Bone Marrow Transplant as Definitive Therapy for β-Thalassemia Major Patients: A literature review

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Abstract

Thalassemia is a group of hereditary hemoglobin disorders characterized by insufficient production of at least one globin chain, resulting in unbalanced production of globin chains. Homozygous mutations in the β-globin gene, resulting in the absence of the β-chain, are the main cause of β-thalassemia major. Because the β-chain in β-thalassemia major is not formed, there is an accumulation of free α-chains in red blood cells, which can trigger apoptosis and hemolysis resulting in ineffective erythropoiesis. Management for β-thalassemia major patients requires lifelong therapy with blood transfusions and medication. However, blood transfusions and routine administration of iron chelation drugs cannot cure β-thalassemia major. Thalassemia can be cured through definitive therapies including bone marrow or stem cell transplantation and genetic therapy. Bone marrow transplantation is a treatment option for children and adolescents suffering from certain types of cancer and other blood disorders such as thalassemia.

Keywords : β-Thalassemia Major, Bone Marrow Transplant, Definitive Therapy

1. Introduction

Thalassemia is a group of hereditary hemoglobin disorders characterized by insufficient production of at least one globin chain, resulting in unbalanced production of globin chains (1). This genetic disease results from the inability of the bone marrow to form the proteins needed to produce hemoglobin (2). Homozygous mutations in the β-globin gene, resulting in the absence of the β-chain, are the main cause of β-thalassemia major (3). Because the β-chain is not formed, there is an accumulation of free α-chains in red blood cells, which can trigger apoptosis and hemolysis resulting in ineffective erythropoiesis (4). This ineffective erythropoiesis can lead to severe anemia, which is the main symptom of thalassemia (5). This chronic anemic condition causes compensation in the form of expansion of the spinal cord to produce more erythrocytes, and results in deformity of the patient's skull and sternum (6). An increased reticulocyte count is a marker of increased bone marrow activity (7). Management for β-thalassemia major patients requires lifelong therapy with blood transfusions and medication. Blood transfusions are intended to increase hemoglobin levels and prevent the production of useless red blood cells. Meanwhile, iron chelation drugs are used to remove iron so that it does not accumulate and damage organs. However, blood transfusions and routine administration of iron chelation drugs cannot cure β-thalassemia major. Thalassemia can be cured through definitive therapies including bone marrow or stem cell transplantation and genetic therapy (6). With a bone marrow transplant, β-thalassemia major patients no longer need blood transfusions for the rest of their lives, but it is inevitable that they can still pass on the thalassemia gene to their offspring (7).

2. Current Therapy for β-Thalassemia Major Patients

Management of β-thalassemia major requires ongoing treatment throughout the patient's life. In general, the management of β-thalassemia major is blood transfusion, iron chelation therapy, supportive medications, management of medical and non-medical complications, and development of the latest definitive therapy which is still rarely applied (8).

2.1. Blood Transfusion

Transfusion therapy aims to correct anemia, suppress erythropoiesis, and inhibit gastrointestinal iron absorption, which occurs in transfused patients as a result of increased, but ineffective, erythropoiesis (9). According to current recommendations, blood transfusion therapy should be started as soon as the diagnosis is made and if hemoglobin levels < 7 g/dl on at least two occasions, > 2 weeks apart (excluding all other contributing causes such as infection) (10). Individuals with hemoglobin levels > 7 g/dl should be measured for a variety of factors such as significant anemia symptoms, growth retardation/failure to thrive, clinically significant extramedullary hematopoiesis such as increasing splenomegaly, and complications from excessive intramedullary hematopoiesis such as pathological fractures and facial changes (10-11). The frequency of blood transfusions is determined by a variety of factors, including the patient's hematocrit and hemoglobin levels, as well as his or her weight (12). The most common conventional goal for pre-transfusion hemoglobin is close to 9 to 10 g/dl, and post-transfusion hemoglobin levels should be 13 to 14 g/dl. This prevents organ damage, growth retardation, and bone malformations, which can lead to a normal quality and activity level of life (13). Blood transfusion therapy should not exceed 15-20 ml/kg of RBCs daily to avoid excessive increases in blood volume. Blood transfusion efficiency can be monitored through hemoglobin and hematocrit levels before and after transfusion as these levels can indicate the patient's iron intake and red blood cell requirements (14). An effective transfusion regimen will result in good growth and development; good energy levels, sufficient suppression of intra and extramedullary hematopoiesis (10).

