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Review Article

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Cardiac Considerations in Hematopoietic Stem Cell Transplantation (HSCT) for Transfusion-Dependent Thalassemia: A Review

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment option for several malignant and non-malignant hematologic disorders, including transfusion-dependent thalassemia (TDT). However, HSCT is associated with short-term and long-term complications. One of the recognized causes of morbidity and mortality in TDT patients is heart-related complications. Additionally, cardiac involvement is likely to be more common in patients proceeding to HSCT. Thus, the risks of cardiac complications should be carefully weighed against the benefits of the primary disease cure. This review attempted to discuss the cardiac considerations in TDT patients undergoing HSCT**.**

Keywords: Transfusion-dependent thalassemia; Hematopoietic stem cell transplant; Cardiotoxicity; Cardiomyopathy; Graft-versus-host disease

INTRODUCTION

Beta-thalassemia is an inherited hemoglobinopathy associated with defects in the synthesis of beta-globin subunits, leading to ineffective erythropoiesis and anemia. Allogeneic HSCT remains the only definitive treatment option for patients with transfusion-dependent thalassemia (TDT)[1]. Over the last four decades, transplants have been successfully performed in patients with TDT, with a cure rate of 80% to 90%[2]. Despite the substantial advances in outcomes, HSCT is still associated with several acute and chronic complications, which significantly affect the quality of life in HSCT survivors, including graft failure, graft-versus-host disease (GvHD), infections, neurologic complications, hormonal disturbances, and cardiovascular toxicities[3]. Although cardiovascular problems are not among the most common HSCT-related complications, they are associated with a high mortality rate and significantly decreased quality of life[4]. Therefore, there is a need for increased awareness and a better understanding of the probable cardiovascular complications so that their diagnosis and treatment take place in a proper and timely manner. This review focuses on the possible cardiac involvements that should be considered in managing patients with TDT during the pre- or post-HSCT period. .

Mechanisms of cardiac involvement in beta-thalassemia

Patients with TDT develop severe symptomatic anemia from the first months of life, so regular blood transfusions become mandatory for them. Iron overload is the main side effect of regular transfusion. Moreover, other contributors to the development of iron overload are ineffective erythropoiesis, increased intestinal iron absorption, and peripheral hemolysis[5]. Diverse categories of cells in the heart, including cardiomyocytes, could be damaged by the generated free iron through the Fenton and Haber-Weiss reactions[6]. Due to excess iron, the full saturation of ferritin permits labile plasma iron to pass into the cardiomyocytes as ferrous iron. Therefore, the three forms of iron storage in cardiomyocytes comprise ferritin, hemosiderin, and labile iron, among which the accessible form for iron chelation and the most toxic form responsible for the free radical reactions is the labile iron[5]. Due to the size and charge resemblance of ferrous iron and the calcium ions, the calcium currents decrease in iron-overloaded cardiomyocytes and shorten the duration of action potential[7,8]. The electrophysiological changes including, re-entry circuits, bradycardia, and arrhythmias, are caused by the direct toxicity of ferrous iron on the ryanodine-sensitive calcium channel responsible for contraction[9,10]. In brief, iron deposition within the myocardium leads to cardiomyopathy and arrhythmias. Chronic hemolysis is also associated with a complex vasculopathy caused by nitric oxide (NO) depletion, endothelial dysfunction, and elastic tissue abnormalities. Thus, pulmonary hypertension in TDT patients occurs due to chronic hemolysis, tissue hypoxia, high cardiac output state, and the pro-coagulant effects of splenectomy[12]. Other factors that could add to the possibility of cardiac dysfunction in beta-thalassemia patients include hormonal disturbances (hypothyroidism, hypoparathyroidism, and hypogonadism), carnitine and thiamine deficiencies, deficits in vitamin D and selenium supplies, and hepatitis C[11].

Pre-transplant cardiac evaluation

In a TDT patient, clinical assessments for cardiac evaluation should be conducted routinely. Electrocardiogram (ECG) analysis is mandatory every three to four months, together with an annual elective Holter monitoring or exercise test in specific patients. Transthoracic echocardiography is performed once or twice per year. Annual cardiovascular magnetic resonance (CMR) with T2 technique is also recommended[2,13,14,15]. A Myocardial T2* value of less than 20 ms is indicative of an abnormal amount of myocardial iron[16]. Delayed gadolinium enhancement could be measured with the fibrosis in the myocardium. The gold standard procedure for identifying pulmonary hypertension (PH) is right heart catheterization, but due to invasiveness, it is only recommended for selected patients[14].

