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Hematopoietic stem cell transplantation for thalassemia

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Abstract

Hematopoietic stem cell transplantation is the only modality that offers the potential of cure for severe thalassemia, including homozygous β-thalassemia and severe Hb E/β-thalassemia. All children with class 1 or 2 disease should be transplanted if they have HLA-identical siblings, and transplantation should be performed as early as possible. Sibling cord blood transplantation is recommended in children with class 1 or 2 of the disease if adequate numbers of cord blood cells from younger siblings are available.

Bone marrow transplantation in class 3 children and adult patients with appropriate conditioning regimen gives results that are superior to those obtained with cord blood. However, we recommend that patients and their families should discuss in detail the risks and benefits, and transplantation should be performed in only motivated patients who have a clear understanding of the entire process. There is new hope that haploidentical transplantation will be successful, but further studies are required to confirm early results.

Keywords: thalassemia, clinical risk factors, hematopoietic stem cell transplantation, indications, benefits

Introduction

The distribution of thalassemia used to be confined to areas from the Mediterranean across the Middle East through Southern Asia to Southeast Asia: the so-called thalassemia belt [1]. At present, migration of people has spread thalassemia throughout the world. Furthermore, with the improvement of medical care, including developing countries, thalassemic children can now survive the early months of life and live long enough to require treatment. Thalassemia is, therefore, now considered to be a global health problem [2].

In Thailand, both α- and β-thalassemias as well as Hb E and Hb Constant Spring are prevalent [3]. There are more than 60 clinical syndromes resulting from various gene interactions, giving 12,000 annual births of thalassemic children. Among them, the common severe thalassemic syndromes with which patients can survive are homozygous β-thalassemia or thalassemia major, and Hb E/β-thalassemia. Hb E/β-thalassemia is the most common severe clinical syndrome in adults and is found more frequently than homozygous β-thalassemia in Thailand [4]. This syndrome is unique to Southeast Asia in general and to Thailand in particular. Clinical manifestations of this syndrome are heterogeneous: at one end, symptoms may be as severe as with thalassemia major, at the other end, patients may have only mild anemia [4]. However, those who show symptoms related to anemia during the first year of life usually have severe manifestations later on.

Therapy of severe thalassemia with regular hypertransfusion and iron chelation has dramatically improved life expectancy [5,6], but there remain many problems related to quality of life, compliance, and expense. Hematopoietic stem cell transplantation is at present the only modality with the potential to

cure thalassemia [7]. The objective of allogeneic transplantation for thalassemia is to replace thalassemic hematopoiesis by normal hematopoiesis through allogeneic stem cell transplantation. Patients require "conditioning" to eradicate thalassemic stem cells and to overcome the immunological barriers (histoincompatibility and transfusion-associated allosensitization).

Bone marrow transplantation from HLA-identical siblings in children with thalassemia

The first successful treatment of thalassemia with bone marrow transplantation from HLA-identical sibling donors was performed in 1981 in Seattle [8]. Most subsequent experience, however, has been reported by the Pesaro group [9-14], and other case series have been presented [15-23]. Most transplants for thalassemia have employed bone marrow from unaffected HLA-identical sibling donors. However, only 25–30% of patients have an HLA-matched sibling donor.

By using conditioning with busulfan, 14 mg/kg given over 4 days, followed by cyclophosphamide, 200 mg/kg over the next 4 days, the Pesaro group reported successful bone marrow transplantation in large numbers of children and identified three risk factors, which predicted outcome after transplantation [9]. These risk factors include hepatomegaly of more than 2 cm, liver histology showing portal fibrosis, and irregular (and therefore ineffective) iron chelation. On that basis patients can be classified into three risk categories: class 1 without any risk factors, class 2 with one or two risk factors, and class 3 with all risk factors.

Results in class 1 and 2 patients

The majority of transplants were performed in children in the class 1 and 2 risk groups using bone marrow from HLA-identical siblings. Overall survival was 87–90% and thalassemia-free survival 85–87% [9,11,15-23]. The incidence of graft rejection and transplant-related mortality was 3% and 10–13%, respectively. On the basis of these recommendations, children with severe thalassemia should undergo bone marrow transplantation if they have HLA-identical siblings, as early in life as possible.

