Blood Reviews 26S (2012) S24–S27

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

Contemporary approaches to treatment of beta-thalassemia intermedia

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ARTICLE INFO

Keywords:
Beta-thalassemia intermedia
Treatment
Splenectomy
Transfusion
Iron chelation
HbF induction

ABSTRACT

Beta-thalassemia intermedia (TI) is associated with a variety of serious clinical complications that require proactive and comprehensive management. These include skeletal deformities and osteopenia, compensatory extramedullary hematopoiesis and tumor formation, progressive splenomegaly, a hypercoagulable state resulting in thromboembolic events and pulmonary hypertension, and increased gastrointestinal iron absorption that often results in nontransfusional iron overload and liver damage. Although TI is generally considered a non-transfusion-dependent thalassemia, transfusion therapy may be an important part of the comprehensive management of this disease. This review describes the current state of the art for medical management of TI, with particular focus on the roles of splenectomy, transfusion, and iron chelation therapy.

1. Introduction

The beta (β)-thalassemia syndromes exhibit extremely diverse phenotypes ranging from the clinically silent β-thalassemia minor to completely transfusion-dependent β-thalassemia major (TM). The term β-thalassemia intermedia (TI) was coined to describe patients who have clinical manifestations somewhere in between.[1] Although tremendous progress has been made over the past decade in characterizing these syndromes from a genotypic and molecular perspective, the diagnosis is still largely based on the clinical severity of the syndrome. In practical terms, a thalassemia patient presenting at age 2 years or older with a hemoglobin (Hb) level between 70 g/L and 100 g/L, with or without splenomegaly, falls into the definition of TI. In addition, TI generally is considered non-transfusion-dependent, but at the more severe end of the spectrum, that definition is problematic. Some children with Hb levels in the range of 50–60 g/L survive early life, but they fail to thrive and often develop severe skeletal deformities. Hence, current clinical practice is to transfuse those children to avoid such complications.[2] Some individuals with TI have Hb levels in the range of 60–90 g/L and develop normally, but they may require red blood cell (RBC) transfusions later in life due to progressive splenomegaly and declining Hb levels, when their condition is complicated by intercurrent infection, pregnancy, or other factors, or to prevent complications associated with TI. The term TI can cover a broad and shifting clinical spectrum, and the optimal treatment strategy must be individualized for each patient. In this review, we will discuss the current state of the art for medical management of TI, with particular focus on the role of splenectomy, transfusion, and iron chelation therapy.

2. Clinical perspective on β-thalassemia intermedia

Ineffective erythropoiesis (IE), chronic hemolytic anemia, and iron overload associated with TI can result in a number of serious clinical sequelae that require proactive and comprehensive management.[3] The severity of anemia is determined by 2 main factors: the degree of IE and the extent of hemolysis of mature RBCs. Ineffective erythropoiesis is also associated with skeletal deformities and osteopenia attributed to erythroid marrow expansion,[3] as well as compensatory extramedullary hematopoietic tumor formation.[4] Hemolysis is also associated with progressive splenomegaly and a hypercoagulable state, which may account for the high incidence of thromboembolic events in patients with TI (see article titled, "Hypercoagulability in non-transfusion-dependent thalassemia"),[2,5–7] and may explain other complications associated with TI such as pulmonary hypertension (PHT).[8–10] Ineffective erythropoiesis and chronic anemia also lead to an increase in gastrointestinal iron absorption that often results in nontransfusional iron overload, predominantly in the liver but with consequences affecting many organ systems (see article titled, "Iron overload in non-transfusion-dependent thalassemia: a clinical perspective").[11,12] Thus, despite being considered a milder form of β-thalassemia at initial presentation and diagnosis, TI is associated with risk for a variety of serious complications that can increase with age. Therefore, optimal and early intervention is extremely important.[13] Unfortunately, despite a number of available treatment options, there are currently no clear treatment guidelines for TI. The OPTIMAL CARE study brought