During HSCT, several factors affect the cardiovascular capacity of the patient. Cytotoxic therapy, anemia, vasoparalysis, and myocardial suppression due to sepsis lead to volume expansion. Almost all patients undergoing HSCT develop sepsis, which is associated with pyrexia, leading to substantial increases in cardiac output and myocardial suppression, causing reduced cardiac contractility and low cardiac output failure[17]. Accordingly, to handle HSCT consequences, a sufficient cardiac reserve for maintaining a doubled cardiac output for several days and for tolerating the 1.5 times expanded intravascular volume is required[18]. In such a critical setting, patients with a pre-transplant impairment in cardiac function, such as TDT, become particularly susceptible to more complications that are hazardous; therefore, a comprehensive assessment of cardiac reserve is required. Identification of baseline malfunctions allows for the adoption of less cardiotoxic transplant regimens and modification of the procedure to minimize the risks[18].

All TDT candidates for HSCT should undergo a complete clinical history and physical examination relating to breathlessness and dyspnea, palpitations, chest discomfort on exertion, and syncope. A 12-lead ECG for evidence of ventricular hypertrophy, conduction abnormalities, and arrhythmias and a chest radiograph for detecting any increase in the cardiothoracic ratio are also recommended.

Performing an echocardiography is a standard practice in all patients undergoing HSCT, and a left ventricular ejection fraction (EF) of 35-40% is considered acceptable evidence for satisfactory cardiac reserve. Other than EF, pericardial effusion, the thickness of the left ventricular wall, dilation of the left atrium, flow patterns of the mitral and pulmonary vein, diameter of the right ventricular, and tricuspid gradient ought to be evaluated. A high BNP or NT-proBNP level has been considered a risk factor during HSCT and is used as a screening test for myocardial injury.

Pre-transplant arrhythmias, such as ventricular extrasystoles (>100/hour), ventricular tachycardia (>3 consecutive beats), atrial tachyarrhythmia (>30s), and high-grade block could be determined by Holter monitoring, and their existence prompts the need for a prolonged monitoring and electrophysiological evaluation. It is postulated that EF weakly correlates with survival and functional status; therefore, in order to evaluate the patient's functional reserve, the ability to increase cardiac output and maintain organ perfusion under stress could be considered a suitable test. Therefore, stress echocardiography or myocardial perfusion imaging in TDT patients older than 15 years and those who have exertional chest pain is essential[18]. In the presence of ongoing cell death, cardiac troponin (I or T) is released from the myocardium. Thus, in iron overload-induced damage, elevated troponin levels may be seen due to the myocardial necrotic damage caused by free radicals, indicating the probability of unforeseen cardiac events. Cardiac catheterization is required whenever**,** according to the initial evaluation, the possibility of pulmonary arterial hypertension (high tricuspid gradient) or pure diastolic dysfunction (high BNP or troponin level) is suggested. A thorough assessment of the coronaries and left ventricular systolic function is conducted by left-heart catheterization. On the other hand, catheterization of the right heart allows for a comprehensive assessment of filling pressures and cardiac output. A mean pulmonary arterial pressure higher than 25 mmHg is defined as pulmonary hypertension. A capillary wedge pressure ≥ 15 mmHg in the patient not receiving diuretics indicates significantly impaired diastolic function. Patients with right atrial pressure exceeding 11 mmHg or cardiac index at rest less than 2.1 L/min/m^2 should be considered at exceptional risk. Magnetic resonance imaging (T2*) is a non-invasive method for cardiac iron overload detection caused by transfusion in TDT patients. As iron overload has an adverse effect on transplant outcomes, quantitative assessment of iron overload in the heart by MRI and effective treatment of iron overload before transplantation can improve the success rate of HSCT[18].

Post-transplant cardiac complications

In the HSCT setting, heart-related complications may be due to the toxicity of the conditioning regimen and radiation, underlying disease cardiac problems, graft-versus-host disease (GvHD), and infections. Cardiac failure, arrhythmias, pericardial effusion and cardiac tamponade, pericarditis, myocarditis, and endocarditis could be addressed as transplant-associated cardiac complications.

Some features have been implicated as contributing factors to cardiac toxicity following HSCT. Age at therapeutic exposure is an identified potential risk factor for long-term cardiovascular disease. Harms to the developing myocardium in childhood could cause irreparable damage and impair the ability to compensate in periods of increased myocardial demand. On the other hand, the capacity to repair tissue damage in older patients is reduced; therefore, coronary artery disease, congestive heart failure, and dysrhythmia occur with a greater risk in these patients.

