

Is blood transfusion therapy the ideal treatment for β -thalassemia intermedia?

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ABSTRACT

The thalassemias represent the most common single gene disorder worldwide. The total annual incidence of symptomatic individuals with β -thalassemia is estimated at 1 in 100,000 throughout the world [1] of which nearly 10% have β -thalassemia intermedia (TI) [2]. Several approaches have been used for treating patients with TI including blood transfusions, splenectomy, iron chelation therapy, modulation of foetal haemoglobin and other agents focusing on specific aspects of clinical presentation. However the exact management of the disease is still controversial. A major issue which is not entirely explored is the effect of blood transfusion in the management of patients with β -thalassemia intermedia. There are certain advantages and disadvantages of initiating blood transfusions in TI patients that must be always taken into account in the management of these patients. Therefore, complications that interact with the clinical outcome of treatment and also patient's quality of life can be avoided to some extent.

INTRODUCTION

Thalassemia is a group of genetically inherited haemoglobin disorders. In thalassemia, a mutation of β globin gene leads to a defective β chain production. This defect leads to an imbalance in α/β globin synthesis causing ineffective erythropoiesis, chronic haemolytic anaemia and iron overload [3]. The severity of clinical manifestations of the disease is used to distinguish this disease into two main subtypes: Thalassemia major (TM) and thalassemia intermedia (TI). Moreover, the use of transfusions is what clinically divides the categories of β -TI from β -TM. When their transfusion requirements

reach > 8 units per year, they are reclassified as β -TM [2].

TI includes a large number of conditions with varying severity. β -TI is a condition with clinically significant problems but with survival being possible without transfusion. Several different genotypes have been identified as responsible for the disease, such as homozygous, heterozygous and compound heterozygous. Clinical presentation of the disease varies over a wide range of symptoms [3]. Common symptoms include: extramedullary haemopoiesis, leg ulcers, gallstones, jaundice, hypercoagulability and pulmonary hypertension.

The three main factors that are responsible for the clinical presentation of the disease are ineffective haemopoiesis, chronic anaemia and iron overload. The milder forms of TI do not require regular transfusions, except in special circumstances such as during an infection, during periods of rapid growth and pregnancy.

A difficult decision in the treatment of TI is whether or not the patient needs a chronic transfusion programme. The decision is mainly clinical but pathological results must be taken into account too. Clear guidelines for the treatment of the disease are still not available and the appropriate time for initiation of blood transfusion is still controversial.

ADVANTAGES OF BLOOD TRANSFUSION

Clinical presentation of TI depends on the severity of the disease. Therefore, the main advantages of early initiation of blood transfusion are to avoid further progression of the disease and also to prevent or ameliorate its associated complications.

Bone deformities and fractures

Thinning of the bone, osteopenia, as well as formation of pathologic fractures lead to bone deformities causing the characteristic maxillary marrow hyperplasia. Also severe malocclusion of the teeth and frontal bossing can be presented [4]. Therefore, with early blood transfusions, deformities can be prevented. Patients with the disease can experience a normal phenotype and avoid being stigmatised due to their physical appearance. Therefore, we avoid leading the patients in psychological hardship that they may experience. Patient's quality of life is ameliorated and their psychosocial life is preserved. It is not morally correct to deprive of the opportunity of living a normal life to these patients.

Extra-medullary masses

Another significant complication of TI is the formation of extra-medullary masses. This is mainly due to ineffective red cell production by the bone marrow which forces the expansion of the haematopoietic tissue outside the marrow medulla. Therefore, there is haematopoietic compensatory involvement, mostly in the form of masses in other regions of the body such as

spleen, liver and the spine [5]. Management options include blood transfusions, radiotherapy of the pseudo tumours or foetal haemoglobin induction by hydroxyurea or in acute cases even surgical intervention may be required. The use of non-surgical intervention for extra medullary masses treatment is preferred, as it can avoid post-operative complications such as bleeding and incomplete excision in cases of diffuse involvement [5]. Recurrent blood transfusion can correct the anaemia in these patients, leading to a decrease in the need of extra medullary haemopoiesis. This can result in a relative inactivity of these tissues leading to shrinkage of the masses [6]. Therefore blood transfusion is a very promising option and should be recommended as a first-line therapeutic approach or as an adjuvant therapy to other methods.

Thromboembolic complications

Thromboembolic complications are common in not transfused patients with TI. An Italian multicentre study showed that more patients with TI experience thromboembolic events than patients with TM, as only 4% patients with TM had complications compared to 10% of TI [7]. Although platelet anti-aggregation and administration of low molecular weight heparin seems to be reasonable choices according to everyday practice. No therapy has been demonstrated to completely prevent any thromboembolic complications that might occur in patients with TI. Therefore, regular blood transfusions might reduce the thrombotic risk by diluting procoagulant thalassaemic red cells [8].

