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# Using the Bone Marrow of the Lost Fetus in the Case of Miscarriage for Transplantation New Bone Marrow for Children with Anaemia

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**Abstract**

Thalassemia is a heterogeneous group of genetic disorders resulting from decreased synthesis of either the alpha or beta chains of hemoglobin (Hb). Hemoglobin functions as the oxygen-carrying component of red blood cells. It consists of two proteins, alpha and beta. If the body does not produce enough of either of these proteins, red blood cells do not form properly and cannot carry adequate oxygen; this causes anemia that begins in early childhood and persists throughout life. Thalassemia is a hereditary disease, meaning that at least one parent must be a carrier of the disease. This occurs either through a genetic mutation or the deletion of certain parts of key genes.

Hematopoietic stem cell transplantation (HSCT) has been proposed as a potential treatment option since the 1980s. Pediatric HSCT has better outcomes than adult HSCT, and in 1990, a risk score was proposed to assess transplant-related mortality in pediatric patients. A bone marrow transplant, also known as a bone marrow transplant or blood stem cell transplant, is a procedure that replaces unhealthy bone marrow with healthy blood-forming cells (stem cells) from a donor. A bone marrow transplant is the only potential cure for thrombocytopenia.

This type of transplant uses healthy blood-forming cells donated by someone else. These healthy cells can come from a family member, an unrelated donor, or umbilical cord blood. First, you receive chemotherapy, with or without radiation, to kill the unhealthy bone marrow. Then, you are given the healthy cells through an intravenous catheter. The new cells migrate into your bones and begin to form healthy blood cells.

**Keywords**: Maritime anemia, sickle cell anemia, aborted fetus, bone marrow transplant, leukemia.

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## Introduction:

Thalassemia is a heterogeneous group of genetic disorders resulting from decreased synthesis of the alpha or beta chains of hemoglobin (Hb). Hemoglobin functions as the oxygen-carrying component of red blood cells. It consists of two proteins, alpha and beta (Borgan-Pignatti et al.,(2005). If the body does not produce enough of either of these proteins, red blood cells do not form properly and cannot carry adequate oxygen. This causes anemia that begins in early childhood and continues throughout life.

Thalassemia is a genetic disorder, meaning that at least one parent must be a carrier of the disease. This occurs either through a genetic mutation or the deletion of certain parts of key genes (Lucarelli et al., 1996).

Maritime anemia is a form of bone marrow failure. The marrow, the soft, fatty tissue inside bones, is where new blood cells are formed. In maritime anemia, the bone marrow fails to produce new cells, leaving the body vulnerable to bleeding and infection. Researchers have discovered that most cases of severe maritime anemia occur when the body's immune system attacks its own tissues and organs (Borgan-Pignatti et al., 2005).

Beta thalassemia major (β-thalassemia) is a common monogenic disorder characterized by abnormal hemoglobin structure. Historically, beta thalassemia occurred primarily in the sub-Saharan Africa, Mediterranean, and Middle East regions, extending into South and Southeast Asia (Anurathapan et al.,2014). However, global migration has led to the spread of beta thalassemia worldwide. The most common mutations causing beta thalassemia are single nucleotide substitutions, microdeletions, or insertions within the beta globin gene (Sruamsiri et al..,2013). These mutations reduce the production of beta globin chains and HbA1. The degree of imbalance between globin chains and beta globin subsequently causes the accumulation of defective alpha globin complexes that damage red blood cells. This condition determines the severity of anemia, transfusion dependence, and overall clinical morbidity in beta thalassemia (Angelucci et al.,2014).

The first treatment developed for alpha thalassemia was a combination of red blood cell transfusions and iron chelation, which has proven effective in delivering blood efficiently. Inadequate iron chelation can lead to tissue overload, leading to heart failure, liver cirrhosis, and endocrine disorders. However, adequate support significantly improves patient survival and quality of life. New approaches to treating alpha thalassemia have also been developed, such as luspatercept, an inhibitor of ineffective erythropoiesis that acts as an activin IIB receptor antagonist. Gene therapy is another proposed strategy, involving the infusion of autologous hematopoietic stem cells (HSCs) modified with a lentiviral vector that expresses β-globin in erythroid progenitor cells. Although this approach has the potential to completely cure beta thalassemia, its cost and long-term safety concerns limit its clinical application (Chiesa et al., 2010).

