

RECENT ADVANCES IN HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR INHERITED BONE MARROW FAILURE SYNDROMES

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ABSTRACT

The inherited bone marrow failure syndromes (IBMFS) are a heterogeneous group of genetic disorders characterized by the inadequate production of at least one of the hematopoietic lineages, leading to the development of both isolated cytopenia (anemia, neutropenia, or thrombocytopenia) or pancytopenia. Different biological mechanisms justify the pathophysiological changes found in the IBMFS, emphasizing the repair pathways in Fanconi anemia (FA), maintenance of telomeres in congenital dyskeratosis, and ribosome biogenesis in Shwachman Diamond syndrome (SSD) and Blackfan Diamond anemia. These disorders are generally associated with the presence of congenital malformations and an increased risk of cancer, mainly hematological, gynecological, and head and neck neoplasms. Although the diagnosis occurs typically in childhood, adult patients, mostly below 40 years of age with signs and symptoms suggestive of IBMFS, should be investigated. Currently, hematopoietic stem cell transplantation (HSCT) is the only curative option for hematological complications related to IBMFS. It is essential to highlight that these patients must be monitored throughout their lives to prevent or detect early treatable neoplasia.

Keywords: Anemia, Diamond-Blackfan, Fanconi Anemia, Shwachman, Telomere Diamond Syndrome, Bone Marrow Transplantation and Hematopoietic Stem Cells

INTRODUCTION

The inherited bone marrow failure syndromes (IBMFS) are genetic disorders characterized by inadequate blood cell production, usually associated with physical malformations and a predisposition to cancer [1,2] IBMFS often presents with isolated cytopenia (pure red cell aplasia, neutropenia, or thrombocytopenia) that may progress to pancytopenia over time (3) Although the diagnosis is usually performed in childhood, an increasing number of patients with IBMFS may present to adult hematologists with atypical presentations. [1,4] Significant overlap between these syndromes is usually observed, and a correct diagnosis is critical to allow for adequate treatment, genetic counseling, and long-term surveillance for

cancer. The patient and the family's history need to be carefully investigated to detect the presence of bone marrow failure, hematological malignancies, pulmonary or hepatic abnormalities, and cancer in other members of the family. Patients with IBMFS should undergo a comprehensive evaluation, and a review of systems involved in these syndromes was recently published by Alter in 2017 [5]. As many individuals lack a specific phenotype and may appear normal, screening family members is essential to exclude them as potential donors.

Over the last few decades, there has been considerable improvement in elucidating the genetic aspects

related to IBMFS, leading to significant progress in better understanding the normal hematopoiesis and how this affected patients with bone marrow failures. These advances provided valuable information about the different biological mechanisms involved in IBMFS, such as the repair mechanism in FA, the maintenance of telomeres in DC, and the biogenesis of ribosomes in Shwachman Diamond syndrome (SDS) and DBA [3,6]. Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for the hematological complications related to the IBMFS [7]. Results are excellent when patients are transplanted from matched donors before complications related to previous infections, transfusions, or clonal evolution are detected. Challenges include the treatment of adult patients, patients with advanced diseases, and the treatment of cancer. An additional concern is the potential of the HSCT procedure, including conditioning regimen, infection, and chronic graft versus host disease (GvHD), to increase the risk of malignancies [2,7]. As a general rule, radiation containing regimens should be avoided for all patients with IBMFS, and bone marrow is considered the preferred stem cell source [7]. While the use of related cord blood from unaffected matched related donors is associated with excellent transplant outcomes, unrelated umbilical cord blood should be avoided whenever possible [7–9]. Increasing awareness of these diseases is of utmost importance, and the decision to proceed with the transplant must be made by a multidisciplinary team. Also, HSCT should be performed in specialized centers, with particular attention to early and long-term toxicity and lifelong medical surveillance for secondary neoplasms. In this paper, we summarize the information and recent advances regarding HSCT for IBMFS.

