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The Risks of Stem Cell Transplantation for Thalassemia Patients

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ABSTRACT

The most prevalent monogenic hematologic illnesses worldwide are thalassemias. Unfortunately, thalassemia transplants make up a very small percentage of all transplants performed worldwide. Therefore, it is imperative that organisations such as the Worldwide Network for Blood and Marrow Transplantation collaborate in order to establish and sustain dedicated transfusion and transplant initiatives aimed at addressing thalassemia in nations where Hematopoietic cell transplantation (HCT) has become a safer procedure and can be utilised to treat a broader spectrum of ailments due to advancements in transplantation techniques and supportive medical practises. However, it is still difficult to choose suitable transplant candidates.

The identification of adult patients who may derive potential benefits from HCT necessitates the comprehensive evaluation of several patient and illness-related criteria. These considerations encompass the patient's overall health status, prior therapeutic interventions, age, presence of comorbidities, as well as the specific disease and its associated risk factors. A risk-benefit analysis should be used to decide which patients are eligible for transplants individually. Various assessment methods benefit the decision-making process, such as the disease risk index and patient-specific criteria like the HCT-specific comorbidity index.

INTRODUCTION

The most prevalent monogenic hematologic illness, thalassemia, affects millions worldwide and claims thousands of lives yearly. In terms of hemoglobinopathies (genetic blood diseases), thalassemia is quite common.

Thalassemia is a group of genetic haemoglobin illnesses in which at least one of the globin chains is not made well enough, which throws off the production of the other globin chains. Anaemia is the end outcome of damaged haemoglobin (Figure 1) (Cappellini *et al.*, 2014). With the exclusion of the fish family Channichthyidae, all vertebrates and certain invertebrates possess haemoglobin (Hb or Hgb), a metalloprotein used to transport oxygen (Burmester & Hankeln, 2014). Thalassemia According to estimates, more than 60,000 newborns each year are diagnosed with significant thalassemia, and more than 80 million people worldwide are B-thalassemia carriers. (Modell and Darlison, 2008). In the 1920s, six months after diagnosis, all thalassemia primary patients would pass away (Lee, 1925).

Since it was first identified in 1925, scientists have been unable to develop a long-term remedy for this fatal illness. A complete study of how this disease works at the molecular level could give new ideas for how to treat it (Shafique *et al.*, 2021).

Whipple and Bradford were the first to describe the cause of the disease in 1932. They found that

most cases were from the Mediterranean, so they called the disease "thalassemia" (How, 2011).

From 1949 to 1957, the proportion of patients in Ferrara who survived until the age of six was found to be just 9%. Furthermore, it was observed that by the conclusion of the 1970s, almost 50% of thalassemic patients throughout Italy had succumbed to the disease before reaching the age of twelve. Since the 1980s, there has been a significant improvement in survival rates because of the implementation of combination safe transfusions, frequent chelation therapy, and/or transplantation. However, despite these advancements, national-level survival rates still need to reach the desired level of effectiveness and satisfaction (Mohamed, 2017).

Thalassemias are classified into two types: Alpha and Beta Thalassemia. Gene mutations induce low amounts and/or malfunctioning of globin proteins, resulting in these deficits. In certain instances, one of these proteins can be entirely missing, resulting in the formation of a pocket or fold by the globin chains. This structural arrangement facilitates the binding of heme (Fe++) and the subsequent transportation of oxygen. On Chromosomes 16 and 11, respectively, are located the genes for the alpha and beta globin proteins. At various times during life, distinct globin genes are used. Globin proteins interact with globin during the embryonic and foetal development phases before being replaced by globin protein. Hemolysis is caused by globin chain anomalies, which limit erythropoiesis. Iron overload in patients with blood transfusions is common, leading to subsequent complications in several physiological systems, including renal or hepatic failure. As a result, thalassemias are currently recognised as a syndrome. The only treatment for Thalassemias is a transplant of bone marrow or gene therapy, both of which have a low rate of success. Overloading iron increases the creation of toxic reactive oxygen species (ROS), causing damage to the hepatic, endocrine, and vascular systems(Ali *et al.*, 2021).

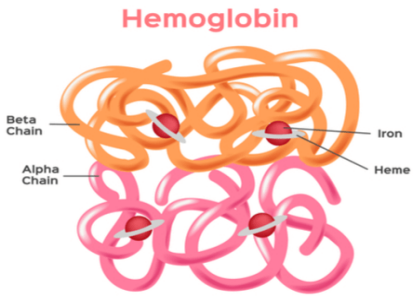

Figure 1: The structure of haemoglobin

Thalassemia screening programs have generally decreased the proportion of afflicted babies, particularly in nations with a high prevalence of thalassemia. Voluntary prenatal screening is advised in both Southeast Asia and Europe. However, in other places, like in several Middle Eastern countries, mandated premarital screening exists(Kattamis *et al.*, 2020). In order to assess and diagnose thalassemia, many diagnostic methods can be utilised, including prenatal testing by genetic analysis of amniotic fluid, examination of blood smears, comprehensive blood cell counts, and DNA analysis (Ali *et al.*, 2021).