2.2. Iron Chelation Therapy (ICT)

Three iron chelators are currently licensed for clinical use, deferoxamine, deferiprone, and deferasirox. The purpose of iron chelation therapy is to keep body iron levels safe or to remove excess iron from the body. If iron-induced heart failure occurs in an emergency, extensive iron chelation therapy is required. Uncontrolled transfusion of iron increases the risk of heart failure, endocrine damage, liver cirrhosis, and hepatocellular cancer (10). Iron chelation therapy advancements and the emergence of MRI techniques to diagnose organ-specific iron overload have resulted in better management and patient outcomes (14). In addition, medication adherence is also very important to improve patient health outcomes. Adherence to iron chelation therapy is related with efficient iron overload reduction and better patient survival (15).

2.3. Splenectomy

In β-thalassemia major patients, the accumulation of free α-chains causes apoptosis and hemolysis of red blood cells. Extravascular hemolysis happens in the reticuloendothelial system, which includes the spleen. This mechanism will cause spleen hypertrophy resulting in splenomegaly (16). In fact, studies

have shown that hypersplenism does not happen if hemoglobin levels are kept above 10 g/dl (17). However, if the child has developed signs of hypersplenism and splenomegaly, then splenectomy is indicated (11). The risk of fulminant sepsis following splenectomy is substantially higher in children under the age of five, hence this procedure should be avoided. Through a decrease in the need for transfusions, an increase in Hb levels, and a reduction in iron buildup, splenectomy safeguards patients against ill health and growth retardation. When a patient needs more than 200 to 220 ml RBC/kg with 70% hematocrit per year or 250 to 275 ml RBC/kg with 60% hematocrit for packed RBC, spleen removal is advised (10).

2.4. Bone Marrow Transplantation (BMT)

Currently, one of the definitive therapies for β-thalassemia major is bone marrow transplantation (BMT), but there aren't many Human Leukocyte Antigen (HLA)-matched blood donors available (18). Less than 30% of patients have an HLA-identical sibling marrow donor (19). The bone marrow transplantation procedure is used to treat abnormal function. Excess immature lymphocytes in the bone marrow occupy a large space, resulting in the production of immature erythrocytes and platelets. Immature RBCs lose their ability to attach to hemoglobin, resulting in thalassemia, which demonstrates the method of bone marrow transplantation to replace abnormally functioning bone marrow with healthy bone marrow (20). Graft versus host disease (GVHD) is the most serious and dangerous problem in bone marrow transplantation, and it can result in the transplant recipient's death (21).

2.5. Hematopoietic Stem Cells Transplantation

Hematopoietic stem cell transplantation is a medical procedure that involves the administration of stem cells following a brief course of chemotherapy, radiotherapy, or both. This procedure can be used to treat a variety of cancers, as well as some benign conditions and even thalassemia (22). Hematopoietic stem cells are mostly found in bone marrow, but also be found in the bloodstream and umbilical cord blood. Selection of alternative hematopoietic stem cell donors (non-HLA-identical family members) has been aided by the establishment of worldwide donor registries that now exceed 3.6 million volunteers and by DNA-based HLA typing to better match potential donors (19). In this therapy, hematopoietic stem cells from healthy people's bone marrow flasks are isolated and transplanted into thalassemia patients. This treatment is effective in nearly 80% of transplant recipients (23).

2.6. Gene Therapy

Some alternative therapy for β-thalassemia major that are currently being investigated are genetic therapies that involve inserting normal globin genes into patients in order to normalize hemoglobin production. This genetic therapy, like bone marrow transplantation, costs approximately 1.8 million USD (24). It is also being examined whether nucleotides can be used to restore normal gene expression. Gene therapy is an emerging experimental treatment that cures diseases without pharmacological, radiotherapy or surgical intervention (25). This therapeutic strategy can be used to provide functional genes among patients with mutated non-functional genes or under-expressed genes. This technique can also be used to express proteins such as growth factors in promoting cell survival (26). Several gene therapies have been approved by the US FDA including Zynteglo™ for thalassemia which is still under consideration (27). The patient's stem cells are used in gene therapy to cure β-thalassemia major permanently. First, the patient's hematopoietic stem cells and progenitor cells (HSPCs) are extracted from the patient's umbilical

cord blood, peripheral blood, or bone marrow. Normal β or γ genes are transferred into the host cell genome via lentiviral vectors. In humans, the transfer of the hemoglobin genome into pluripotent hematopoietic cells is also intentional (28). Cells containing the desired gene are reintroduced into human bone marrow and allowed to proliferate. This method isolates fibroblasts from the patient and then transforms them into pluripotent cells (29). The induced pluripotent stem cells are then capable of undergoing the anticipated gene changes. Induced pluripotent stem cells are differentiated into hematopoietic stem cells and progenitor cells after adequate development. These HSPCs cells are then returned to the individual (30).