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0268-960X/$ – see front matter

new clarity to the management of TI. This large retrospective overview of 584 patients with TI managed in the Middle East and Italy was designed to assess the rate of disease-associated complications in relation to current clinical practice.[14]

3. Currently available treatment options

3.1. Splenectomy

The role of splenectomy in the management of TI is complex. Although clinically indicated in certain situations (Table 1),[2] splenectomy can increase the risk of complications. In patients with non-transfusion-dependent TI who receive either no transfusions or sporadic transfusions, the size of the spleen inevitably increases with time, resulting in a gradual worsening of anemia and the requirement for RBC transfusion.[15] Neutropenia and thrombocytopenia also may worsen over time. Splenectomy typically reverses this process, resulting in a short-term increase in Hb levels by as much as 10–20 g/L, and reduces transfusion requirements in the majority of patients.[2,15] However, clinical observations suggest that splenectomy in patients with TI can contribute to an increased susceptibility to venous thrombosis,[6,16] PHT,[17,18] and silent brain infarcts.[19] Recently, the OPTIMAL CARE study confirmed an independent association between splenectomy and increased occurrence of thromboembolism, PHT, heart failure, iron-related endocrinopathy, and leg ulcers.[14] Splenectomy also increases the risk of infection, which carries a high mortality rate, especially in children with underlying hematologic disorders.[20] Recommendations from the British Committee for Standards in Haematology for the prevention of post-splenectomy infections[21,22] include antibiotic prophylaxis; however, compliance with these regimens can be problematic. Immunization against *Haemophilus influenzae* and serogroup C meningococci also is recommended. Based on these considerations, a guarded approach to splenectomy is advised, and the procedure should be delayed unless considered vitally necessary.

3.2. Transfusion therapy

In patients with TI, the most challenging therapeutic decisions are whether and when to initiate regular transfusion therapy.[2,15] Many patients require intermittent RBC transfusions due to intercurrent infection or pregnancy, and more regular therapy often is indicated for growth failure, skeletal deformity, exercise intolerance, or when Hb levels decline due to progressive splenomegaly (Table 2).[2,15,23] In addition, there may be clinical benefit to initiating transfusions earlier or prophylactically to reduce the risk of alloimmunization and to prevent complications that can occur with delayed initiation of transfusions.[2,24] In the OPTIMAL CARE study, patients who were placed on either intermittent or regular transfusion regimens had fewer complications (e.g., extramedullary hematopoiesis [EMH], PHT, and thrombosis), but had a higher rate of iron overload-related endocrinopathy.[14] Observational studies have confirmed that transfused patients with TI experience fewer thromboembolic events, PHT, and silent brain infarcts compared with transfusion-naïve patients.[2,6,14,19,25] This may be due to correction of the underlying IE and resulting damaged RBCs with thrombogenic potential.[2,7] Although earlier introduction of RBC transfusions does increase iron accumulation, effective iron chelating agents are available, and the benefits of transfusion therapy may outweigh the cost and inconvenience of iron chelation therapy.[2] Patients in the OPTIMAL CARE study who received both transfusions and iron chelation therapy had a lower incidence of complications, including endocrinopathy, compared with patients who received no treatment or either treatment alone.[14] Moreover, a recent study comparing health-related quality of life (HRQoL) in patients with transfusion-independent TI and regularly transfused patients with TM showed that TI patients had worse HRQoL, possibly because of more frequent complications.[26]

Table 1
Indications for splenectomy in β-thalassemia intermedia.[2]

Indication	Comment
Increased transfusion demand	If patient can maintain normal LIC with chelation therapy, splenectomy may not be necessary
Hypersplenism	Leucopenia or thrombocytopenia may cause recurrent bacterial infection or bleeding
Splenomegaly	Accompanied by symptoms such as left upper quadrant pain or early satiety Concern about possible splenic rupture

