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ORIGINAL ARTICLE

Outcomes in pediatrics patients diagnosed with bone marrow failure disorders treated in a tertiary care center

Desenlace de los pacientes pediátricos con falla medular tratados en un centro de alta complejidad

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What do we know about the subject matter of this study?

Bone marrow failure syndromes have a low prevalence and acquired etiology predominates. In acquired bone marrow failure syndrome, the first-line treatment is allogeneic stem cell transplantation from an identical relative and, if not available, immunosuppressive therapy is.

What does this study contribute to what is already known?

Response rates to immunosuppressive therapy are lower than those reported in developed countries. In acquired bone marrow failure syndrome, allogeneic transplantation including haploidentical transplant is a good option as salvage therapy.

Abstract

Bone marrow failure (BMF) syndromes are rare disorders with an annual incidence of 2-4 cases per million. Treatment options include immunosuppressive therapy (IST) and hematopoietic stem cell transplantation (HSCT). **Objective:** To analyze the outcomes of pediatric patients diagnosed with BMF treated in a tertiary care center. **Patients and Method:** Retrospective study of pediatric patients diagnosed with BMF who consulted at *Fundación Valle de Lili*, Cali. Descriptive statistical analysis was performed according to Acquired BMF (ABMF) and Inherited BMF (IBMF). The outcomes include treatment, complications, overall survival (OS) in transplant patients, calculated using the Kaplan-Meier method. **Results:** We included 24 patients with BMF, average age 6.5 ± 4 years, and 50% were women. 58% presented IBMF, 9 with Fanconi anemia (FA), 2 dyskeratosis congenita, 2 congenital amegakaryocytic thrombocytopenia, and 1 presented Diamond-Blackfan anemia. 12 patients treated with HSCT had a 5-year OS of 83%. ABMF represented 42%. 6 patients received IST-HSCT, 3 recei-

Keywords:
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ved IST, and 1 received HSCT. The OS of the IST-HSCT group was 86%. Six patients died, four of them related to infection. **Conclusions:** In this series, there was a higher number of cases with IBMF. The OS of patients treated with HSCT is similar to that reported in recent studies. The most frequent cause of death was of infectious origin which has also been previously reported. The treatment established in the patients showed favorable results in a Latin American tertiary care center.

Introduction

Bone marrow failure (BMF) syndrome is a rare disorder which has an estimated annual incidence of 2-4 cases per million, its most frequent age range is from 10 to 25 years and after 60 years, affecting both sexes equally[1]. It is characterized by the decrease or absence of hematopoietic stem cells in the bone marrow, altering its hematopoietic function[2,3]. It typically presents with persistent cytopenias in at least one stem cell lineage, which may lead to pancytopenia[4].

Regarding its etiology, it can be classified as Congenital BMF (CBMF) and Acquired BMF (ABMF) Syndrome[5,6]. ABMF represents 85-90% of cases, and its primary treatment is Immunosuppressive Therapy (IST) or Hematopoietic Stem Cell Transplantation (HSCT), which depends on the availability of the best donor[6,7]. In relation to CBMF, it accounts for 15%-20% of cases and its treatment is usually identical and, in some cases, haploidentical HSCT[8]. Among the main etiologies of CBMF in children are Fanconi Anemia (FA), Dyskeratosis Congenita (DC), Shwachman-Diamond Syndrome (SDS), and Congenital Amegakaryocytic Thrombocytopenia (CAMT). These syndromes can occur with or without physical abnormalities and do not necessarily present complete pancytopenia, especially during the early stages of the disease[3]. The objective of this study is to describe the outcome of pediatric patients treated for bone marrow failure syndrome between 2011 and 2017 in a high complexity institution.

Patients and Method

Population studied

Observational, case series-type study of pediatric patients diagnosed with BMF, who between 2011 and 2017 consulted at the *Fundación Valle del Lili*, a high complexity institution and reference center in Cali, Colombia, for patients requiring HSCT. Within the sampling strategy, we used the ICD-10 codes related to BMF registered in the clinical record, identifying 2,491 patients aged between 0 and 17 years who consulted during the study period. The following selection criteria were applied: patients treated at the Institution, with a diagnosis of BMF according to clinical symptoms, paraclinical studies, and verified through bone marrow biopsy.

The diagnosis of FA was made using the Chromosomal Breakage Test. The diagnosis of DC was made with next-generation sequencing (NGS) panel of bone marrow failure, CAMT with bone marrow biopsy, and Diamond-Blackfan Anemia (DBA) according to classic diagnostic criteria[9]. A patient was excluded due to the etiology of BMF could not be determined. This study was approved by the Institutional Ethics Committee.