Treatment

Patients with thalassemia major are anticipated to experience a significantly reduced life expectancy, often within a few months following their diagnosis, without receiving blood transfusions or undergoing organ transplantation (Mohamed, 2017).

In contrast, the implementation of long-term transfusion and chelation therapy poses considerable challenges in several impoverished nations where the illness's prevalence is high, creating a substantial and unmanageable health burden. The only therapy for thalassemia is a stem cell transplant. It has advanced significantly, making it less hazardous, more effective, and

accessible to more patients with diverse comorbidities and donors (Mustafa *et al.*, 2020). The progress made in human leukocyte antigen typing has significantly enhanced the process of selecting alternative donors, resulting in comparable outcomes between matched unrelated donors and matched sibling donors. Patients with no healthy donors now have a higher chance of surviving and avoiding chronic transfusion issues because of cutting-edge therapies like haploidentical and cord blood transplantation. Allogeneic stem cell transplantation can treat patients with thalassemia major. Previously, patients were limited by the donor pool. The donor pool has been significantly expanded due to the progress made in haploidentical stem cell transplantation (haplo-SCT) (Wang *et al.*, 2021). The outcomes of haplo-SCT in TM patients, however, differ according on the programme. The use of transplantation as the preferred therapeutic approach is warranted when a suitable related or unrelated donor is available and when the medical facility possesses the necessary proficiency in the field of transplantation, specifically in managing patients diagnosed with thalassemia. Unfortunately, only a small number of transplants are done for thalassemia worldwide. Because of the high demand for transplants, transplant organisations such as the Worldwide Network for Blood and Marrow Transplantation should work together to develop and promote specialised transfusion and transplant programmes for thalassemia treatment in low-resource nations (Mohamed, 2017).

HCT is a significant therapeutic strategy for various malignant and nonmalignant hematologic diseases. HCT has been comparatively safer and more useful as transplantation technology and supportive care procedures have advanced, as have stem cell sources. However, there are still issues with transplant-related morbidity and death, especially in elderly patients. Transfer risk must be weighed against the expected benefit of a longer, disease-free life for transplant-related sickness and death after autologous and allogeneic transplants. As a result, individuals who need autologous or allogeneic hematopoietic cell transplantation must undergo a thorough clinical assessment and get extensive guidance from duly competent physicians and medical personnel (Okamoto, 2017).

There has been a notable increase in survivors undergoing autologous and allogeneic hematopoietic cell transplants (HCT). It is thought that 80–90% of donor patients who go into remission in the first 2–5 years will live another 5 years. Nevertheless, the death rates of these patients continue to be higher compared to the general population, mostly due to late complications that significantly contribute to long-term morbidity and mortality. In order to provide patient-specific screening and preventative therapy, it is advised that HCT survivors be evaluated for the remainder of their lives (Majhail, 2017).

Risk of hematopoietic cell transplantation

Health issues related to HCT The American Society for Blood and Marrow Transplantation and the European Blood and Marrow Transplantation Group (EBMT) recommend disease-based HCT diagnosis (Majhail *et al.*, 2015; Sureda *et al.*, 2015) . The recommendations divide target illnesses and disease states into three levels of indications based on current data. The levels encompassed in this classification system consist of the standard of care, clinical alternative, developing, and not usually suggested. The suitability of the concentration is contingent upon the categorization of the transplant, whether it is allogeneic or autologous, as well as the origin of the hematopoietic stem cells (Okamoto, 2017). Transplant recipients have potential long-term complications due to both pre- and post-transplant exposures and risk factors (Majhail *et al.*, 2012).

Late problems following HCT

Late complications are medical issues that occur after many months to years following transplantation. Secondary cancers, transplanted organ complications, late-onset infections, QOL impairments, psychosocial issues, sexual and fertility issues, and reintegration are among these

complications. Late non-relapse mortality in transplant patients is affected by cardiovascular disease, end-stage renal disease, and bronchiolitis obliterans. Additional disorders, including dry eyes, xerostomia, and avascular necrosis, may not directly increase mortality but can significantly affect QOL. These issues are partially or entirely attributable to transplantation-related exposures. In addition, it should be noted that numerous factors can influence the likelihood of certain outcomes, including pretransplant treatment exposures, such as disease-specific chemotherapy or radiation, and modifiable or unmodifiable lifestyle variables, such as smoking and hereditary cancer risk factors (Majhail, 2017).

