

Stem Cell Transplantation for Thalassemia

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Abstract

Thalassemia, one of the most common genetic disorders, is considered to be a global problem. Several millions of the patients suffer from severe thalassemic diseases. Stem cell transplantation is currently the only curative therapy. Bone marrow transplantation offers a high probability of cure when performed in young children. There is a higher risk as the patient becomes older, especially the high incidence of graft rejection. Modified conditioning regimens have been developed to overcome graft rejection in patients with class III or full blown manifestations. The alternative use of stem cell from cord blood makes possible earlier transplant with better chance of cure, although the engraftment is slower compared to bone marrow transplantation. More experiences with regard to stem cell transplantation in adult patients, the use of stem cell transplantation from related donors as well as matched unrelated donors are necessary.

Thalassemia has been distributed from Mediterranean across the Middle East through Southern Asia to Southeast Asia [1]. However, recent migrations of people during the last decade have spread thalassemia genes throughout the world. Therefore, thalassemia is at present considered to be a global health problem [2]. In Thailand, with the population of 60 million, there are 600,000 affected individuals [3]. More than 60 clinical syndromes with different gene interactions have been described [3]. Among those, homozygous β -thalassemia or thalassemia major is the most severe form in which patients can be born alive. Hb E, the hallmark of Southeast Asia is frequently found in Thailand [3,4]. Double heterozygosity between Hb E and β -thalassemia so called Hb E β -thalassemia is the most common severe thalassemia in adults [3,4].

Therapy with hypertransfusion and iron chelation can improve life expectancy and quality of life. However, this modality of treatment is not curative; must be given throughout life and only the minority of patients can afford it. The alternative treatment option is stem cell transplantation which offers the high probability of cure especially in children. The risks of transplant related mortality as well as late complications are low. Although stem cell transplantation is costly but the overall life-long expense is lower than therapy with hypertrans-

fusions and iron chelation.

This review aims to discuss the current results of stem cell transplantation in thalassemia and the future perspective.

1. Indications for Stem Cell Transplantation in Thalassemia

Stem cell transplantation should be indicated in severe thalassemia syndromes. Homozygous β -thalassemia or thalassemia major is the most severe form and the patients usually have full blown manifestations and die before the age of 10 years due to heart failure or severe infections unless hypertransfusions and iron chelation are administered. Stem cell transplantation has been therefore performed mostly in patients with homozygous β -thalassemia.

Hb E β -thalassemia is common in Thailand [3]; the clinical manifestations are heterogenous ranging from a mild form of thalassemia intermedia to severe transfusion dependency similar to thalassemia major [4]. In those with severe disease, the symptoms initially appear during the first decade of life. Stem cell transplantation is recommended in patients with severe Hb E β -thalassemia.

2. Results of Stem Cell Transplantation for Thalassemia

The largest series of bone marrow transplantation for thalassemia in a single center has been reported by the Pesaro group. The risks of bone marrow transplantation using an HLA-identical sibling donor can be predicted according to the presence or absence of three factors including hepatomegaly, irregular chelation and portal fibrosis [5,6]. Patients can be classified into class I without any risk factors, class II with any one or two risk factors and class III with all three risk factors [5,6]. Update results of bone marrow transplantation in patients below 16 years indicate that 1) The overall survival was 78% and event-free survival of 71% and 2) class I (good risk) had survival, event-free survival, transplant related mortality and rejection rates of 94, 87, 6 and 7% respectively; class II (intermediate risk) 84, 81, 15 and 4% and class III (poor risk) 80, 56, 18 and 33% [7]. The results for class III are unfavorable; previous report showed survival, event-free survival, non rejection mortality of 61, 53 and 47% at 3 years and a rejection rate of 12% [5]. Reduction of conditioning regimen (cyclophosphamide 200 mg/kg to 120 mg/kg) for class III has decreased transplant related mortality to 18%, giving overall survival of 80%, however the rejection rate was high at 33% and event-free survival of 56% [7].

By using the conditioning of busulfan 14 mg/kg and cyclophosphamide 200 mg/kg and short course of methotrexate and cyclosporin for GvHD prophylaxis, the overall survival in our studies was 91%. In good risk patients the overall survival and event-free survival were 94 and 82%, those with moderate risk were 100 and 83% and poor risk patients were 67 and 17% respectively.