Pulmonary hypertension (PHT)

Recent studies have shown that pulmonary hypertension is a typical feature in TI patients who do not receive blood transfusion as almost 60% of patients develop pulmonary hypertension. It has been proved that it is not an age-related effect due to prolonged survival of these patients, as there is evidence of increased pulmonary vascular resistance, systemic vascular stiffness and right heart failure [4]. In another study which evaluates the risk factors for PHT in TI patients, it is suggested that there is a potential role of blood transfusion, iron chelation or hydroxyurea therapy in decreasing the risk of PHT. The same study supports that transfusion therapy is associated with a lower incidence of PHT [9]. Moreover,

observational studies support the beneficial effect of blood transfusions, as they document a lower occurrence of thromboembolic events and PHT in transfused patients compared to non-transfused patients with TI. These findings support the significant role of transfusions in correcting the underlying ineffective erythropoiesis and the production of damaged red blood cells with thrombogenic properties [9].

Gallstones

Presentation of gallstones has been reported with a variable incidence in homozygous β -thalassaemia. The pathophysiology of the disease in these patients is not fully understood yet. Many patients need cholecystectomy as a result of this very common complication. Moreover, jaundice is a very common symptom of not transfused patients with TI as a result of haemolytic anaemia. Therefore early use of blood transfusion can reduce the incidence of these complications.

Ulceration

Leg ulcers are a common presentation in patients with TI. Although exact mechanism is yet not established, several factors contribute to their pathogenesis. These factors include chronic anaemia, reduced oxygen delivery to the distal regions, venous stasis and erythrocytes rheological abnormalities [10]. Leg ulcers are often refractory to conventional treatment. Although blood transfusions may favour ulcer healing, ulceration often reoccurs after treatment is withdrawn. In a recent study, it has been reported that in a small number of patients who had a short treatment with recombinant erythropoietin or hydroxyurea may be associated with a rapid improvement and even a healing of leg ulcers [10].

Older patients

Blood transfusion treatment is currently unavoidable for the elderly. Delay of their treatment will make their access to it limited as a great proportion of them will have already developed red cells (RC) mismatch. Moreover in older patient, treatment will have minimal effect to the previously established complications as most of them are only partially reversible [4]. Therefore, if blood transfusions are initiated early in the treatment of TI patients, there will be

less limitations in their management later on.

Psychosocial aspects

It is being more and more acceptable that earlier initiation of blood transfusion in patients with TI may improve quality of life especially in patients with more severe clinical manifestations. Patient's quality of life is ameliorated and their psychosocial life is preserved. It is not morally correct to deprive of the opportunity of living a normal life to these patients by refusing treatment. However, many patients with TI do not receive regular blood transfusions due to inconvenience. Also delay of initiation of blood transfusion will avoid possible complications of such as iron overload and its treatment, even though effective treatments of iron chelation are now available [11]. Also, it has been noted that early initiation of blood transfusion is cost effective. Preventing complications is more cost effective than spending enormous amounts of money in treating complications of the disease with minimum improvement in many cases.

DISADVANTAGES OF BLOOD TRANSFUSION

Iron overload

Although iron overload is a major issue in TM, it also exists to a lesser extent in TI patients. Iron overload and iron deposition in TI results from peripheral haemolysis and ineffective haemopoiesis. It is also a result of increased intestinal iron absorption [4]. Therefore, with regular blood transfusions iron overload is further increased. Major complications arise from iron deposition on tissues. The most significant complications are cardiomyopathy, diabetes, liver cirrhosis, hypogonadism and delayed puberty. As soon as the patient initiates transfusion therapy must be closely monitored for iron overload. Although there are no clear guidelines for the management of iron overload in patients with TI, it is widely acceptable that chelation therapy is essential after the initiation of blood transfusions. However, TI patients may not require life-long iron chelation therapy as it might be relatively easy to reduce iron. In the OPTIMAL CARE study patients who received both transfusion and chelation therapy had fewer complications compared to patients who received no treatment at all [12]. However there are not enough data on the use of

chelation agents in patients with TI. Our knowledge and understanding is based on data from TM studies. Therefore, the practical limitations and inconvenience of frequent and prolonged chelation treatment is a key consideration on the impact on quality of life.

Alloautoimmunisation

Alloimmunisation to red blood cells (RBC) is a significant complication of this therapy. It is caused by RBC antigenic difference between blood donor and transfused patient. A great proportion of thalassaemic patients develop alloimmunisation as a result of multiple blood transfusions. This incidence ranges from 5 to 22% in different studies which puts alloimmunisation high on the list of complications of blood transfusion therapy [13]. Several factors influence antibody specificity such as sex, age and the number of transfusions. Also a very significant factor is the time interval between transfusion and performance of antibody detection test. Results from a recent study demonstrate that relative immunogenicity is dependent on the interval of testing after transfusion. The best time for testing is calculated to be 3 to 6 months after transfusion, when most antibodies have developed and are still detectable [14]. Autoimmunization is also present in thalassaemic patients who received multiple transfusions. The reported incidence of autoantibodies was 25 percent, 18 percent of which had clinical significant hemolysis, and they were mostly immunoglobulin G warm antibodies. Patient's genetic, acquired factor as well as patient's immune status influence how they respond [14]. Age plays a major role in the development of alloimmunisation as older patients tend to have greater prevalence in relation to patients who had transfusion in a younger age. Alloimmunisation results in chronic haemolytic anaemia and thus early initiation of blood transfusion aims for prevention rather than palliation of anaemia complications [8]. Moreover, a situation where alloantibody development is a major fear is during pregnancy. They can aggravate anaemia and cause severe haemolytic anaemia refractory to transfusions leading to an increase in the complications rate [15].