BMF treatment

The therapeutic options used were based on the care guidelines for patients with ABMF, with a multidisciplinary approach, managing with HSCT as a first option if there was an identical donor or IST in patients without an indication for HSCT or who did not have an identical related donor[6]. In CBMF, treatment is based on transfusion support, androgens, and HSCT in severe cases or with poor response[10].

Transplantation

The conditioning regimen for each patient was made according to the type of donor, based on Fludarabine[11,12]. In the case of transplantations with haploidentical donors, we used a reduced intensity protocol based on the Baltimore regimen[13,14].

Graft-versus-host disease (GVHD) prophylaxis

The prophylaxis schemes for GVHD used varied according to the type of transplant performed. Regimens based on combined cyclosporine and methotrexate therapy were used for identical family donor transplants[15,16]. In haploidentical transplantations, the post-transplant cyclophosphamide-based regimen was used[17-19].

BMF severity

The BMF severity was classified according to Camitta's criteria, as severe BMF if it meets at least two of three characteristics (absolute neutrophil count (ANC) < 0.5×10^9/L, platelet count < 20×10^9/L, or reticulocyte count < 20×10^9/L), very severe BMF when presenting the same characteristics of severe BMF but with ANC < 0.2×109/L, and non-severe BMF when it

does not meet any of the characteristics of severe or very severe BMF[20].

Response to Immunosuppressive Therapy (IST) Criteria

It was considered complete response when achieving transfusion independence and Hemoglobin counts > 11 g/dL + Platelets > $100x10^9$/L + Neutrophils > $1.5x10^9$/L; partial response having transfusion independence, but without achieving the complete response values in the blood count, confirmed in two follow-up visits 4 weeks apart; and non-response when not achieving transfusion independence[6].

Statistical analysis

A descriptive statistical analysis was made for all variables considered, dividing patients into two groups: ABMF and CBMF. The categorical variables are summarized in proportions and the continuous ones are expressed as means ± standard deviation (SD) or median with their interquartile range (IQR), depending on the distribution of the variable. The primary outcomes of the study were treatment, complications, overall survival (OS) in months, calculated from the date of diagnosis or date of transplantation to the date of death or last follow-up at the institution. These results were analyzed with the Kaplan-Meier method using the statistical software STATA® 12.1.

Results

Population studied

Between 2011 and 2017, 24 pediatric patients with BMF were treated in the pediatric hematology-oncology service. Figure 1 shows the flow of patients in the study.

Table 1 and Table 2 show the demographic and clinical characteristics. The average age was 6.5 ± 4 years, 50% were female, and the most frequent symptom was anemic syndrome (87%). The most frequent diagnosis was ABMF (42%), followed by FA (37%). There were 19 (79%) patients who underwent HSCT and had a median follow-up of 22 months (IQR: 13-65) and OS of 84% at 5 years.

Acquired Bone Marrow Failure Syndrome (ABMF)

Ten patients (42%) were included in this group. Of these, 9 were treated with IST (one case treated at another institution) and 6 of them were transplanted due to non-response to treatment. There was one patient who directly underwent HSCT with an identical donor. In this group, the OS at five years was 70%, the transplanted patients presented an OS at five years of 86% vs. 33% in the non-transplanted ones (Figure 2). Three patients died, one due to multiple organ failure after undergoing HSCT and two due to infection after treatment with antithymocyte globulin (ATG) without HSCT.

Congenital Bone marrow Failure Syndrome (CBMF)

There were 14 (58%) patients in this group, most of them with FA (9/14). 12 patients underwent HSCT (2 at another institution with subsequent follow-up at our institution) and two patients received only transfusion support. The OS at 5 years was 83% in the transplanted patients (Figure 2). Three patients died after HSCT, two due to causes associated with HSCT (infection by adenovirus and cytomegalovirus) and one due to liver and lung involvement secondary to DC.

Discussion

We present a series of pediatric patients with BMF treated in a high complexity institution between 2011 and 2017. Our experience showed that CBMF was the predominant etiology, which differs from the reports in the literature[2] and could be explained by the national patient referral system that includes this institution as a reference center for HSCT.

