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Hematopoietic Cell Transplantation for Thalassemia: A Global Perspective BMT Tandem Meeting 2013

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A B S T R A C T

Hematopoietic cell transplantation (HCT) remains the sole available curative option for patients with β-thalassemia major. Expanded and improved supportive therapies for thalassemia now routinely extend the life span of affected individuals well into adulthood. Consequently, in regions of the world where this care is readily available, HCT has been pursued infrequently, in part owing to concerns about an expected lack of balance between risks and benefits. More recently, however, recognition of significant health problems in older patients with thalassemia, along with recognition of increased risks of graft-versus-host disease (GVHD), graft rejection, and impaired organ function leading to inferior HCT outcomes in this particular group, seem to be turning the wheels and tipping the balance again in the direction of consideration for earlier HCTs. In contrast, in countries where thalassemia is most prevalent (>100,000 new children born each year in Middle East and southeast Asia), lack of supportive care standards together with often insufficient access to dedicated health care facilities, results in the majority of these children not reaching adulthood, further supporting the need for expanded access to HCT for these patients. The cost of HCT is equivalent to that of a few years of noncurative supportive care, such that HCT in low-risk young children with a compatible sibling is justified not only medically and ethically but also financially. International cooperation can play a major role in increasing access to safe and affordable HCT in countries where there is a considerable shortage of transplantation centers. In this article, we review the current status of bone marrow transplantation for thalassemia major, with particular emphasis on a global prospective.

INTRODUCTION

β-thalassemia is the most common genetic disease worldwide. Although improvements in conservative treatment have improved the prognosis of thalassemia considerably, disease- and treatment-related complications in affected patients progress over time, causing severe morbidity and shortened life expectancy, along with substantial health care expenses in countries with high carrier rates, ranging between 5% and 30% [1]. Significant progress in hematopoietic cell transplantation (HCT) for thalassemia has been made over the last 3 decades [2], such that disease-free survival (DFS) rates exceeding 80% have been consistently reported in young, low-risk patients with a histocompatible family donor [3]. In addition to improved DFS, HCT is also associated with improved quality of life.

TRANSPLANTATION RISK ASSESSMENT

The largest experience with HCT for thalassemia comes from Pesaro, Italy, where a standard pretransplantation risk assessment was developed. The standard "Pesaro" risk stratification scheme [4] based on liver size by physical examination, fibrosis detected on liver biopsy, and chelation history has been used for years to risk stratify patients before HCT and has been shown to correlate well with transplantation outcomes. However, this stratification is not readily applicable in settings where liver biopsy analysis might not be performed routinely. Moreover, this scheme was developed largely in patients with regular access to RBC transfusions and might not apply to chronically undertransfused children in whom hepatomegaly may not necessarily reflect severe iron overload and can potentially be partially corrected with an appropriate pre-HCT transfusion program. More recently, alternative-risk group assignments independent of liver biopsy have been proposed. One such risk stratification scheme based primarily on age and liver size reported cure rates exceeding 70% for MSD HCT in children aged <7 years with liver palpated ≤5 cm below the costal margin, regardless of chelation history or liver fibrosis [5]. A report from the Center for International Blood and Marrow Transplant Research (CIBMTR) on results of HLA-matched sibling HCT for thalassemia major performed in locations other than Italy confirmed that age at transplantation and liver size are independent predictors of mortality after transplantation. In patients aged <7 years and without hepatomegaly (liver palpated <2 cm below the costal margin), the 5-year probabilities of OS and DFS were 98% and 94%, respectively [6].

SPLENECTOMY AND HCT

Many children with thalassemia who do not receive optimal care and regular transfusions will have hepatosplenomegaly. Enlarged spleen per se is not associated with higher rejection rates but may increase transfusion requirements and delay engraftment [7]. Retrospective data

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suggest that splenectomy may be associated with increased transplantation-related mortality [7], but whether this is an independent risk factor is not clear [5]. At present, most centers probably would not recommend routine splenectomy before HCT for thalassemia.

HEPATITIS C

Hepatitis C virus (HCV) infection remains an additional pretransplantation consideration in patients from many developing countries with a history of multiple transfusions [8] and is associated with progression to both liver fibrosis and hepatocellular carcinoma [9]. Reportedly, however, it can clear spontaneously in approximately one-third of patients. To date, there is no evidence that HCT has any influence on the course of HCV infection or vice versa [10]. In fact, given the synergism of HCV and iron overload in accelerating the progression of liver fibrosis [11], HCV positivity might lend support to the decision to move forward with HCT in selected patients.

TRANSPLANTATION CONSIDERATIONS

Results of HCT for patients with thalassemia have improved steadily over the last 3 decades owing to the development of new preparative regimens and effective control of transplantation-related complications. The earliest studies used conditioning regimens with a myeloablative backbone of busulfan and cyclophosphamide for matched sibling donor (MSD) HCT and demonstrated successful outcomes.