Hematopoietic stem cell transplantation (HSCT) has been proposed as a potential treatment option since the 1980s. Pediatric HSCT has better outcomes than adult HSCT, and in 1990, a risk score was proposed to assess transplant-related mortality in pediatric patients (Mathews et al.Acute and chronic graft-versus-host disease (GVHD), a potentially multisystem disorder resulting from the destruction of host tissues by donor lymphocytes, remains the leading cause of treatment-related death in patients with thalassemia A treated with hematopoietic stem cell transplantation. However, continued advances in our understanding and better management of transplant-related complications have improved outcomes over the years (Luznik et al.Moreover, physicians now use different sources of stem cells and donors such as umbilical cord blood (CB) stem cells, peripheral blood stem cells (PBSC), matched unrelated donors (MUD) or matched siblings even in non-cancerous diseases such as beta thalassemia. The development of treatment regimens and modification of drug combinations or doses has improved the outcomes of hematopoietic stem cell transplantation for beta thalassemia patients (Luznik et al., 2012).

A bone marrow transplant, also known as a bone marrow transplant or a blood stem cell transplant, is a procedure that replaces unhealthy bone marrow with healthy blood-forming cells (stem cells) from a donor. A bone marrow transplant is the only potential cure for SAA (Borgan-Pignatti et al., 2005).

Stem cell transplantation is used to treat thrombocytopenia. This type of transplant uses healthy blood-forming cells donated by another person (Anurathapan et al.These healthy cells can come from a family member, an unrelated donor, or umbilical cord blood. First, you receive chemotherapy, with or without radiation, to kill the unhealthy bone marrow. Then, you are given the healthy cells through an intravenous catheter. The new cells migrate into your bones and begin to form healthy blood cells (Angelucci et al.,

2014).

A bone marrow transplant provides a patient with healthy stem cells – immature cells that develop into different types of blood cells. These stem cells come from the marrow, the soft, fatty tissue inside bones, to replace marrow that is not functioning properly. Aplastic anemia was one of the first diseases for which a bone marrow transplant was found to be effective (Sruamsiri et al., 2013) In this treatment, the patient's non-functioning bone marrow is destroyed with medications or radiation and replaced with bone marrow from a compatible donor, usually a sibling or other family member.

**History of hematopoietic stem cell transplantation in thalassemia:**

Hematopoietic stem cell transplantation for thalassemia has evolved into accepted routine clinical practice, primarily due to the experience of the Pesaro group during the 1980s and early 1990s. During that period, over 1,000 unselected thalassemia patients were transplanted at Pesaro, with a 20-year overall thalassemia-free survival rate of 73%, calculated from 900 consecutive patients (Figure 1) who received transplants from an HLA-identical sibling. These results have been confirmed by the Pescara group, which has conducted a similar trial in over 100 selected patients since the early 1980s (Figure 2).

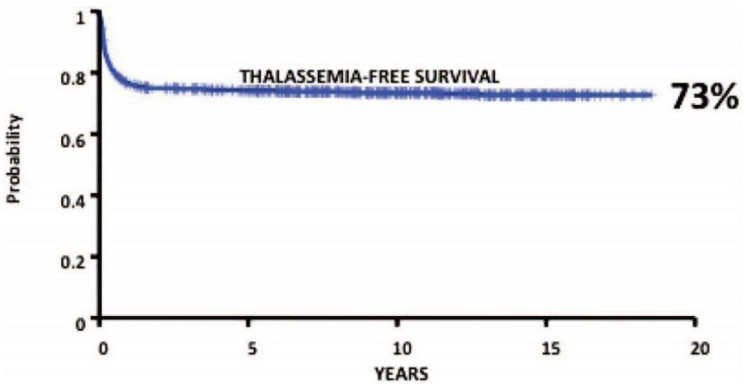


Figure 1: Results of 900 consecutive unselected bone marrow stem cell transplants for thalassemia, performed in Pesaro since 1982. Reprinted with permission from Angelucci and Baronciani.