Class 3 patients

By using busulfan at 14 mg/kg and cyclophosphamide at 200 mg/kg as conditioning, the Pesaro group reported lower overall survival (61%), thalassemia-free survival (53%) and higher transplant-related mortality (47%) [12] than that observed in class 1 and 2 patients. Conditioning comprising busulfan 14 mg/kg and *lower dose of cyclophosphamide* (160 or 120 mg/kg) improved the overall survival to 80%; however, the graft rejection rate was increased to 33%, giving a thalassemia-free survival of 56% [12]. This conditioning regimen is, therefore, inadequate to eradicate the marrow erythroid hyperplasia related to the disease.

A new preparative regimen was developed by the Pesaro group in an attempt to eradicate more effectively thalassemic marrow erythropoiesis [14]. This protocol comprises intensified preparation with hydroxyurea 30 mg/kg and azathioprine 3 mg/kg daily on day -45 to day -11, followed by fludarabine 20 mg/m^2/day from day -17 to day 11, and busulfan at, 14 mg/kg and cyclophosphamide at 160 mg/kg . With this approach overall survival, thalassemia-free survival, graft rejection and transplant-related mortality were 93%, 85%, 8% and 6%, respectively. Thus, the use of this regimen has improved outcome in class 3 patients to the level observed in class 1 and class 2 patients conditioned with a less intensive regimen.

Transplantation in adult patients

Early trials from the Pesaro group showed unfavorable results in adult patients, who typically had more advanced disease with marked erythroid expansion and therapy-related organ complications. With conditioning regimens comprising busulfan 14 mg/kg and cyclophosphamide 200 mg/kg in class 2, and busulfan 14–16 mg/kg and cyclophosphamide 120–160 mg/kg in class 3 patients, the overall survival, thalassemia-free survival, rejection, and transplant-related mortality were 66%, 62%, 4%, and 37%, respectively.

By using a new preparative regimen similar to that used for children with class 3 risk (cyclophosphamide dose lowered to 90 mg/kg), the overall survival, thalassemia-free survival, rejection, and transplant-related mortality were 65%, 65%, 7%, and 28%, respectively [14]. Thus, this strategy has improved transplant results in adult patients with thalassemia; however, transplant-related mortality is still significant.

Bone marrow transplantation for thalassemia in Thailand

The first successful bone marrow transplant for thalassemia in Thailand was performed in 1988 at Siriraj Hospital, Mahidol University. Subsequently, transplant programs were also developed at Ramathibodi and Chulalongkorn hospitals. By 2008, 241 patients with thalassemia had undergone bone marrow transplantation in Thailand. Of these, 48 (22%) had homozygous β-thalassemia, and 155 (72%) had severe Hb E/β-thalassemia. Patients with Hb E/β-thalassemia with anemic symptoms for the first time during the first year of life are considered to have severe disease and should undergo bone marrow transplantation if they have HLA-identical siblings. Only a few patients received hypertransfusion and iron chelation. The results showed that overall survival and thalassemia-free survival in class 1 and 2 children were 89% and 80%, respectively. However, results in class 3 children were unfavorable. By using modified conditioning with busulfan 600 mg/m^2 and cyclophosphamide 200 mg/kg, outcome was improved to 90% overall survival, and 85% thalassemia-free survival [15].

Cord blood transplantation from related donors

We reported the first successful use of cord blood from an unaffected younger sibling to transplant a child with Hb E/β-thalassemia [24]. The use of cord blood circumvents the need for a donor bone marrow harvest, is associated with a lower incidence of GvHD, and allows for prompt transplantation. So far, 14 patients have undergone cord blood transplanta-

tion for thalassemia at our institution. Three patients had homozygous β-thalassemia, and 11 had Hb E/β-thalassemia. Patients were 1 to 8 (a median of 4) years old, 8 were males and 6 were females. One patient died early, and one patient failed to engraft. Twelve patients had documented engraftment, and 10 of them are surviving thalassemia-free. Two patients, both in risk class 3, rejected their grafts. Based on our experience from a single institution, we recommend that sibling cord blood transplantation should be performed only in children with class 1 or 2, not in advanced disease. An adequate cell dose of cord blood is important to guarantee success.