Results from the Italian group for MSD HCT for Pesaro class I, II, and III recipients show thalassemia-free survival probabilities of 87%, 85%, and 80%, respectively. Despite these improvements, however, pretransplantation transfusion exposures and organ damage from iron overload continue to have a negative impact on transplantation outcomes. In a recent update, transplantation-related mortality was 3% in class I or II patients and 10% in class III patients, and 8% to 12% of pediatric recipients experienced graft rejection after HCT [12].

The most recent MSD HCT experience from outside Italy comes from the CIBMTR data, which confirm that HLA-MSD HCT for thalassemia major is a suitable therapeutic option to consider, with DFS rates exceeding 90% in children with good-risk features. However, as noted in the initial Pesaro experience, children with high-risk features fared much worse, with an event-free survival rate approaching 50% [6]. Modifications to the transplantation regimen that might improve the safety of the procedure are important; for example, investigators in Italy have reduced the cyclophosphamide dose in high-risk patients [13]. Alternatively, replacing cyclophosphamide with fludarabine might also mitigate the risk of significant transplantation-related toxicity [14]. In contrast, the use of antithymocyte globulin does not appear to reduce the risk of graft failure.

The major limitation of HCT for thalassemia is the lack of an HLA-identical sibling donor for the majority of recipients. Currently, with high-resolution HLA typing, it is possible to perform HCT with unrelated donor grafts for thalassemia; however, this is associated with significant treatment-related mortality, graft rejection, and chronic GVHD. Patients who lack both an MRD and a suitable unrelated donor could also benefit from haploidentical mother-to-child transplantation. Although the number of patients undergoing HCT using this strategy is small, the results of this transplantation approach are encouraging.

Our current understanding of stable mixed chimerism in patients with hemoglobinopathies also provides a rationale for the use of less-intensive conditioning regimens. In this regard, several recent patient series have shown progress in addressing the problems of graft rejection and regimen-related toxicity, which in turn should help expand the use of HCT even beyond the scope of MSD HCT. Examples include extending the duration and intensity of pretransplantation immunosuppression by administering azathioprine and hydroxyurea 6 weeks before HCT and adding fludarabine to the conditioning regimen. The use of treosulfan in lieu of busulfan also appeared to generate excellent results in the unrelated donor setting [15].

POST-HCT COMPLICATIONS

Veno-Occlusive Disease of the Liver

VOD does not seem to be a major or frequent complication in the Italian experience of more than 1000 HCTs for thalassemia (P. Sodani, personal communication). The incidence of VOD is higher in Indian patients [16]. Potential explanations for this discrepancy include differences in busulfan dosing and/or sensitivity related to pharmacogenetic variables among populations. However, a low rate of VOD, similar to the Italian experience has also been reported in Pakistani children, who have a more similar genetic background to Indians [17].

Late Affects

Data on long-term outcomes after HCT for thalassemia remain limited. Second malignancies after HCT do not seem to be a major issue, possibly because conditioning regimens generally do not incorporate irradiation. In contrast, infertility remains common, occurring in approximately 60% of patients undergoing HCT for thalassemia regardless of sex. In countries where thalassemia is most prevalent, this problem might be particularly relevant, and fertility preservation strategies like sperm banking and ovarian tissue cryopreservation should be considered whenever feasible. In addition, fertility problems should be clearly addressed with patients during pre-HCT counseling and consent procedures.

ALTERNATIVE DONOR HCT FOR THALASSEMIA IN DEVELOPING COUNTRIES

Despite large average family sizes in many thalassemia-prone areas, an MRD might not be available for the majority of children with thalassemia. Having a thalassemic child is a dramatic event per se that often dissuades parents from taking the risk of having other children with the disease, and it can also drain most of a family's resources. It should be kept in mind, however, that particularly in areas with high rates of consanguineous marriages, MRDs may be found in the extended family, and HLA typing of first-degree relatives, starting with grandparents, who are often healthy and young enough to donate marrow, should be considered [18]. This may be especially useful in families with 2 children with thalassemia, which is not infrequent, where there is double the chance that at least 1 of the 2 children will find a match.

Unrelated donors (URDs) have been used successfully; however, the need for extended histocompatibility matching hinders identification of suitable URDs, most of who belong to ethnic groups underrepresented in donor registries [19]. The prohibitive cost of donor searches and unrelated marrow procurement is another limiting factor.

In the European experience, unrelated cord blood transplantation for thalassemia major has been associated with

high rates of rejection and transplantation-related morbidity and mortality [20], making unrelated cord blood an undesirable stem cell source. Moreover, cord blood is a very expensive stem cell product subject to stringent quality control and regulatory standards. The same technical and cost-related issues apply to related cord blood transplantation. In fact, cost is a major factor determinant of any transplantation procedure for lower-income patients with thalassemia. In addition, the elevated risk of extensive chronic GVHD, which actually might worsen quality of life compared with thalassemia itself, should be taken into consideration.