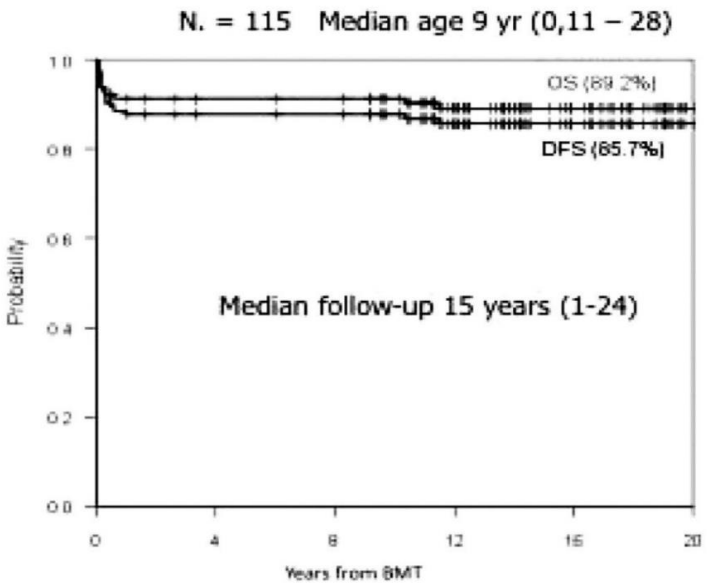


Figure 2: Results of 115 consecutive hematopoietic stem cell transplants for thalassemia in Pescara since 1984. Reprinted with permission from Di Bartolomeo et al.

Figure 3 shows the number of thalassemia transplants referred to the European Group for Blood and Marrow Transplantation (EBMT).

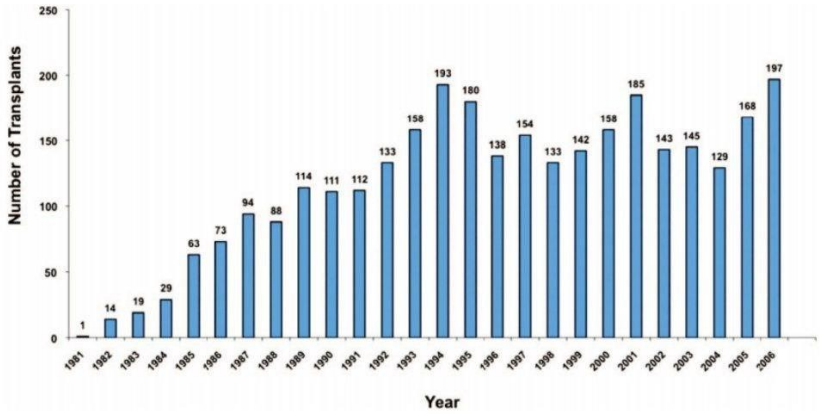


Figure 3: Hematopoietic stem cell transplants in thalassemia patients by year. Data from the Hemoglobinopathies Registry of the European Group for Blood and Marrow Transplantation. Reprinted with permission from Angelucci and Baronciani.

The hemoglobinopathy registry crossed the threshold of 100 transplants per year in 1989, and from 2000 onwards ranged from a low of 129 transplants per year to a high of 197 transplants per year.

In the 1980s, the Pesaro group developed a prognostic nomogram to predict transplant outcomes in patients under 17 years of age (Wang et al.,2011). This predictive scheme included three variables, all related to iron burden :

(1) The quality of chelation therapy the patient received throughout his life before transplantation;

(2) Hepatomegaly;

(3) Presence of liver cirrhosis on liver biopsy examination before transplantation.

These variables classified patients into three groups based on the absence of any, presence of one, two, or all three risk factors. Overall survival and thalassemia-free survival differed significantly across the three groups: 94% and 87% in the low-risk group, 84% and 81% in the intermediate-risk group, and 70% and 58% in the high-risk group, respectively. Similar results were not achieved in adult patients, where overall survival and thalassemia-free survival peaked at 67% and 63%, respectively, and the transplant mortality rate was 35%.12 The risk stratification for pediatric patients was not applicable to adult patients, largely because few adult patients were able to receive regular full chelation therapy in the deferoxamine era. The rejection/recurrence rate of thalassemia was significantly higher in patients with thalassemia than in patients who underwent organ transplantation for malignancy. Several factors have been suggested to explain this difference:

1-Excessive exposure to blood products prior to transplantation

2- Not receiving any chemotherapy before transplantation.

3- Enlargement of the bone marrow that forms red blood cells, and possibly splenomegaly.

Interestingly, the phenomenon of high thalassemia recurrence rate was limited to patients under 17 years of age (Switzer et al., 2006).