Abbreviations: LIC, liver iron concentration.
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Table 2
Indications for red blood cell transfusions in β-thalassemia intermedia.[2]

Hb <50 g/L
Declining Hb level in conjunction with enlargement of spleen at a rate of >3 cm/year*
Poor growth and/or development: • Height abnormal for age • Poor performance at school • Failure of secondary sexual development in conjunction with bone age
Diminished exercise tolerance (usually associated with Hb <70 g/L and chronic hypoxia)
Severe bony changes or deformities
Pregnancy
Infection
Other disease-specific complications: • Heart failure • Pulmonary hypertension • Thromboembolic disease • Leg ulcers • Priapism • Pathologic fracture • Cord compression

Abbreviations: Hb, hemoglobin.
*At least in periods of maximal growth and development.
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3.3. Iron chelation therapy

Iron overloading in patients with TI can occur as a result of both increased intestinal absorption and transfusion therapy, but regardless of the source, iron overload can be monitored and chelation therapy can readily control this condition.[2,11,27] The initiation of chelation therapy in patients with TI depends primarily on the extent of iron overload and rate of accumulation but, as with other aspects of the management of TI, clear disease-specific guidelines are not available. Because of increased iron absorption, patients with TI may have a positive iron balance at 5 years of age,[28] even in the absence of transfusions; thus, iron chelation therapy may be indicated.[2] The greatest challenge in these patients is monitoring iron levels because serum ferritin levels are not a good indicator of iron overload in patients with TI (see article titled, "Iron overload in non-transfusion-dependent thalassemia: a clinical perspective").[29] Therefore, direct assessment of liver iron concentration (LIC) either by biopsy or imaging every 1–2 years is recommended, and chelation therapy should be initiated in patients with elevated indices of iron overload (see article titled,

"Iron overload in non-transfusion-dependent thalassemia: a clinical perspective").[2,11] In most cases, intermittent iron chelation with careful periodic assessment is sufficient in patients with TI.

Currently available iron chelating agents include subcutaneous deferoxamine (DFO), which is used extensively in TM, oral deferiprone, and oral deferasirox (Table 3).[30–33] All appear to be effective and well tolerated, although data are limited in patients with TI. The practical limitations and inconvenience of prolonged subcutaneous therapy with DFO can potentially affect quality of life and compliance,[2,34,35] which has heightened interest in the use of oral iron chelators. In 2 small studies in minimally transfused TI patients, many of whom were noncompliant with DFO, oral deferasirox at doses ranging from 10 to 30 mg/kg per day for up to 2 years was shown to significantly reduce both LIC and serum ferritin levels.[36,37] In these studies, deferasirox was associated with mild gastrointestinal side effects, but there was no evidence of hepatic or renal toxicity. These promising results led to the initiation of the THALASSA study (NCT00873041), a large, randomized, double-blind, placebo-controlled phase 2 trial of deferasirox in 166 patients with non-transfusion-dependent thalassemia and iron overload (LIC $\geq$5 mg Fe/g dry weight and serum ferritin levels >300 ng/mL). This is the first large study to evaluate the efficacy and safety of iron chelation therapy in this patient population. Preliminary results of this trial were presented at the 16th Congress of the European Hematology Association in June 2011;[38] and efficacy outcomes were presented at the 2011 American Society of Hematology Annual Meeting.[21] Deferasirox significantly decreased LIC, the primary endpoint, compared with placebo after 1 year of treatment (P = 0.001 and $P < 0.001$ for 5 and 10 mg/kg/day deferasirox vs placebo, respectively). Deferasirox also significantly decreased mean serum ferritin levels compared with placebo ($P < 0.001$ for both doses vs placebo) and was associated with a manageable toxicity profile.

3.4. Areas of unmet need

A number of other medical interventions have been investigated in patients with TI to induce fetal Hb (HbF) production, overcome incomplete erythropoiesis, or manage complications, but results from these studies should be interpreted with caution.