FANCONI ANEMIA

Fanconi anemia (FA) is a chromosomal instability syndrome resulting from a DNA damage repair defect. [10]. It is considered the most frequent IBMFS and is characterized by progressive BMF, various congenital abnormalities, and a predisposition to developing malignancies, especially myelodysplasias, acute leukemias, tumors of the head and neck, and gynecological cancers [11]. Patients with FA usually present with a clinical manifestation variable like short stature, skin abnormalities, a triangular “Fanconi” face, upper limb abnormalities, renal and heart anomalies, genitourinary abnormalities, and cardiac defects [12,13]. Endocrinological complications are also persistent before and after transplant in FA patients. The majority exhibit at least one difficulty, such as growth hormone deficiency, hypothyroid-

ism, dyslipidemia, hypogonadism, and infertility [14]. The risk of insulin resistance and abnormal glucose metabolism is also higher and may be aggravated by GVHD treatment with steroids [14]. Patients with FA should be evaluated annually and, when necessary, treated according to the recommendation for the general population [15]. HSCT outcomes have improved dramatically over the past decades, and it is indicated when patients develop pancytopenia, MDS, or acute myeloid leukemia (AML). Overall survival after HSCT for young patients transplanted in aplasia from matched related or matched unrelated donors with 80–90% overall survival in experienced centers [16–18].

Currently, RIC regimens are considered standard. In addition, for matched related transplantation, the use of low dose cyclophosphamide with or without fludarabine and r-ATG is sufficient to achieve excellent engraftment and low incidence of GVHD [17]. It is essential to remind that irradiation is not necessary for the conditioning regimen for this group of patients [19]. Curitiba’s group has transplanted 91 patients in aplastic phase using CY 60mg/kg with or without ATG with an excellent 95% overall survival and a median follow-up of 7 years [20].

Although HSCT outcomes are excellent for patients in aplastic phase transplanted below the age of 10, transplant strategies for adults and those with advanced diseases need to be improved. A recent publication by Bearings *et al.*, including almost 200 adults, demonstrated an overall survival and non-relapse mortality at four years of 38% and 51%, respectively. Factors associated with improved outcomes in multivariate analysis were the use of fludarabine and an HLA-matched donor [16]. FA patients with a clonal evolution have a dismal prognosis, usually related to increased toxicity to the preparatory regimens and higher risk of relapse [15,21]. To improve outcomes for this group of patients, the French and Brazilian groups treated 18 patients with FA in advanced MDS or AML with FLAG chemotherapy followed by sequential HSCT in aplastic phase using a RIC regimen. With this approach, the 3-year cumulative incidence of relapse and progression-free survival was 13% and 53%, respectively [22]. Patients without a matched related or unrelated donor may also benefit from haploidentical transplants performed with or without in vivo T cell depletion [23,24]. Bonfim *et al.* demonstrated a one-year OS of 73% (95% CI, 64% to 81%) using a modified haplo-PTCY platform [24]. These results were also achieved by Ayas *et al.* using a similar haplo-PTCY platform with an overall survival of almost 90% in 19 patients [25].

Patients with FA are expected to live longer, and the risk of cancer increases with age. Long-term follow-up is essential in this population with particular attention to detect cancer and other specific complications. Thus, dental and head and neck physician exams should be done every [6-12] months. Early detection of cancer with brushing/biopsy of suspicious lesions and consequent treatment (surgery) is associated with better results considering the patients do not tolerate irradiation or chemotherapy [26,27]. Also, new drugs may have less side effects and may be very useful to treat cancer [28]. Importantly, patients whose FA is due to mutations in FANCD1/BRCA2 or FANCN/ PALB2 need genotype-specific cancer screening because of increased risks of medulloblastoma, Wilms tumor, and other cancers [26].

DYSKERATOSIS CONGENITA

Dyskeratosis congenital (DC), a severe form of telomere biology disease (TBD), is a rare IBMFS characterized by abnormal skin pigmentation (reticulated skin hyperpigmentation), nail dystrophy, and oral leukoplakia. DC is frequently associated with BMF and organ involvement, mainly pulmonary fibrosis and liver abnormalities. There are two severe forms of DC; Hoyeraal Hreidarsson syndrome (HHS), a classical DC disease associated with BMF, intrauterine growth retardation, microcephaly, and cerebellar hypoplasia, and Revesz syndrome (RS), which is related to progressive bilateral exudative retinopathy (Coats retinopathy), intrauterine growth retardation, fine, sparse hair, fine reticulate skin pigmentation, ataxia secondary to cerebellar hypoplasia and cerebral calcifications [29,30].