The most frequent congenital diagnosis was FA, as reported in other series[21]. In this series, most of the patients in the CBMF group were treated with HSCT, with a survival rate of 83% at five years. In the ABMF group, a large proportion received IST with ATG as first-line treatment. Despite this, most of them required HSCT as a second line of treatment, showing a different behavior to the therapeutic outcomes of developed countries which present a success rate of first-line treatment around 60%[22] and similar to developing countries with 34%[23,24].

In Colombia, a retrospective study of patients aged between 4 and 60 years with BMF, who received allogeneic stem cell transplantation from an identical relative between 1993 and 2011, found that most cases (74.3%) had ABMF, 22.9% FA, and 2.9% DBA, but did not specify the proportion of children under 18 years of age[25].

Current international guidelines suggest the use of IST, ATG, and cyclosporine as first-line therapy for patients with severe aplastic anemia who have not an HLA-identical related donor[6,7,26]. In our series, 9 out of 10 patients were managed with ATG as a first-line treatment, of which 6 patients required second-line treatment with HSCT, which could be interpreted as non-response to first-line treatment. This could be explained in some way by the use of rabbit-derived ATG which has been used in most cases in our center. Some authors have reported that rabbit-derived ATG has a lower response rate compared with horse-derived ATG, which may be associated with better outcomes in patients with BMF[27].

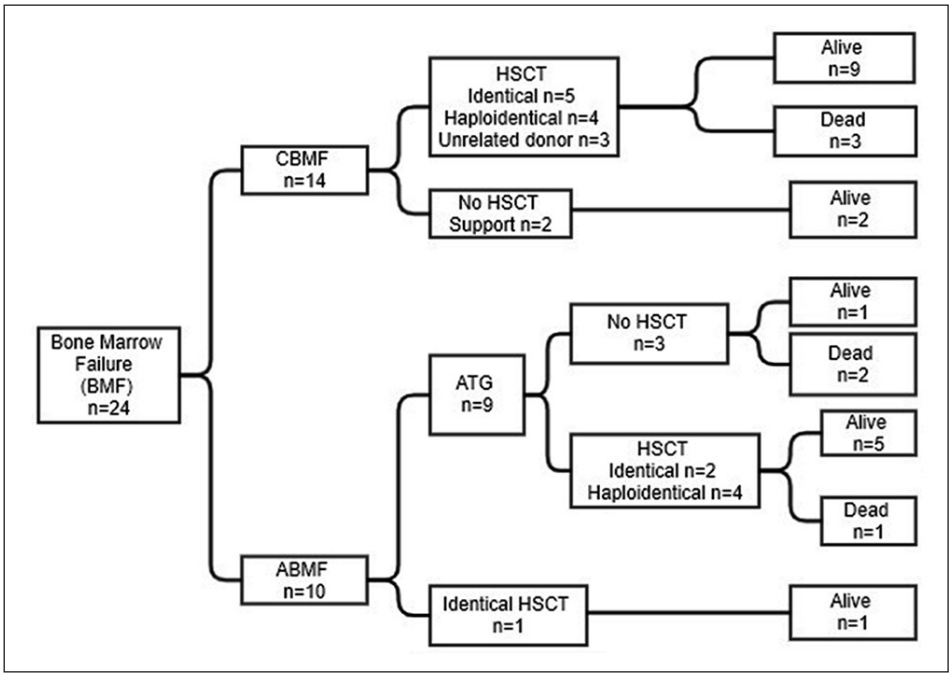

Figure 1. Flowchart of patient with BMF. BMF: Bone marrow failure, ABMF: Acquired bone marrow failure, CBMF: Congenital bone marrow failure, HSCT: Hematopoietic stem cell transplantation, ATG: Antithymocyte globulin.

Table 1. Demographic and clinical characteristics of pediatric patients with BMF in a tertiary care center

