BONE MARROW TRANSPLANTATION IN BONE MARROW FAILURE SYNDROMES: EXPERIENCE AT QUEEN RANIA AL-ABDULLA HOSPITAL FOR CHILDREN

Omaimah aljarrah, MD, Ruba alhazaimeh MD*,Mais jzzaz,MD*,Suliman Aljaafreh MD*,Atwa Altawarh MD*,Atwa Altawarh MD*,Ola Alhasanat SN**,Lara Mikhi MD***,Maher K. Mustafa MD**

ABSTRACT

Objective: This study aimed to explore the outcomes of bone marrow transplantation in pediatric patients with various bone marrow failure syndromes whether acquired or inherited.

Methods: The study involved 46 pediatric patients (<16 years old) with bone marrow failure from 2013 to 2023. Patients underwent either matched sibling or haploidentical bone marrow transplantation, and outcomes were evaluated based on their disease type, graft versus host disease (GVHD) status, cytomegalovirus (CMV) reactivation, and CD34 levels.

Results: The patient cohort consisted mostly of acquired severe aplastic anemia (50%) and Fanconi anemia (43%). Matched siblings bone marrow transplants were conducted in all patients. GVHD and CMV reactivation were observed in 8.7% and 22% of patients, respectively. The mean CD34 level was 3.6106 (2.25106). The overall survival rate showed no significant difference across different disease groups or transplantation types, with a mortality rate of 10.9%.

Conclusion: Significant improvements have been made in the use of hematopoietic stem cell transplantation to treat both acquired and inherited bone marrow failure. Outcomes for matched sibling HSCT for inherited and acquired BMF syndromes are good, and HSCT is the treatment of choice for BMF patients who have available matched related donors.

In our study, the outcomes of bone marrow transplantation in pediatric patients with hematological disorders were not significantly influenced by the disease type or transplantation type. The study highlights the need for larger, multi-center investigations to corroborate these findings.

Key words: Bone marrow transplantation, hematological disorders, pediatrics, graft-versus-host disease

JRMS DECE 2024; 31 (3): 10.12816/0062041.

INTRODUCTION

The study of bone marrow failure disorders such as Fanconi anemia, acquired severe aplastic anemia, pure red cell aplasia, and congenital amegakaryocytic thrombocytopenia (CAMT) has been a significant focus of medical research due to their impact on the quality of life and survival of patients. These disorders often require interventions like bone marrow transplantation, which can be matched sibling or haploidentical, depending on the availability of a suitable donor [1].

From the departments of:
*hematology department QRH,
** bone marrow transplant unit at QRH
***pediatric resident at QRH

Fanconi anemia is a rare genetic disorder characterized by bone marrow failure, congenital abnormalities, and an increased risk of malignancies [2]. Severe aplastic anemia, on the other hand, is a condition where the body stops producing enough new blood cells, leading to fatigue and a higher risk of infections and uncontrolled bleeding [3].

Pure red cell aplasia is a syndrome defined by normocytic normochromic anemia with severe reticulocytopenia and marked reduction or absence of erythroid precursors from the bone marrow and CAMT is a rare, inherited disorder characterized by a severely low number of megakaryocytes, a type of bone marrow cell that makes platelets that are important for clotting and preventing bleeding. [4].

Bone marrow transplantation has been a cornerstone in the treatment of these hematological disorders. Matched sibling bone marrow transplantation involves the transfer of bone marrow from a healthy donor to the patient [5]. Haploidentical transplantation, a newer approach, involves the transfer of bone marrow from a half-matched donor, typically a parent or sibling [6]. These procedures, while lifesaving, are associated with complications such as graft-versus-host disease (GVHD), where the donated bone marrow or peripheral blood stem cells view the recipient's body as foreign and attack the body [7].

Cytomegalovirus (CMV) reactivation is another significant concern in these patients, especially those undergoing bone marrow transplantation. CMV is a common virus that can cause severe complications in individuals with weakened immune systems, such as those undergoing bone marrow transplantation [8]. The relationship between CMV reactivation and the outcomes of bone marrow transplantation is an area of active research.

CD34 is a protein that is expressed on the surface of stem cells, including the hematopoietic stem cells that are transplanted during bone marrow transplantation. The level of CD34+ cells is often used as a measure of the quality of the stem cell graft, and higher levels are generally associated with better transplantation outcomes [9].

In this study, we aim to explore the outcomes of bone marrow transplantation in a cohort of patients with various bone marrow failure syndromes whether acquired or inherited, focusing on the impact of factors such as the type of disorder, the type of transplantation, GVHD status, CMV reactivation, and CD34 levels.

Materials and Methods

Study design and participants

We included all pediatric patients (age < 16 years) in the period between 2013 to 2023. Patients suffered from various etiologies of bone marrow failure including Fanconi anemia, severe aplastic anemia, CAMT, and pure red cell aplasia. Data were extracted including patients' demographic such as age and sex, type of hematological disorder, type of transplantation, whether patients had a CMV reactivation and CD34 levels.

Management of patients (conditioning regimens):

The conditioning regimens used for patients with severe aplastic anemia (fully matched donor) were cyclophosphamide 160 mg/kg divided over 4 days, anti-thymocyte globulin (ATG) 20 mg/kg divided over 4 days, and fludarabine 160 mg/m^2 divided over 4 days.