Bone marrow failure and hematologic malignancies (MDS or AML) represent the main indication for HSCT. Although transplant is the only curative option for DC, the results are still disappointed with a poor long-term survival rate. Pulmonary and vascular complications, hepatic cirrhosis, graft failure, graft-versus-host disease (GVHD), and sinusoidal obstruction syndrome still represent the most important causes of morbidity and mortality after transplant, which explain the disappointing long term survival [31–33]. Gadalla *et al.* studied 34 cases who underwent HSCT between 1981 and 2009 and demonstrated a probability of overall survival of 70, 57, and 15% in 1, 5, and 12 years respectively. In this study, almost 80% of patients received a myeloablative conditioning regimen, and the authors highlighted the severe transplant-related toxicities observed over the years. [34] Similar results were published by Barbaro *et al.*, where the long-term cumulative survival rates were

57% and 23% at 5 and 10 years post HSCT in a series of 109 cases [32]. Considering these poor results, some groups have recommended reduced-intensity conditioning containing fludarabine as a standard regimen [35,36]. Regarding a Brazilian experience, the OS of 28 patients transplanted for TBD in Curitiba between 1993 and 2019 was 53,6% at a median follow-up of 6 years [37].

DIAMOND BLACKFAN ANEMIA

Diamond-Blackfan anemia (DBA) is a rare inherited red cell aplasia caused by an intrinsic defect of erythropoietic progenitors leading to severe anemia in early infancy ninety percent of the patients diagnosed within the first year of life [38,39]. Currently, DBA is classifying as a “ribosomopathy” once haploinsufficiency of either a small or large subunit-associated ribosomal protein is present in the majority of patients [38,40]. Diagnosis should be suspected in all children under one year of age presenting with macrocytic or normocytic anemia and reticulocytopenia, with normal marrow cellularity and a decrease or absence of red cell precursors in the bone marrow [41]. Approximately 50% of patients have congenital anomalies associated [41]. Similar FA and DC, DBA is considered a cancer predisposition syndromes, with a higher risk of hematologic (AML) and solid tumor (colon carcinoma and osteogenic sarcoma) development [42,43]. The therapeutic approach is based on red cell transfusions, corticosteroid therapy, and HSCT. Steroids, considered the first-line treatment with about 80% success response, should be started in the second year of life considering its negative effect on infants’ physical and neurocognitive development. Thus, red cell transfusions are used mainly in infants and patients refractory to corticosteroid therapy [41,44,45]. HSCT, potentially curative treatment for DBA, is indicated for patients who are non-response to steroids or remain transfusion-dependent despite the use of steroids (dose requirement ≥ 0.3 mg/kg/day). Other indications are erythroid alloimmunization, progressive pancytopenia, and progression to SMD / AML [7,46]. HSCT should preferably be performed between 2 and 5 years, as older patients tend to have a worse evolution due to iron overload and alloimmunization [7,47].

In the last decades, HSCT has been employed with success in DBA patients. In 2006, data from North American DBA Registry reported an OS of 73% with MSD and 19% with alternative donors ($P= 0.01$) (48). Besides, the International Bone Marrow Transplant Registry, published in 2005 a 3-year OS of 64% (76% for MSD and 39% for alternative donor transplants) while the

Italian Group (AIEOP HSCT Registry) reported an OS of 74.4% in patients transplanted between 1990 and 2012 [47,49]. All of these findings are similar to those published by the Pediatric Study Group of the Brazilian Society of Bone Marrow Transplantation (SBTMO), which included 44 patients and had a 5-year OS of 70% (95% CI: 57 – 85%) in pediatric patients transplanted for DBA in Brazil. It was 80% (95% CI: 65-97%) from an MSD (n=25), 73% (95% CI: 52-100%) from a MUD (10/10 HLA Matched, n=12) and 29% (95% CI: 9-92%) from a MMD (n=7) [50]. Recently German DBA group and French HSCT registries published an excellent OS of 91% (95% CI: 84-98%) with a median follow-up of 4.5 years [51]. Myeloablative conditioning with busulfan-based regimens is currently recommended for patients with DBA, although treosulfan-based reduced-toxicity regimens have been demonstrating promising results [7,51,52]. It is important to keep in mind that the use of intravenous busulfan and adjustable pharmacokinetic monitoring correlates with better OS and EFS in children transplanted for non-malignant diseases like DBA [53,54]. Patients with DBA should benefit from a pretransplant and early posttransplant iron chelation therapy once the high iron overload is associated with inferior outcomes after HSCT [55,56]

SHWACHMAN-DIAMOND SYNDROME

Schwachman-Diamond syndrome (SDS) is a rare autosomal recessive disorder caused by mutations in the Shwachman-Bodian-Diamond Syndrome (SBDS) gene localized on chromosome 7 and found in 90% of the cases. It is characterized by exocrine pancreatic dysfunction with malabsorption, skeletal abnormalities, BMF, and predisposition to hematologic neoplasia [57,58]. In addition, like DBA, the molecular pathogenesis of SDS is associated with defective processing of rRNA and ribosome assembly. Some patients' clinical manifestations include short stature, with metaphyseal dysostosis, particularly at the hips and femurs in about half the patients, variable immune dysfunction, delayed dentition, and structural and functional abnormalities of the liver. Neutropenia is the most common hematological abnormality, although they may have other cytopenias present in up to 80% of the patients [59].