Characteristic	Total n = 24	ABMF n = 10	CBMF n = 14
Age at diagnosis, years			
Mean ± SD	6.5 ± 4.4	7.8 ± 4.3	5.5 ± 4.3
Range	0.03 - 15	1 - 15	0.03 - 12
Female gender, n (%)	12 (50)	4 (40)	8 (57)
Symptoms, n (%)			
Hemorrhagic syndrome	17 (68)	7 (70)	9 (64)
Anemic syndrome	21 (87)	10 (100)	11 (78)
Severe and/or recurring infections	9 (37)	5 (50)	4 (29)
BMF Etiology, n (%)			
Acquired Bone Marrow Failure	10 (42)	10 (100)	0 (0)
Fanconi Anemia (FA)	9 (37)	0 (0)	9 (64.3)
Dyskeratosis congenita (DC)	2 (8)	0 (0)	2 (14.3)
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	2 (8)	0 (0)	2 (14.3)
Diamond Blackfan Anemia	1 (4)	0 (0)	1 (7.1)
Frequency of severe and very severe BMF, n (%)	14 (70)	10 (100)	7 (50)
ATG	9 (37)	9 (90)	-
Transplant, n (%)	19 (79)	7 (70)	12 (86)
Identical	8/19	3/7	5/12
Haploidentical	8/19	4/7	4/12
Unrelated donor	3/19	0/0	3/12
Post transplant follow-up, months			1
Median (IQR)	22 (13-65)	28 (20-95)	6 (11-55)
Range	1.7-105.7	1.7-105.7	2.4-88
Months between BMF diagnosis and HSCT,			
Median (IQR)	15 (5-21)	5 (1-8)	18 (7-25)
Range	1-46	1-34	4 46
Acute GVHD, n (%)	7 (29)	3/10	4/7
Chronic GVHD, n (%)	7 (29)	2/6	5/11

BMF: Bone marrow failure, ABMF: Acquired bone marrow failure, CBMF: Congenital bone marrow failure, SD: Standard deviation, GVHD: Graft-versus-host disease, HSCT: Hematopoietic stem cell transplantation, IQR: Interquartile range.

Table 2. Pediatric patient with BMF in a tertiary care center

ID	HSCT	Age/Gender	BMF Etiology	Severe and/or recurring infections at diagnosis	ATG	Chronic GVHD	Outcome (alive/dead)
1	No	M/15	Acquired	No	Sí	NA	Dead-Infection
2	No	F/9	Acquired	Yes	Sí	NA	Dead-Infection
3	No	F/7	Acquired	No	Sí	NA	Alive
4	Yes	F/12	Acquired	Yes	Sí	Yes	Alive
5	Yes	M/6	Acquired	No	Sí	Yes	Alive
6	Yes	F/9	Acquired	Yes	Sí	No	Dead-Adenovirus
7	Yes	M/11	Acquired	Yes	Sí	No	Alive
8	Yes	M/2	Acquired	Yes	Sí	No	Alive
9	Yes	M/1	Acquired	No	Sí	No	Alive
10	Yes	M/6	Acquired	No	No	No	Alive
11	Yes	F/6	Fanconi anemia	No	No	No	Alive
12	Yes	F/12	Fanconi anemia	No	No	No	Alive
13	Yes	M/7	Fanconi anemia	Yes	No	No	Alive
14	Yes	M/9	Fanconi anemia	No	No	No	Alive
15	Yes	M/5	Fanconi anemia	No	No	Yes	Alive
16	Yes	F/9	Fanconi anemia	Yes	No	Yes	Alive
17	Yes	F/12	Fanconi anemia	No	No	No	Dead-Adenovirus
18	Yes	F/1	Dyskeratosis congenita	No	No	Yes	Alive
19	Yes	F/1	Dyskeratosis congenita	No	No	Yes	Dead-Pulmonary progression
20	Yes	F/3	Congenital Amegakaryocytic Thrombocytopenia	Yes	No	No	Alive
21	Yes	M/1	Congenital Amegakaryocytic Thrombocytopenia	Yes	No	No	Dead-CMV
22	Yes	M/2	Diamond Blackfan anemia	No	No	Yes	Alive
23	No	M/5	Fanconi anemia	No	No	NA	Alive-transfusion support
24	No	F/9	Fanconi anemia	No	No	NA	Alive-transfusion support

HSCT: Hematopoietic stem cell transplantation, BMF: Bone marrow failure, ATG: Antithymocyte globulin, GVHD: Graft-versus-host disease.