For example, hydroxycarbamide (also known as hydroxyurea) has been widely studied to induce HbF production (see article titled, "The emerging role of fetal hemoglobin induction in non-transfusion-dependent thalassemia") and is commonly used in patients with TI based on evidence that it can increase Hb levels and reduce transfusion requirements. Indeed, the OPTIMAL CARE study documented the benefits of hydroxycarbamide in TI patients, especially when combined with transfusion and iron chelation therapy.[14] Although hydroxycarbamide is generally well tolerated with short- and medium-term use in patients with TI,[39] results from recent studies suggest that the beneficial effects on HbF production are transient and attenuate with longer duration of therapy.[40] However, more studies in this area are needed. Studies to identify additional HbF inducers are ongoing. Findings from other studies[41,42] suggest that hydroxyurea – either alone or in combination with L-carnitine or magnesium – may improve cardiac status and/or reduce PHT, but results are mixed. Hydroxyurea in combination with transfusion therapy also may decrease demand for EMH and reduce the risk of developing tumors. Paraspinal involvement is common and requires intervention due to the debilitating consequences of spinal compression.[2,4] In this setting, hydroxyurea often is used in conjunction with transfusion and radiotherapy to treat these tumors.

Finally, sildenafil citrate, a selective smooth muscle relaxant, has been evaluated in the management of PHT, but available data are limited.[2] A National Heart, Lung, and Blood Institute study (NCT00872170) of sildenafil in 27 patients with thalassemia and PHT was recently completed. Studies of other therapeutic targets and interventions that could potentially ameliorate the disease burden in patients with hemoglobinopathy including TI are ongoing.[43–45]

4. Conclusions

Improved understanding of the complex pathophysiology of TI has led to improvements in medical therapy. However, despite the availability of effective therapies, there remains a lack of prospective studies assessing the relative benefits of transfusion and other interventions with respect to preventing serious disease-related complications. Recent results from the OPTIMAL CARE study have provided important information on the effectiveness of various disease management strategies, but further research and comprehensive treatment guidelines are needed.

Conflict of interest statement

Dr. Cappellini has disclosed that she has received consulting fees from Novartis and Genzyme.

Dr. Karimi has no real or apparent conflicts of interest to disclose.

Dr. Musallam has no real or apparent conflicts of interest to disclose.

Table 3
Available iron chelators

	Deferoxamine[30]	Deferiprone[33]	Deferasirox[31,32]
Dosing schedule	25–60 mg/kg/day 8–12 h, 5 days/week	75–99 mg/kg/day 3 times daily	20–40 mg/kg/day once daily
Route	SC, IM, IV	PO	PO
Elimination half-life	~20–30 min[46]	~2 h	8–16 h
Excretion	Urine, fecal	Urine	Fecal
Adverse events	Local reactions, ocular, auditory, growth retardation, allergic reactions, hepatic dysfunction, renal dysfunction	GI disturbances, chromaturia agranulocytosis/ neutropenia, arthralgia, elevated liver enzymes	GI disturbances, rash, creatinine increase, ocular, auditory, elevated liver enzymes; renal/ hepatic failure and/or GI hemorrhage also reported
Licensing status	US	US and Europe	US and Europe
Approved indications	Acute iron intoxication and treatment of chronic iron overload due to transfusion-dependent anemias	Transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate	Treatment of chronic iron overload due to blood transfusions

Abbreviations: GI, gastrointestinal; h, hour; IM, intramuscular; IV, intravenous; min, minute; PO, oral; SC, subcutaneous; US, United States.

Dr. Taher has disclosed that he has received consulting fees and research funding from Novartis.

Acknowledgment

The authors wish to acknowledge Marithea Goberville, PhD, Maria Uravich, ELS, Tristin Abair, PhD, and Trudy Grenon Stoddert, ELS, for their assistance in preparing this manuscript for publication.

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