3. Conditioning Regimens

In good and moderate risk patients, the Pesaro regimen comprising busulfan 14 mg/kg followed by cyclophosphamide 200 mg/kg has been widely used with good outcome. Severe risk patients had a high non-rejection mortality of 47% and a rejection rate of 12% [5]. The regimen with reduced doses of cyclophosphamide to 120-160 mg/kg, can reduce the non-rejection mortality rate to 20% but increase the probability of rejection to 30% [6].

We used busulfan 600 mg/m² and cyclophosphamide 200 mg/kg in severe risk patients [8]. Although the number of studied patients was small, the overall survival and event-free survival were 90 and 90% respectively and no graft rejection was observed. Recently the Pesaro group has developed a new preparative regimen consisting of hydroxyurea 30 mg/kg and azathioprine 3 mg/kg starting on day-45 until day-11, fludarabine 20 mg/m² from day-17 to day-11 followed by busulfan 10 mg/kg and cyclophosphamide 90-160 mg/kg. The results are favorable with overall survival of 97 and 90% respectively [9].

4. Long Term Effect of Bone Marrow Transplantation

Almost all ex-thalassemics have moderate to severe iron-overload which improves slowly after transplant. Persistent iron overload can continuously cause tissue damage. It is therefore recommended that ex-thalassemics should have total iron burden reduced towards normal by regular phlebotomy or desferrioxamine beginning 1-2 years after transplant [10,11].

Data from Pesaro indicated that children transplanted before the age of 8 years had normal growth after transplant whereas older children and children with class III especially those with chronic GvHD have growth retardation [12,13]. Failure to enter puberty was found in 37% of boys and 60% of girls transplanted before puberty [13,14]. Most girls transplanted after puberty developed secondary amenorrhea [15].

5. BMT in Adults with Thalassemia Major

The only report was from Pesaro group; 107 patients mostly class II and III aged 17-35 years were transplanted using busulfan 14 mg/kg and cyclophosphamide 120 mg/kg. The overall survival and event-free survival were 64 and 61% respectively [16]. Surprisingly the rejection rate was only 3%, much lower than in the children class III patients. The high mortality indicates that bone marrow transplantation in adult should be performed only in those with limited organ damage.

6. Bone Marrow Transplantation from Alternative Donors

Recent report from Pesaro group of bone marrow transplantation in 29 patients using alternative family donors (mainly mismatched sibling, parent and relative) showed unfavorable results [17]. The overall survival was 65% and event-free survival of 21%. Graft rejection rate was high at 55% and acute GvHD was observed in 47%; chronic GvHD 38%.

We performed parental purified CD34+ve transplantation in 2 patients; one with homozygous α -thalassemia 1 and the other with Hb E β -thalassemia. Both of them had evidence of full engraftment. However, the first patient had graft rejection with autologous recovery and is still alive with hypertransfusions. The second patient died of severe infections from CMV and aspergillosis.

7. Matched Unrelated Donors Transplantation

The only study reported the outcome in 23 patients with the overall survival of 82% and event-free survival of 61% [18]. Further studies are required to determine the benefit of matched unrelated donor transplantation in patients with thalassemia.

8. Cord Blood Transplantation

We first reported the success of cord blood transplantation in a patient with thalassemia major in 1995 [19]. The advantage of this approach is to allow sufficient stem cells to be obtained from sibling donors at birth rather than waiting until the donor is older and ready to be a marrow donor. Transplantation can be therefore performed earlier with better chance of cure.

Up to present, we have performed cord blood transplantation in 12 patients with severe thalassemia. The results are favorable although the hematologic recovery is slower than bone marrow transplantation.

9. Conclusion and Perspective of Stem Cell Transplantation for Thalassemia

Stem cell transplantation is the only curative therapy for thalassemia at present. By using standard Pesaro conditioning regimen, transplantation performed early when the patients are young has a very high probability of cure. Patients with class III or full blown manifestations have a higher risk of graft rejection. Modified conditioning regimens have been reported to overcome graft rejection. Transplantation using cord blood can be performed earlier with better chance of cure.

Experiences of bone marrow transplantation in adult patients are limited. The use of matched unrelated transplantation is reported only in a minority of the patients. The results of haploidentical CD34+ve transplantation from family donors were unfavorable.

Nonmyeloablative transplantation was reported in thalassemia and the results suggest a low mortality but high risk of rejection [20], although further infusions of donor lymphocytes post transplant can reverse the relapse of thalassemia [21]. More studies are required to determine the role of nonmyeloablative transplantation in thalassemia, especially those with full blown diseases.

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