**Sickle cell disease (SCD)**

Sickle cell disease (SCD) is associated with significant health morbidity, resulting in reduced quality of life and a shortened life expectancy.Life expectancy. Survival rates have improved significantly over the past two decades, and 94% of children with sickle cell anemia now live to age 18 thanks to better

monitoring, pneumococcal vaccination, penicillin prophylaxis, and hydrourea therapy. However, mortality remains significant once patients reach adulthood (Wang et al., 2011).

Morbidity and mortality associated with sickle cell anemia in young people are largely due to as yet unpreventable complications, such as priapism, avascular necrosis, chronic pulmonary dysfunction, switzer et al. 2006, hypertension, stroke, and recurrent veno-occlusive episodes (Switzer et al., 2006).

The only curative approach to sickle cell anemia is hematopoietic stem cell transplantation. Historically, the indication for hematopoietic stem cell transplantation in sickle cell disease was based primarily on the comorbidities associated with sickle cell disease: the sicker the child, the stronger the indication (Walters et al..,1996). With the declining incidence of the disease in recent years, and with increasing awareness of the severity of complications in untreated patients, the acceptable indications for hematopoietic stem cell transplantation have become less restrictive.

**Identical organ transplantation from siblings:**

In the past ten years, data on the outcomes of more than 200 patients who underwent hematopoietic stem cell transplantation from an HLA-matched sibling donor have been analyzed and published. The overall survival rate was found to be approximately 95%. Bernaudin et al. reported on 121 patients who underwent organ transplantation in France after 2000 with a 95% disease-free survival rate after three years (Bernaudin et al.,2010). Taking into account the following:

1) Overall survival is equal to or even better in patients who undergo hematopoietic stem cell transplantation compared to those receiving supportive therapy, and disease-free survival exceeds 95%;

2) Disease-related morbidity and mortality rates increase with age, and disease-free survival after hematopoietic stem cell transplantation is significantly better in patients who undergo stem cell transplantation before the onset of organ damage associated with sickle cell disease (SCD);

3) In children, the rate of TRM increases with age, so the use of early hematopoietic stem cell transplantation is justified in children with any symptoms or events associated with sickle cell disease.5,64,77 Young adults who develop more severe disease as they age also benefit from hematopoietic stem cell transplantation (Van Besien et al., 2000).

However, cases of severe chronic GVHD have been described after hematopoietic stem cell transplantation in adult patients with end-stage sickle cell disease who have undergone massive blood transfusions.

The main obstacle to hematopoietic stem cell transplantation in patients with sickle cell disease is the limited availability of donors. Overall, only 18% of sickle cell patients have a matched healthy sibling donor, and the probability of finding an unrelated donor is extremely low (Eapen et al.., 2004). The incidence of chronic GvHD after hematopoietic stem cell transplantation from matched siblings for non-malignant diseases has been shown to be significantly higher in patients receiving peripheral blood cells compared to red blood cells. This justifies the recommendation to use red blood cells for transplantation in patients with sickle cell anemia (Levine et al., 2000).

**Stem cell transplantation from alternative donors for thalassemia patients:**

One of the most significant barriers to transplant success is the limited number of HLA-matched donors within families. Approximately 60% of patients lack a suitable family donor. Some of these patients may benefit from a hematopoietic stem cell transplant (HSCT) from unrelated, matched donors. However, the chance of finding an unrelated, matched donor depends largely on the patient's ethnic background.

One study reported the outcomes of bone marrow transplantation (BMT) from matched unrelated donors prospectively selected using high-resolution molecular typing of HLA class I and class II loci; this study included 68 patients with thalassemia major who received BU/CY or BU/FLU (fludarabine) and/or thiotepa (TT) as a conditioning regimen (La Nasa*et al.,*2005) aThe study included 14 patients with class I, 16 with class II, and 38 with class III. The overall survival, thalassemia-free survival, rejection, and

transplant-related mortality (TRM) rates for the entire cohort were 79.3%, 65.8%, 14.4%, and 20.7%, respectively. Grade II-IV or grade III-IV acute GVHD were 40% and 17%, respectively. Ten of 56 evaluable patients (18%) developed chronic GVHD. Class I and Class II patients had significantly better overall and disease-free survival (96.7% and 80%, respectively) than Class III patients (65.5% and 54.5%, respectively). These researchers also recently reported encouraging results in adult thalassemia patients who received bone marrow from matched unrelated donors, with survival, thalassemia-free survival, TRM, and rejection rates of 70%, 70%, 30%, and 4%, respectively (La Nasa*et al.*.2005) Similar results were reported in another study from Asia that included 21 children who received transplants from matched unrelated donors, as well as 28 patients who received transplants from matched related donors (Hongeng*et al.,*2006The two-year thalassemia-free survival rate for patients who received transplants from matched unrelated donors was 71%, compared to 82% for patients who received transplants from matched unrelated donors.

