,4] does not recognize a very high risk subset of Class III in these populations perhaps because such patients hardly exist in Western countries. With allo-SCT being increasingly offered in many developing countries where this category of patients exist in large numbers, recognizing this high risk group is extremely important to suitably modify their HSCT protocols [2,5,6].

Retrospective analysis of factors impacting clinical outcome on large data set from our center done in 2007, helped us to identify age ≥7 years old and had a liver size ≥5 cm in a patient pre-transplant to constitute what has been shown to be a very high risk subset of a conventional Class III group (Class III Vellore high risk or Class III VHR) [2]. The adverse impact of age (≥7 years) and liver size (>2 cms) was further validated by an international collaborative analysis in 2010 [7]. The significance of this differentiation has been emphasized by the fact that outcomes of HSCT were clearly different in these two groups when treated with the same protocols. Class III and more specifically Class III Vellore high risk [8] subset have a high risk of graft rejection and regimen related toxicity (RRT), especially sinusoidal obstruction syndrome (SOS) leading to multi-organ failure and death. These complications are perhaps related to the high degree of allo-immunization and iron over load related end organ damage in this cohort. The poor clinical outcome in this subset of older patients with very poor pre-transplant medical therapy, as reported previously, is not reflected in the Western literature as such patients are distinctly uncommon there. However, when such a population is transplanted even in a developed country with expertise in such transplants the rejection rate is as high as 34% [9].

3. Challenges to select conditioning regimen: reducing graft rejection and RRT

At our center we evaluated two different regimens of busulfan to see their effect on graft rejection, we also added anti-lymphocyte globulin in one of them to see its effect on graft rejection and GVHD [10]. While we did succeed in demonstrating an association with graft rejection and busulfan pharmacokinetics we were not able to see any effect of anti-lymphocyte globulin in this study on graft rejection or GVHD (data not shown for GVHD), we were also not able to address the relatively high incidence of RRT in this population [10]. The increased incidence of RRT, particularly in the high risk patients with thalassemia major, has led to the evaluation of a number of novel conditioning regimens to improve the clinical outcome among these patients [3,4,11–16] (summarized in Table 1). Early efforts to reduce the RRT among Class III patients involved reducing the cumulative dose of cyclophosphamide from 200 mg/kg to 160 mg/kg[13]. While this approach did significantly reduce the RRT associated mortality it was also associated with an increased incidence of graft rejections (from 13% to 35%) [13]. An increased risk of graft rejections was noted in all subsequent attempts at reduced intensity conditioning regimens to reduce RRT [17,18] and hence for the most part such an approach has been abandoned as an option in patients with transfusion dependent hemoglobinopathies such as Thalassemia major. The first successful attempt at improving clinical outcomes in Class III patients by modifying the conditioning regimen was reported by Sodani et al. [12]. They used the same template of reducing the cyclophosphamide dosing to 160 mg/kg but based on their initial adverse experience with this approach augmented the immune-suppression by adding fludarabine and azathioprine to the conditioning regimen. Additional elements starting from day −45 included intensive chelation and hyper-transfusion therapy along with hydroxyurea and growth factors. They achieved <10% graft rejection with a >85% event free survival in a relatively small series of 33 consecutive Class III patients. There have been no subsequent series from the same or other centers that have replicated these results. Intravenous busulfan along with therapeutic dose monitoring and dose modifications was a promising strategy to reduce RRT and potentially reduce the risk of graft rejection as illustrated in the study by Gaziev et al. [19]. However, as demonstrated in the study by Chiesa et al. this approach while effective in reducing RRT was not able to reduce the risk of graft rejection in patients with very high risk thalassemia major [9]. More recently, Anurathapan et al. reported a novel approach of administration of one or two courses of immune-suppressive therapy with a combination of fludarabine and dexamethasone one to two months prior to start of conditioning and followed this up with a reduced toxicity myelo-ablative conditioning regimen consisting of fludarabine, intravenous busulfan and anti-thymocyte globulin with promising results in another small series of 18 patients with Class III VHR thalassemia major [20]. The caveat to interpretation of the above studies is that the proportion of Class III patients varies and the subset of patients who would fulfill the criteria for Class III VHR is often not available. These variables, especially the proportion in Class III VHR would significantly impact the clinical outcome and make comparison across different studies difficult unless they are clearly identified in all reports.

4. Novel conditioning regimen

Treosulfan (dihydroxy-busulfan), in the recent past, has attracted a lot of attention as an agent to replace busulfan in view of its favorable toxicity profile [21]. While treosulfan is structurally similar to busulfan, unlike busulfan it is water soluble and easy to reconstitute and administer intravenously. It also has a linear pharmacokinetic profile but with large intra and inter individual variability in pharmacokinetic profile of nearly 30 fold [22,23]. However, again unlike busulfan, it has a huge therapeutic window because in Phase I studies at even at cumulative doses of 56 gm/m^2 (a dose not usually reached when used as an agent in conditioning regimens) there were no dose limiting hepatic, renal, neurological