HSCT is the only potentially curative treatment for SDS and should be recommended for all patients with progressive pancytopenia and clonal evolution, mainly acute leukemia, and MDS. HSCT should also be considered for patients refractory to high doses of G-CSF (10 µg/kg or more per injection at least three months a year) to maintain protective neutrophil values (between 1.0 and 5.0 × 10⁹/L), [5,7,60].

A RIC regimen is considered standard once patients with SDS are more susceptible to transplant-related toxicity, especially cardiac and pulmonary toxicities [61,62]. Recently, Cesaro et al. published the results of 74 patients with SDS treated with HSCT between 1988 and 2016. The 5-year overall survival and non-relapse mortality were 63.3% (95% CI 50.8–73.4) and 19.8% (95% CI 10.8–30.8), respectively [60].

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare IBMFS caused by mutations in the gene coding for the thrombopoietin receptor MPL. It is characterized by isolated thrombocytopenia and a reduction or absence of megakaryocytes in the bone marrow. Most patients develop hypocellular bone marrow and progressive pancytopenia within the first decade of life. Unlike other IBMF, clonal evolution is an infrequent event [63–65]. HSCT is the only curative therapy for CAMT. As with many rare genetic disorders, there are only a few reports about HSCT for CAMT in the literature since the first case in 1990.

Nevertheless, the transplant should be offered to patients with transfusion-dependent thrombocytopenia or alloimmunization, pancytopenia, or clonal evolution (MDS or AML) [64,65]. As for other IBMF syndromes, HSCT from an HLA- matched sibling is the treatment of choice for SAA while Matched [10/10] unrelated donor is an acceptable choice. MAC conditioning based on fludarabine and either busulfan or treosulfan is considered standard [7,64–66]. Until now, increased regimen toxicity usually present in Fanconi anemia, and DC has not been reported with MAC [67]. Regarding UCB, a report from the Eurocord group suggests that UCB transplantation is a reasonable option for patients with CAMT, mainly if a sibling donor is used [8]. On the other hand, data from unrelated HSCT demonstrated inferior results [65].

SEVERE CONGENITAL NEUTROPENIA

Severe neutropenia is a heterogeneous group of congenital disorders characterized by impaired maturation of neutrophil granulocytes and persistent absolute neutrophil count (ANC) of less than 0.5 × 10⁹ /L. Among several associated genetic mutations, ELANE and HAX1 genes are responsible for 60% of cases. Usually, clinical manifestations include bacterial infections, including deep tissue infections, sepsis, and fever. The regular use of granulocyte colony-stimulating factor (G-CSF) is routine [68,69]. An additional concern, clonal evolution (leukemia and MDS) affects about 10% of patients [70]. Despite the excellent re-

sults achieved using G-CSF therapy, HSCT is still considered the only curative treatment. Currently, non-response to G-CSF treatment, and patients who develop AML or MDS are the main indications for transplantation. Bone marrow is considered the standard stem cell source, and myeloablative conditioning, usually with busulfan and Cyclophosphamide, and GVHD prophylaxis regimen consist of CSA and methotrexate are preferred. [7,71]. In 2015, Fioredda *et al.* reported the analysis of 136 patients transplanted from 1990 and 2012 by the European Bone Marrow Transplant group. The 3-year overall survival was 82 % and TRM 17 %. In multivariate analysis, HSCT below ten years of age from a matched related or unrelated donor in recent years was associated with better results (71).

CONCLUSION

The IBMFS is a group of rare genetic diseases associated with inadequate blood cell production, and up until now, allogeneic HSCT is considered the only cu-

ative option. Ideally, HSCT is indicated as soon as the patients begin to develop pancytopenia and before severe infections, clonal evolution, or the need for multiple transfusions. As these diseases may present with subtle findings, screening of family members should be performed before transplantation. However, it is essential to keep in mind that transplantation may only correct damaged hematopoiesis without changing the course of other complications related to the disease. Thus, we recommend that the decision to proceed to allogeneic HSCT should be discussed with the experts' team. Patients/families should be advised about the increased risk of cancer and organ damage progression. Finally, we strongly recommend that patients have a continued follow-up after HSCT, focusing on early detection, prevention, and treatment of head and neck squamous cell carcinoma, hematological neoplasia, and solid tumors (colon carcinoma and osteogenic sarcoma).

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