Infection transmission

Infectious complications are the main cause of mortality and morbidity in β -thalassaemia

patients. First of all, with blood transfusions there is an increased chance of transmitting blood borne infections. Although the risk of transmitting HIV and Hepatitis C virus has been decreased the last decade due to screening, new agents such as West Nile Virus and babesiosis which are not screened, may contaminate the blood supply from asymptomatic donors [2]. This is a major issue in developing countries where affordable safety for blood supply is not quarantined [16]. Moreover, these patients have an increased susceptibility to infections due to a coexistent immune deficiency. This immune deficiency can be attributed to iron overload which disturbs the immune balance.

Psychosocial factors

Regularly transfused patients will have self-perception of being different from others and this will be associated with lifelong hardship. In closed communities people who have regular transfusion might be stigmatised. Moreover, in some religions such as Jehovah's witnesses blood transfusions with whole blood or blood products are not allowed therefore, alternative methods must be used to treat these patients.

Blood supplies

Treating patients in the early stage of the disease and preventing their complications might be more cost effective, however if we start transfusing TI patients regularly, we will need an enormous amount of blood supplies, especially in countries with high prevalence of the disease such as Cyprus, Greece and Italy. This will probably lead to blood supply shortage, having a great impact on other cases that blood transfusions are needed. Moreover, these resources are not available in developing countries where cheaper treatment options must be used. Also blood screening and safety has to be a priority, therefore financial aid is needed to achieve both issues. It is still unclear whether or not the government or the families will be willing to offer the financial resources needed for excellent standard of care.

OTHER AVAILABLE TREATMENTS

Also there are a number of other treatments currently available for treating patients with TI. These options include splenectomy, iron chelation therapy, modulation of foetal haemoglobin and several other agents

focusing specific clinical manifestations [3]. Continuous folic acid supplementation is recommended for all patients with TI. Splenectomy is the first line of treatment to consider improving anaemia before starting regular transfusions. Moreover, modulation of foetal haemoglobin production can improve the clinical presentation of TI by decreasing the non- α/α globin chain imbalance. Hydroxyurea is an effective drug which can modulate foetal haemoglobin. Therefore, combination therapy including both current treatment options and transfusion therapy can ameliorate the future of TI patients. New approaches on the use of stem cell transplantation and gene therapy give very promising results on the management of TI patients.

FUTURE TREATMENTS-GENE THERAPY

The only potential lifelong cure of the disease currently available is bone marrow stem cell transplantation. Even though this treatment is promising, it is not available to all patients as it has certain limitation such as donor restriction, graft-versus-host disease, high cost and lifelong need of immunosuppressive therapy.

On the other hand, many researches have focused their studies into gene therapy which is very promising in giving patients a life-long cure for these diseases and a quality of life unachievable with current treatments. β -thalassemia is an excellent candidate disease for genetically based therapies in autologous HSCs.

The main goal of gene therapy is the long term expression of missing proteins at levels high enough to cure the main symptoms of the disease. Even though gene therapy has established a new prospective in the treatment of patients with thalassemia, it is not ideal as it has a significant risk of insertional mutagenesis. The reality of this risk was most clearly demonstrated during gene addition therapy for X-linked Severe Combine Immunodeficiency Disease (X-SCID) where 3 out

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of 22 patients treated with a gamma-retroviral vector developed leukaemia by insertional activation of Lmo-1 proto-oncogene [17]. Although this risk may be reduced by use of Lentiviral vectors, it is unlikely to be eliminated. Gene correction is a newer approach to gene therapy, in which the patient's mutated gene is corrected by the process of homologous recombination (HR) and probably it offers a solution to this problem. Different tools of genetic engineering are used for increasing the rate of HR in both yeast a mammalian cells such as Zinc Fingers and Toll-activator endonucleases [18]. Another achievement in the treatment of thalassemia is the understanding of the role of fetal haemoglobin (HbF) in the severity of the disease. Differences in the amount of HbF that persists into adulthood affect the clinical presentation of β -thalassemia syndromes. Genetic association studies have identified sequence variants in the gene BCL11A that affect HbF levels. A recent study showed that a down-regulation of BCL11A expression in adult red blood cells leads to a robust HbF expression [19]. A recent meta-analysis study has that BCL11A is a major modifier of HbF [20]. Therefore, BCL11A is a major therapeutic target in β -haemoglobin disorders.

CONCLUSION

No clear guidelines are identified for treating patients with TI and given the high variability in the clinical picture of the disease no standardised treatment can be proposed. Therefore, until clear evidence-based guidelines are available, treatment must be specific to each patient individually. According to the severity of the disease and the spectrum of complications, optimal treatment strategy using a multidisciplinary approach must be offered.

CONFLICT OF INTEREST

The author has no conflicts of interest or financial disclosures to report.

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