Taken together, these data strongly suggest that improvements in donor selection and transplant preparation have improved the safety of stem cell transplantation from unrelated donors for the treatment of thalassemia. This appears to be an effective treatment option for selected patients in the absence of a suitable sibling donor.

**Non-myeloid stem cell transplantation systems :**

Non-myeloid stem cell transplantation has the theoretical advantage, based on experience in malignant tumors, of obtaining allogeneic grafts with a very low early mortality rate. However, the increasing reliance on immunological effects necessary for the survival of the transplantation calls for a cautious approach when using this system extensively (Kapoor et al., 1981).

So far, very few cases have been reported. Lucarelli et al..,2011) reviewed limited international trials in the treatment of thalassemia and sickle cell disease, where the results generally showed poor and a very low success rate of transplantation (only one transplant in 11).

Recently, a successful trial was published in a small group of adult patients with sickle cell disease (11 patients) who underwent total body irradiation with a dose of 300 cGy. However, this study cannot be directly applied to thalassemia (Nesci et al.,1998). In fact, there are several important differences between thalassemia major and sickle cell disease, which affect hematopoietic stem cell transplantation strategies.

Thalassemia major is characterized by ineffective red blood cell formation and uneven red blood cell expansion. This ineffective formation and chronic blood transfusions lead to increased iron levels in the body. Therefore, treatment of thalassemia requires a regimen capable of eradicating expanded bone marrow and providing sufficient immunosuppression to maintain transplant success while minimizing iron-damaged tissue toxicity. These challenges are not present in sickle cell disease.

**Chimerism after stem cell transplantation for thalassemia treatment :**

Mixed hematopoietic (MC) chimerism is an interesting phenomenon that occasionally occurs after stem cell transplantation for the treatment of thalassemia. The incidence of MC was studied in 335 patients who underwent bone marrow transplantation from HLA-matched family donors. The results showed a chimerism rate of 32.2% two months after transplantation (Lucarelli et al., 2002).

Of the 227 patients with complete donor chimerism, none rejected their graft, while graft loss occurred in 35 of 108 patients (32.4%) with mixed hematopoietic chimerism, suggesting that mixed hematopoietic chimerism is a risk factor for graft rejection in thalassemia patients. The percentage of residual host hematopoietic cells (RHCs) determined two months after transplantation was predictive of graft rejection, with nearly all patients experiencing graft rejection when RHCs exceeded 25%. The risk of graft rejection was only 13% in patients with <10% RHCs and 41% in patients with 10%–25% RHCs. Unlike hematologic malignancies, in which residual host cells are a predictor of relapse, thalassemia patients can have stable mixed hematopoietic cells for life without rejection after transplantation. Among patients receiving bone marrow transplantation for thalassemia after myeloablative conditioning, 10% developed

persistent mixed allo-helical cells and became transfusion-independent, suggesting that once donor and host tolerance is established, a limited number of transplanted donor cells may be sufficient to provide significant improvement in the disease phenotype in patients with thalassemia major (Andreani*et al.*, 2011b) .

We recently published a research paper describing four long-term transplant patients with hemoglobinopathies (Andreani*et al.*, 2011a). These patients were characterized by the presence of few donor-derived nucleated cells, both in the peripheral blood and in the bone marrow; the majority of erythrocytes were of donor origin. Furthermore, by analyzing individually captured blast-forming erythrocyte colonies, we showed that the proportion of donor-derived erythrocyte precursors was equivalent to that observed in mature nucleated cells, rather than erythrocytes. These findings suggest that in patients characterized by the presence of PMCs after HSCT, the selective advantage of donor erythrocyte precursor maturation may successfully contrast with the problems associated with ineffective erythropoiesis in the recipient (Andreani*et al.*, 2011b).