Gender-specific cardiotoxicity due to the differences in body fat composition between males and females has also been proposed. Females have a higher preponderance of drug-induced cardiotoxicity compared with males due to a higher percentage of body fat for the same body surface area and greater drug concentrations in non-adipose tissues, such as the heart[19,20,21,22,23].

Another potential risk factor for developing cardiac toxicity in thalassemia patients could be the usage of high-dose cyclophosphamide[21]. According to the results of serial echocardiographic studies conducted on pediatric patients who had received more than 80

mg/kg of cyclophosphamide, Steinerz et al. reported that at least half of the patients developed cardiac abnormalities[24]. Like TDT patients, reduced pre-HSCT ejection fraction has been associated with an increased risk of post-transplant heart-related complications[25]. Moreover, vascular insults such as transplant-associated thrombotic microangiopathy may lead to the depletion of the cardiopulmonary reserve or otherwise affect hemodynamics, leading to earlier congestive heart failure[26].

Given the timing, problems during the pre-HSCT period may be acute or delayed, occurring for weeks to years. Although cardiac complications rarely occur in the pre-HSCT period, they could be life-threatening, most commonly being dysrhythmias, heart failure, and cardiac tamponade. However, most cardiac manifestations caused by the imposed harms of the pre-HSCT period occur in a delayed manner. Therefore, lifelong cardiac monitoring (at least annually with ECHO and ECG) is recommended for post-HSCT patients.

Dysrhythmias and acute ventricular fibrillation, progressive heart failure, and cardiac tamponade have been reported as cardiac complications in HSCT patients. Cardiac tamponade can affect 2 to 4% of pediatric TDT patients after allogeneic HSCT[27,28]. Decreased cardiac function due to iron overload prior to HSCT in thalassemia patients often increases the risk of cardiac complications in these patients[29]. The time to develop an effusion in a review ranged[28]. Patients should be monitored for this complication in the pre-transplant period because appropriate intervention can prevent mortality[28].

Graft-versus-host disease (GVHD) is one of the most important causes of morbidity and mortality after HSCT. In the acute form of GVHD, skin, gastrointestinal tract, and liver are commonly involved, but the possibility of GVHD in other organs also exists[30]. Acute GVHD of the heart is mostly seen in autopsies as an incidental pathological finding[31]. However, in pediatric patients undergoing HSCT for malignancies or primary immune deficiencies, cases of possible acute GVHD of the heart have been reported[32]. Preexisting cardiac problems have been suggested to be a risk factor for cardiac GVHD. Clinically, heart GVHD can present with pericarditis, coronary disease, bradycardia, complete heart block, and sudden death[33]. Direct lymphocytic infiltration of the heart in chronic GVHD explains its cardiac side effects. Elevated markers of inflammation, such as interleukin-6 and tumor necrosis factor-α, cause endothelial injury and impair myocardial contractility, contributing to premature arterial events in long-term survivors after allogeneic HSCT[34,35]. Pericardial effusion could be linked to acute and chronic GVHD in pediatric and adult patients as intensifying immune suppression or initiation of steroid therapy has been shown to prevent the development of tamponade[36,37,38,39].

Long-term cardiovascular complications in HSCT survivors include heart failure, valvular heart disease, vascular disease, dysrhythmias, hypertension, and metabolic syndrome[40]. Long-term health-related outcomes in survivors of childhood HSCT have revealed that the risk of severe or life-threatening cardiovascular complications in these patients is nearly 13-fold their healthy siblings[41]. It is suggested that pre-HSCT therapeutic exposures and the cardiac insults due to the underlying disease, such as beta-thalassemia, may increase the risk of post-HSCT late cardiovascular complications[42,43,44]. Decreased cardiac reserve due to the pre-existing cardiac systolic and diastolic dysfunction in these patients could diminish their tolerability towards subsequent cardiac insults. However, on the contrary, it should be mentioned that cardiac status in these patients may also benefit from HSCT as resolution of iron excess could alleviate cardiac complications. [45].

In HSCT survivors at high risk of cardiac complications, such as TDT patients, screening of late effects with surveillance modalities is recommended[46]. Assessment of cardiovascular risk factors, such as lifestyle, tobacco use, lipid profiles, and fasting glucose, should be done annually. Electrocardiogram and echocardiogram should be conducted at 1, 3, and 5 years after HSCT, then every 5 years. Evaluation of cardiac MRI is recommended for patients with a history of significant red cell transfusion (i.e., those with thalassemia) one year after HSCT[46].

As the success rate of HSCT continues to improve in TDT patients, the necessity to decrease long-term side effects is augmented. Further studies are needed to implement the most beneficial heart-

protective strategies and appropriate long-term screening for modifiable cardiac risk factors.

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