2.7. Induction of Fetal Hemoglobin Production

Individuals with long-term thalassemia who induce fetal hemoglobin increase the life span of RBCs. Various drugs, including hydroxyl urea, are used to stimulate fetal hemoglobin production. Hydroxyurea is a treatment for sickle cell disease and thalassemia. Hydroxyurea stimulates γ-globin production (31-32). Hydroxyurea is a cytotoxic compound for the cell cycle's synthesis phase, as well as a ribonucleotide reductase inhibitor (33). It regulates and increases the expression of the fetal hemoglobin GATA-2 gene, which is involved in apoptosis and the cell cycle, while suppressing the expression of the GATA-1 gene. This substance can also stimulate progenitors. It can also stimulate progenitor cell proliferation and increase erythropoietin levels (34). Other therapies may include decreasing the production of α-globin chains, increasing the production of normally functioning β-globin chains, and increasing the production of gamma globin chains.

3. Bone Marrow Transplantation (BMT) as Definitive Therapy

Bone marrow transplantation is a treatment option for children and adolescents suffering from certain types of cancer and other blood disorders such as thalassemia. The only definitive therapy available to thalassemia sufferers is bone marrow transplantation (35). However, BMT has several drawbacks, such as the requirement for suitable donors who match human leukocyte antigens for this healing procedure (36). With extremely young people, the best results are: 23% rejection rate, 7% mortality rate, and 70% thalassemia-free survival rate (37). In low-income nations, bone marrow transplantation has not been used to treat thalassemia; instead, most β-thalassemia patients are treated with successful chelating treatment, iron overload management, and constant packed red blood cell transfusions (38).

Because the dangers are so high, this bone marrow transplant surgery is rarely undertaken. One of the potentially fatal effects is donor cell rejection, often known as graft versus host disease (GVHD). As a result, greater study of the benefits and hazards of transplantation is required. Finding a suitable donor is critical to reducing the occurrence of GVHD problems, however due to the difficulties of finding donors who are very suited for patients, it is currently done utilizing haplotype or half-match donors. Furthermore, patients must take immunosuppressant medicines on a daily basis, which suppress the immune system and make them susceptible to infection (39). The limitation of applying bone marrow or stem cell transplantation is that it is very expensive, around 2-3 billion rupiah (40). Some alternative therapy for β-thalassemia major that are currently being investigated are genetic therapies that involve implanting normal globin genes into patients in order to normalize hemoglobin production (6). This therapy has been approved by the European Medicines Agency (EMA), however it is still being evaluated by the American Food and Drug Administration (FDA) for use in the United States.

A bone marrow transplant provides a long-term cure. The principles of bone marrow transplantation include destroying and preventing the regeneration of damaged stem cells; providing adequate immunosuppression for good engraftment; infusing stem cells with normal genes; and preventing graft versus host disease (GVHD) with the appropriate immunosuppression and infection management (41). The quality of life after bone marrow transplantation is significantly impacted by the pretransplantation condition. The duration of life may become more difficult as a result of several factors, including the presence of hepatomegaly within 2 cm of the below the costal margin; the presence of portal fibrosis; and iron overload as indicated by serum ferritin levels > 1000 ng/ml. Based on the above factors, children have been divided into three classes: Class I, when all these factors are absent; Class II, when one or two factors are present; and children with the presence of all factors referred to as Class III. Event-free survival is seen in more than 97% of cases in Class I and 66% in Class III cases. All children should be treated with the current protocol to maintain them in Class I and perform BMT as early as possible (18).

4. Conclusion

β-thalassemia is caused by a modification of the globin gene resulting in the absence or decrease in the rate of synthesis of normal globin chains. The absence of β-globin chains and the incomparable excess of α-globin chains cause oxidative tension and premature destruction of red blood cells resulting in severe anemia. Blood transfusion therapy restores anemia but worsens iron overload. Bone marrow transplantation remains the only absolute definitive therapy currently accessible to thalassemia patients (11).

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