**Mixed hematopoietic stem cell transplantation after bone marrow ablative transplantation:**

A subset of patients who undergo hematopoietic stem cell transplantation for SCA develop lifelong stable MC once donor and host tolerance is established (Andreani*et al*., 1996), noteWalters*et al.*, 2001)) MC was stable in 13 of the 50 patients (26%), who demonstrated a median SCD-free survival of 6.9 years (range 4.2–13 years). Notably, among these patients, five had mixed donor chimerism <75% (range 11%–74%), and none developed sickle cell-related complications during the follow-up period, which ranged from 22 to 70.2 months (median36.3 months).

We recently documented the clinical case of a six-year-old girl who underwent a bone marrow transplant for sickle cell anemia. Four years after the procedure, the patient demonstrated stable mixed chimerism, with 39% of donor-derived red blood cells in her bone marrow and 80% of donor-derived red blood cells in her peripheral blood. The patient received bone marrow from her Hb AA-identical sister after a treatment regimen of 14 mg/kg BU, 200 mg/kg CY, and 10 mg/kg antithymocyte globulin (ATG). For graft-versus-host disease (GVHD) prophylaxis, the patient received cyclosporine (starting on day 1) and a short course of methotrexate (MTX; 10 mg/m on days 1, 3, and 6 posttransplant with folinic acid rescue. The course after allogeneic hematopoietic stem cell transplantation was uneventful, with rapid hematopoietic engraftment and no signs of acute or chronic GVHD. Molecular analysis of sorted cell subsets revealed the presence of MCs in nucleated cells, CD34+ progenitor cells, and CD40+ cells.and red blood cells in the PB and BM. Four years after transplantation, the donor NCs level reached 39% in the PB and 36% in the BM, paralleling a very high proportion of donor-derived red blood cells (80%) in the PB. The proportions of donor-derived red blood cells and BFU-E units in the bone marrow were 40% and 46%, respectively, indicating a quantitatively different hybridization between red blood cells and nucleated cells. A possible explanation for the higher proportion of donor-derived red blood cells may lie in the improved survival of donor primary red blood cells, compared to their host counterparts, which may be destroyed during ineffective erythropoiesis.Walters*et al.*, 2001)) .

**Sustained and complete fetal hemoglobin production after failed bone marrow transplantation:**

An increase in hemoglobin levels was recorded in three patients who underwent bone marrow transplantation after the transplant failed (Ferster*et al.*, 1995). Recent clinical observations by our group strongly support these innovative approaches. Reactivation of hemoglobin synthesis after failed bone marrow transplantation (BMT) and autologous reconstitution in patients with beta-hemoglobin disorders have been documented (Paciaroni*et al*., 2009).

It is likely that after myelomeningocele treatment, the vast majority of committed autologous erythroid progenitor cells were destroyed, and only autologous hematopoietic stem cells survived in the marrow cavities, restoring the existential hemoglobin (HbF) regulatory mechanisms (Bank. 2006). Alternatively, the elevated hemoglobin level may be the result of a de novo condition, resulting from modifications and influences in the bone marrow transplant environment (the microenvironment and cytokines specific to

each stage), which reprogram globin gene expression or determine the proliferation of the "fetal copy." These conditions strongly support additional research efforts to find ways to reverse hemoglobin conversion and stimulate HbF production in adults to treat beta hemoglobin disorders.

**Conclusions:**

The only definitive cure for homozygous thalassemia is bone marrow transplantation from a donor who is HLA-matched (normal) or heterozygous for thalassemia and capable of producing and maintaining normal hemoglobin levels in the recipient. All thalassemia patients, as well as their parents and siblings, should be HLA-tested for this purpose. When an HLA-matched donor is available, we believe bone marrow transplantation should be mandatory for patients with type 1 and type 2 thalassemia, as well as for type 3 patients under the age of 17. Adult patients should also have this possibility of cure, but 30% of them will die from transplant-related mortality. Patients who do not have matched consanguineous or unrelated donors can benefit from genetically identical mother-to-child bone marrow transplantation, which has shown encouraging results, although it is still in the experimental stage.

High cure rates have also been achieved with hematopoietic stem cell transplantation (HSCT) for children with SCA using current myeloablative conditioning protocols. We reiterate the need for HLA typing for all family members of a child with SCA. If a genetically or phenotypically identical sibling or parent is identified, HSCT should be performed for all SCA patients younger than 17 years of age, before major disease complications affect the child. The new non-myeloablative transplant protocol for SCD patients could serve as a platform for widespread application, not only in adults but also in children at risk for SCD.

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