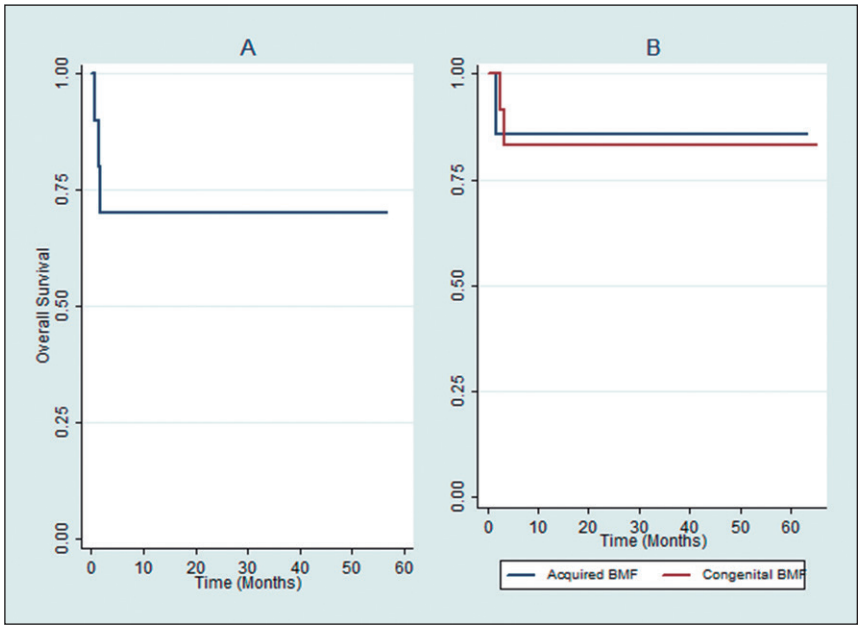

Figure 2. Overall survival of patients with Hematopoietic stem cell transplantation (HSCT) and bone marrow failure (BMF) diagnosis. A. Patients with HSCT and BMF. B. Patients with HSCT according to BMF type.

Hematological response rates vary, at least in part due to the lack of consensus on the parameters used in their definition (transfusion independence and absolute or relative improvement in blood counts). About 60% of patients respond within 3-6 months after starting ATG treatment[28,29]. In our series, the period between ABMF diagnosis and transplantation was shorter than 8 months in most cases, suggesting short non-response times to first-line treatment.

HSCT is the treatment of choice for patients diagnosed with moderate or severe BMF[1], ideally from an HLA-identical donor[30,31], preferring bone marrow as the source which is associated with lower GVHD rates, however, peripheral blood or cord blood can also be used[32]. Recent studies show good results using haploidentical transplants as first-line or salvage therapy, including comparable results with an identical related donor, making them a safe alternative[33-35]. In this series, equal numbers of HSCT are reported with identical and haploidentical donors, with an OS of 84%, which coincides with recent reports where OS rates are similar with different donor types[13,26,33,34,36].

In this series, 29% of the patients presented acute and chronic GVHD, similar to what was reported in the literature with different types of donors, between 21.1 and 47.7%[26,34,37].

The study conducted by Sallfors-Holmqvist et al. (BMTSS-2), between 1974 and 2010, in which patients under 21 years of age were treated with HSCT due to BMF, obtained an OS of 86.4% at 15 years after HSCT[38]. In our case, we achieved an OS of 84% at 5 years, and 86% specifically in the ABMF group. However, this procedure implies a high risk of related mortality and may be associated with significant early or late morbidity[6]. In our series, we had three cases of transplant-related mortality, representing 15% of total transplant recipients, which is lower than the six deaths in a series of 27 patients (22%) with BMF reported by Muñoz-Villa et al.[24].

Among the good prognostic factors identified in patients who will undergo HSCT are younger age, shorter interval between diagnosis and transplantation, fewer pre-transplant transfusions, use of irradiated blood components, fewer pre-transplant infections, higher degree of donor-recipient histocompatibility, conditioning without total body irradiation (TBI), and sufficient infused hematopoietic stem cells[6].

In these patients, the main cause of transplant-related mortality was infectious complications, where adenovirus and cytomegalovirus were the most frequent. Similar results have been found in the literature of related and unrelated donors, where infections and graft failures are mentioned as the main causes of death[37,39-41].

Some limitations of this work include the retrospective collection of information that limited access to information available in the medical records. We consider that this study could have a referral bias of patients for treatment since the institution is a center of high complexity and national reference for referral of patients from different places in Colombia who require HSCT. Another limitation was the lack of genetic information of the cases to identify in a more precise and complete way the described cases.

In conclusion, the outcomes observed in this series of pediatric patients with BMF show similarities with other series regarding the OS results of transplant recipients. The distribution of the pathologies within the CBMF was similar to that reported in the literature.

In this series, the number of cases with CBMF was higher. In patients with ABMF, the number of patients who were treated with HSCT may suggest a failure in the use of ATG and with a favorable post-transplant survival that allowed good results in that group. In general, the most frequent cause of death was due to infections, which have also been previously reported in the literature. The treatment administered in the patients of this study showed favorable results in a high complexity center in a Latin American country.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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