Infections that occur later in life

Adequate restoration of the cellular and humoral immune systems in allogeneic HCT recipients can take two years or longer; it can also be further delayed in patients who have graft-versus-host disease (GVHD). Consequently, autologous and allogeneic HCT recipients are susceptible to infection-related late morbidity and mortality. Encapsulated bacteria, including Streptococcus, Neisseria meningitides, and Hemophilus influenza, are more likely to infect chronic graft-versus-host disease (GVHD) patients who need long-term immunosuppression. They are also susceptible to fungal infections caused by Aspergillus species, Candida species, Pneumocystis jiroveci, and viral infections, including cytomegalovirus and varicella zoster virus. It is recommended that vaccinations be initiated within 6-12 months following transplantation, whereas patients undergoing hematopoietic cell transplantation (HCT) should adhere to the infection prevention recommendations established by consensus (Tomblyn *et al.*, 2009).

Survival after HCT

During the initial 2-4 years following transplantation, the primary factor contributing to treatment failure is the recurrence of the illness. Patients who do not encounter illness recurrence during the initial phase exhibit a significantly elevated likelihood of long-term survival. Many important studies have shown the long-term survival rates of transplant patients who remain disease-free for 2–5 years (Atsuta *et al.*, 2016; Bhatia *et al.*, 2007) . Despite methodological and patient attribute differences, all studies show that this patient population has an excellent long-term survival rate. However, it is important to note that individuals who have had nonetheless have a reduced life expectancy compared to those of the general population of similar age and gender. This discrepancy persists significantly, ranging from 15 to 20 years following the transplantation procedure. In addition, they indicate disease recurrence, chronic graft-versus-host disease (in allogeneic HCT patients), organ failure, and secondary malignancies, all of which are substantial causes of mortality in the later stages. Over time, registries for hematopoietic stem cell transplantation (HSC) outcomes have developed into several databases encompassing local and global transplant activities and results. These registries have made significant contributions to identifying trends, patterns, and treatment outcomes in HSCT across time (Hussain *et al.*, 2017).

Secondary cancers

Secondary cancers, which are broadly characterised as post-transplant lymph proliferative diseases (PTLD), hematologic malignancies, and solid cancers, account for 5-10% of mortality among HCT patients who live for two years or longer (Majhail & Douglas Rizzo, 2013; Majhail, 2008, 2011, Wingard *et al.*, 2011). Generally, there is a 3-5 year latency before secondary solid tumours develop following HCT. Nevertheless, the frequency of their occurrence continues to increase with time, and a point of stabilisation in their prevalence has yet to be identified. The cumulative incidence after hematopoietic cell transplantation (HCT) is shown to be 1-2% within 5 years, 2-6% within 10 years, and 4-15% within 15 years (Majhail *et al.*, 2011; Ringdén *et al.*, 2014; Rizzo *et al.*, 2009). According to written norms, all HCT survivors should get cancer screenings for the rest of their lives (Inamoto *et al.*, 2015; Majhail *et al.*, 2012) .

Infections that develop later

CMV remains the primary cause of morbidity and mortality among HCT patients, despite advances in molecular technology for cytomegalovirus (CMV) detection and the introduction of extremely effective prophylactic medications. CMV can induce disorders that reach deep into the tissues of the body, such as asthma, hepatitis, colitis, retinitis, and encephalitis. Patients with HCT with a CMV infection might have a death rate of nearly 60%. The occurrence of CMV infection has been linked to an elevated susceptibility to secondary bacterial and fungal infections, graft-versus-host disease, and heightened non-relapse death rates subsequent to HCT (Camargo & Komanduri, 2017).

Conclusions

1. Suppose patients do not get transplantation or substantial transfusion and chelation therapy. In that case, thalassemia major is a disorder with morbidity and mortality rates comparable to or greater than leukaemias.
2. It is recommended that patients diagnosed with thalassemia major have a transplant promptly, preferably before the onset of end-organ damage and complications related to iron overload.
3. In order to mitigate the risk of hemosiderosis, it is recommended that individuals, particularly adolescents and young individuals, have thorough blood transfusion and iron chelation treatment. Additionally, when considering transplantation, seeking specialised thalassemia centres for optimal care is advisable.
4. HCT patients continue to run the risk of fatal complications and late effects. Our knowledge of risk factors, underlying causes, and methods to prevent late impacts grows as we do more studies.
5. When assessing if a patient is eligible for HCT, it is crucial to give them enough time to fully explain the procedure's benefits and realistic expectations based on the results of the approaches discussed above. HCT necessitates a cooperative, knowledgeable, and insightful patient.
6. Utilising CMV-specific T-cell responses in biomarker-driven preventative methods may aid in risk assessment and clinical decision-making, albeit considerable clinical and immunological data linkage is required.

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