Partially matched related donors—typically a parent—are readily accessible. In the sole series published to date, in which extensively T cell–depleted maternal stem cells were used for HCT, 14 of 22 patients with thalassemia (63%) achieved transfusion independence. Transplantation-related mortality was 9%, the rejection rate was 28%, and no patient developed acute or chronic GVHD [21]. The use of post-HCT high-dose cyclophosphamide as a means of bidirectional in vivo allodepletion with its associated faster immunologic recovery, tolerable delays in hematologic engraftment [22], along with decreased costs, could potentially be an attractive and realistic alternative in lower-resource settings.

INTERNATIONAL COOPERATION PROJECTS: THE CURE2CHILDREN FOUNDATION EXPERIENCE

A nonprofit project supporting HCT for thalassemia in emerging countries, the Cure2Children Foundation (C2C) was developed by a group of Italian parents who lost their children to cancer. C2C's primary mission is to increase sustainable access to care for all children with cancer and severe blood disorders.

This initiative aimed at offering HCT to low-risk children with a compatible donor on a nonprofit basis directly in Pakistan. The primary objective was to obtain cure rates comparable to international standards in young low-risk children with thalassemia with an available compatible sibling donor, while minimizing expenses by implementing primarily evidence-based recommendations. Although the children were admitted to single rooms with private bathrooms but stringent air-control systems, masks and gowns were not required. Nursing personnel were specifically trained on strict handwashing and central line management and were exclusively dedicated to the transplantation unit. The nurse:patient ratio was limited to 1:3. Onsite training was performed by a team of experienced C2C professionals. This included 3 weeks of focused hands-on training for the initial 2 transplantation procedures, followed by ongoing 24/7 online intensive assistance and tutoring via established management/conferencing tools. Patient-specific treatment plans designed according to good clinical practice, with the goal of minimizing prescription errors, were also used and provided clear and simple operating instructions to point-of-care professionals. This model was implemented in 2 newly established transplantation units, one in Islamabad, Pakistan, and the other in Jaipur, India.

The predetermined HCT strategy included a preparative regimen containing thiotepa, busulfan (oral), and cyclophosphamide. The stem cell source was unmodified bone marrow, and GVHD prophylaxis consisted of cyclosporine, methotrexate, and prednisone. This regimen was based on the protocol used by Lucarelli's group in younger children with thalassemia, in which thiotepa was introduced to reduce the rejection rate observed with a standard busulfan/cyclophosphamide regimen [23]. All patients received irradiated blood products, and cytomegalovirus DNA copies were monitored by real-time PCR.

For the first 12 children, aged <6 years with liver size ≤ 2 cm, thalassemia-free survival was 91% at a median follow-up of 24 months. One child died from sepsis/meningitis, possibly tuberculosis. None developed severe acute or extensive GVHD, overt cytomegalovirus disease, or invasive aspergillosis.

In both Islamabad and Jaipur, the cost of setting up a 3-bed transplantation unit was less than $100,000 USD, and the cost of HCT for each patient was in the $10,000 USD range. A patient coordinator, as well as housing and a monthly allowance, were provided as needed throughout the first 8 months post-HCT.

POTENTIAL INDIRECT POSITIVE EFFECTS OF HCT

Involvement of Extended Family in Prevention Programs

Screening and prevention remains the only realistic way to effectively control thalassemia. In countries where this disease is most prevalent, there is a general lack of preventive programs. Previous studies have shown that cascade screening, stemming from an affected case or a carrier, may identify a substantial proportion, if not the majority, of cases. This is particularly true in cultures with high rates consanguinity, where the thalassemia gene tends to remain "trapped" within extended families [24]. These families might be engaged in screening, counseling, and prevention programs through the offer of cure for their affected children, although, unfortunately, there is often resistance to performing a test that might stigmatize a thalassemia carrier as "less fit."

Promotion of Compliance with Supportive Care

Offering a realistic prospect of a definitive cure is a strong incentive for many families to better comply with supportive care for their affected children.

Health Care Empowerment and Higher Medical Education

Many factors contribute to HCT for thalassemia providing a unique opportunity for capacity building, including the following: (1) Thalassemia represents the major indication for HCT in many developing areas; (2) young low-risk children may enjoy very high success rates after HCT with good quality of life; (3) HCT for thalassemia is financially justified; (4) in the wide spectrum of HCT procedures, the procedure for low-risk thalassemia is relatively simple, safe, and amenable to focused training and task-shift strategies; and (5) increasing evidence suggests that complex infection control environments with HEPA filtration and positive pressure gradients might not be required.

In the Cure2Children-supported thalassemia HCT project in developing countries, results in low-risk patients have been comparable to those obtained in Italy with a fraction of the cost (ie, approximately $10,000 USD per transplantation). Moreover, HCT for thalassemia was performed by personnel with limited experience within a structured training and collaboration program.

CONCLUSION

Thalassemia is one of the most prevalent chronic life-threatening noncommunicable diseases affecting children in lower-income regions worldwide. There is a growing demand for HCT for thalassemia, which provides the only curative treatment for these children. In low-risk young

children with an available MSD, very high cure rates can be obtained with good quality of life and a fraction of the costs compared with affluent countries. HCT also reduces the financial burden of thalassemia on affected families and health care systems and may help increase compliance with supportive care, as well as awareness of prevention.

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