Data from Eurocord show a high survival rate (100%) and thalassemia-free survival of 89% for class 1, and 62% for class 2 patients [25]; however, graft rejection was high (21%), presumably reflecting the importance of cell dose, although cell dose did not predict engraftment. Graft rejection was decreased when thiotepa was added to the conditioning regimen, and when methotrexate was omitted from GvHD prophylaxis.

Transplants from donors other than HLA- identical siblings

Only 25–30% of patients have an unaffected HLA-identical sibling donor. The remaining patients may receive stem cells from alternative donors including matched unrelated donors, unrelated cord blood, and haploidentical donors. However, it should be emphasized that thalassemia is not a malignant disease, and although bone marrow transplantation can cure the disease, patients can live a long time with a satisfactory quality of life with hypertransfusion and iron chelation, and without transplantation. Transplants from donors other than HLA-identical siblings should be considered only when patients and their parents fully understand the potential risks and benefits and are motivated to perform transplantation.

Marrow transplantation from HLA-matched unrelated donors

The outcome of matched unrelated donor transplantation has improved substantially, primarily due to more refined histocompatibility typing and selection of donors on the basis of matching at the molecular level. Earlier reports using conditioning with busulfan and cyclophosphamide with or without thiotepa showed thalassemia-free survival of 66%, graft rejection of 12%, and transplant-related mortality of 19% [26]. Favorable results were also obtained in adult patients with overall survival, thalassemia-free survival, graft rejection, and transplant-related mortality of 70%, 70%, 4%, and 30%, respectively [27].

A recent report from Thailand confirms this data, showing overall survival, thalassemia-free survival, graft rejection, and transplant related mortality of 82%, 71%, 13%, and 18% respectively [28]. By 2008, 53 patients had undergone matched unrelated bone marrow transplantation (40 "full" HLA matches, 13 1 or 2 antigen mismatches) in Thailand. Of these 53 patients, 28 were in class 1, 24 in class 2, and 5 in class 3. Overall survival was 87%, and thalassemia-free survival, 80%. Thus, HLA-matched unrelated donor transplantation is an excellent option and may have success rates superior to those achieved with cord blood.

Unrelated cord blood transplantation

Unrelated cord blood transplantation is increasingly used to treat hematological malignancies [29]. The advantages of using cord blood are as follows: faster availability, acceptability of partial HLA mismatching, and low incidence of GvHD; however, engraftment is usually delayed. Recent data from 14 transplant centers showed encouraging results with overall survival and thalassemic-free survival of 77%, and 65%, respectively [30]. Results were better when transplants were performed at experienced centers (overall survival 87% and thalassemia-free survival 77%).

To overcome the cell dose barrier some centers have begun to use two partially HLA-matched cord blood units for transplantation [31].

Transplantation from haploidentical donors

Almost all patients have haploidentical donors. A recent report described a successful use of T-cell depleted CD34+ peripheral blood and bone marrow cells from haploidentical mothers in children with thalassemia [32]. However, the methodology to purify CD34+ cells and deplete T cells is sophisticated and expensive.

Graft failure and graft rejection

Graft failure and rejection is more common after transplant for thalassemia, especially in poor-risk patients, than it is in other diseases. Failure of primary engraftment with persistent aplasia is rare and has a poor prognosis, because second transplants following second course of conditioning yield poor results (overall survival 49%, thalassemia-free survival 33%) [33]. Most patients with graft rejection show autologous recovery of thalassemic hematopoiesis resulting in recurrence of the disease. Graft rejection most often occurs within the first 6 months after transplantation [34], therefore monthly determination of chimerism is recommended for the first 6 months as patients with residual detectable host cells are likely to develop graft rejection [35]. If the proportion of donor cells is declining, withdrawal of immunosuppressive drugs may allow for enhancement of donor hematopoiesis [36].

Mixed chimerism was found in one third of thalassemia patients at 2 months after transplantation. The risks of graft rejection was nearly 100%, 41%, and 13% when residual host cells accounted for more than 25%, 10–25%, and less than 10% of all cells, respectively [35]. None of the patients with complete chimerism at 2 months rejected the graft [35].

A cohort of 295 patients who underwent transplantation showed that at 2 months 95 (33%) had mixed chimerism. At 24 months 42 had become complete chimeras, 33 progressed to rejection, and 20 had persistent mixed chimerism of 30–90% donor cells [34]. These results indicated that engrafted donor cells, as evidenced by stable mixed chimerism, are adequate to cure the disease phenotype once donor-host tolerance has

been established. Therefore, complete eradication of donor hematopoiesis may not be necessary for cure.

Reduced intensity conditioning and transplantation for thalassemia

The findings that *stable mixed chimerism* is sufficient to suppress thalassemic hematopoiesis, have provided the rationale for using reduced intensity conditioning in thalassemic patients. Such an approach can reduce the conditioning-related toxicity, especially in patients with advanced disease. Early results using reduced intensity conditioning were disappointing [37-40]. A more recent report describes the use of busulfan, 8–12 mg/kg, fludarabine, 175–210 mg/m^2, antilymphocyte globulin 20–40 mg/kg with or without thiotepa, and total lymphoid irradiation for conditioning, and cyclosporine or tacrolimus and mycophenolate mofetil for GvHD prophylaxis in 8 patients with class 3 disease [41]. Initial engraftment was observed in all patients, although two patients lost donor chimerism later on. Further studies are needed.

Conclusions

Hematopoietic stem cell transplantation is the only modality that offers the potential of cure for severe thalassemia, including homozygous β-thalassemia and severe Hb E/β-thalassemia. All children with class 1 or 2 disease should be transplanted if they have HLA-identical siblings, and transplantation should be performed as early as possible. Sibling cord blood transplantation is recommended in children with class 1 or 2 disease, if adequate numbers of cord blood cells from younger siblings are available.

Bone marrow transplantation in class 3 children and adult patients with appropriate conditioning regimen gives results that are superior to those obtained with cord blood. However, we recommend that patients and their families should discuss in detail the risks and benefits, and transplantation should be performed only in motivated patients who have a clear understanding of the entire process. There is new hope that haploidentical transplantation will be successful, but further studies are required to confirm early results.

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Трансплантация гемопоэтических стволовых клеток при талассемии

Иссарагризил Сурапол

Резюме

В данной обзорной статье представлены сведения о трансплантации гемопоэтических стволовых Трансплантация гемопоэтических стволовых клеток является единственной возможностью потенциального излечения при тяжелой талассемии, в том числе при гомозиготной β-талассемии и тяжелой талассемии с гемоглобином Е/β. При заболевании 1-го или 2-го классов риска всем детям должна проводиться трансплантация, если они имеют HLA-идентичных братьев или сестер, и такую трансплантацию следует осуществлять как можно раньше. Пересадка клеток пуповинной крови от братьев или сестер рекомендуется детям с заболеванием 1-го или 2-го классов риска, если имеются в наличии адекватные количества клеток пуповинной крови от младших сиблингов.

Трансплантация костного мозга детям 3-го класса риска и взрослым больным с применением соответствующих режимов кондиционирования дает лучшие результаты по сравнению с теми, которые получаются при использовании пуповинной крови. Мы рекомендуем, однако, чтобы больные и их семьи могли обсудить в подробностях возможные факторы риска и преимущества лечения, и трансплантация должна проводиться только мотивированным пациентам, которые имеют четкое понятие обо всем процессе. Новые надежды связаны с возможным успехом гаплоидентичной трансплантации, но требуются дальнейшие исследования для подтверждения предыдущих результатов.

Ключевые слова: талассемия, клинические факторы риска, трансплантация гемопоэтических стволовых клеток, показания, преимущества