For haploidentical transplant patients with severe aplastic anemia, the conditioning regimen used was Cytoxan 29 mg/kg divided over 2 days, ATG 10 mg/kg divided over 3 days, fludarabine 150 mg/m^2 divided over 4 days, rituximab 200 mg/mL on days -8 and -1, IVIG 400 mg/kg/day over 3 days and total body irradiation (TBI) of 200 cGY * 2 on day -1.

As for patients with Fanconi anemia, the conditioning regimen in fully matched donors were reduced-intensity regimens due to chemosensitivity in these patients, the regimens included cyclophosphamide 40 mg/kg divided over 4 days, ATG 10 mg/kg divided over 4 days, and fludarabine 150 mg/m^2 divided over 5 days.

For patients with pure red cell aplasia and CAMT, the conditioning regiment used was the myeloablative regimen consisting of busulfan (9-16 mg/kg) over 4 days, cyclophosphamide 200 mg/kg over 4 days, and ATG 16 mg/kg over 4 days.

A prophylactic therapy against GVHD was given to all patients in the form of cyclosporin 3 mg/kg IV on day -2 along with a short course of methotrexate at doses of 15 mg/m^2 on day +1 and 10mg/ m^2 on days +3, +6 and +11 with folinic acid rescue given at dose of 15mg/m^2/dose*4 on days +2, +4, +7 and +12 post-BMT.

For patients with haploidentical transplant, the prophylactic regimen for GVHD was Cytoxan® at a dose of 50 mg/kg divided over 2 days in Fanconi anemia and for other conditions 100 mg/kg divided over 2 days (days +3 and +4), tacrolimus and mycophenolate mofetil on day +5.

Ethical considerations

The study received approval from the Royal Medical Services' Institutional Review Board (IRB). It adhered to the principles outlined in the Declaration of Helsinki from 1975. Since the study was retrospective and practically impossible to conduct without a waiver, the IRB committee decided to waive the requirement for informed consent. Moreover, the research posed minimal risk to the patients and would not compromise their rights or privacy, considering the valuable knowledge it could provide. All patient data were anonymized and treated with strict confidentiality.

Statistical analysis

Continuous data in this study were summarized using means and standard deviations (SD), while categorical data were presented as frequencies and percentages (%). Statistical analyses included the student's t-test for continuous variables. Categorical variables were analyzed using Chi-squared test. Overall survival data was analyzed using Kaplan-Meier plots and log-rank p-values. Missing data were handled using the pairwise deletion method, assuming missing completely at random. Statistical significance was set at a two-sided p-value of ≤ 0.05. All data analyses were performed using R statistical language (version 4.3.1, Vienna, Austria).

Results

A total of 46 patients were enrolled, with a mean age of 8.7 (3.5) years. Twenty patients (43%) had Fanconi anemia, 23 (50%) patients had severe aplastic anemia, 2 (4.3%) had pure red cell aplasia, and one (2.2%) had Amegakaryocytic thrombocytopenia. Graft-versus-host diseases (GVHD) status was acutely positive in 2 (4.3%) patients, one patient (2.17%) had chronic liver GVHD, and one patient (2.17%) had chronic lung GVHD. The majority of patients 96% (44/46) had an matched sibling bone marrow transplant, while two patients (4.3%) had a haploidentical bone marrow transplant. CMV reactivation was positive in 10 (22%) patients, while 33 (73%) were negative for CMV reactivation. Mean CD34 levels was $3.6*10^6$ ($2.25*10^6$). Two patients (4.3%) had a second transplant, the mortality in a transplanted patient is due to, one (2.2%) patient having liver GVHD ascites and bleeding, one patient having hyponatremia and hypokalemia due to severe diarrhea and late visit to hospital after arrest at home, one patient having lung GVHD bronchiolitis obliterans, one patient had pericardial effusion with CMV reactivation, and one patient had failure to engraft as shown in **Table 1**. CD34 levels did not show a significant correlation with the day of engraftment as shown in **Figure 1**.

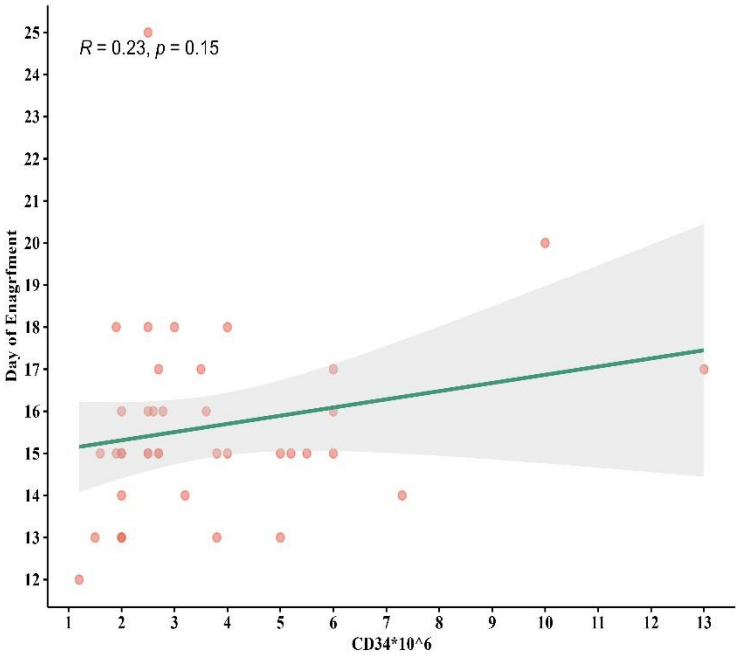

Figure 1: Scatter plot showing the Spearman correlation between CD34 levels and days of engraftment.

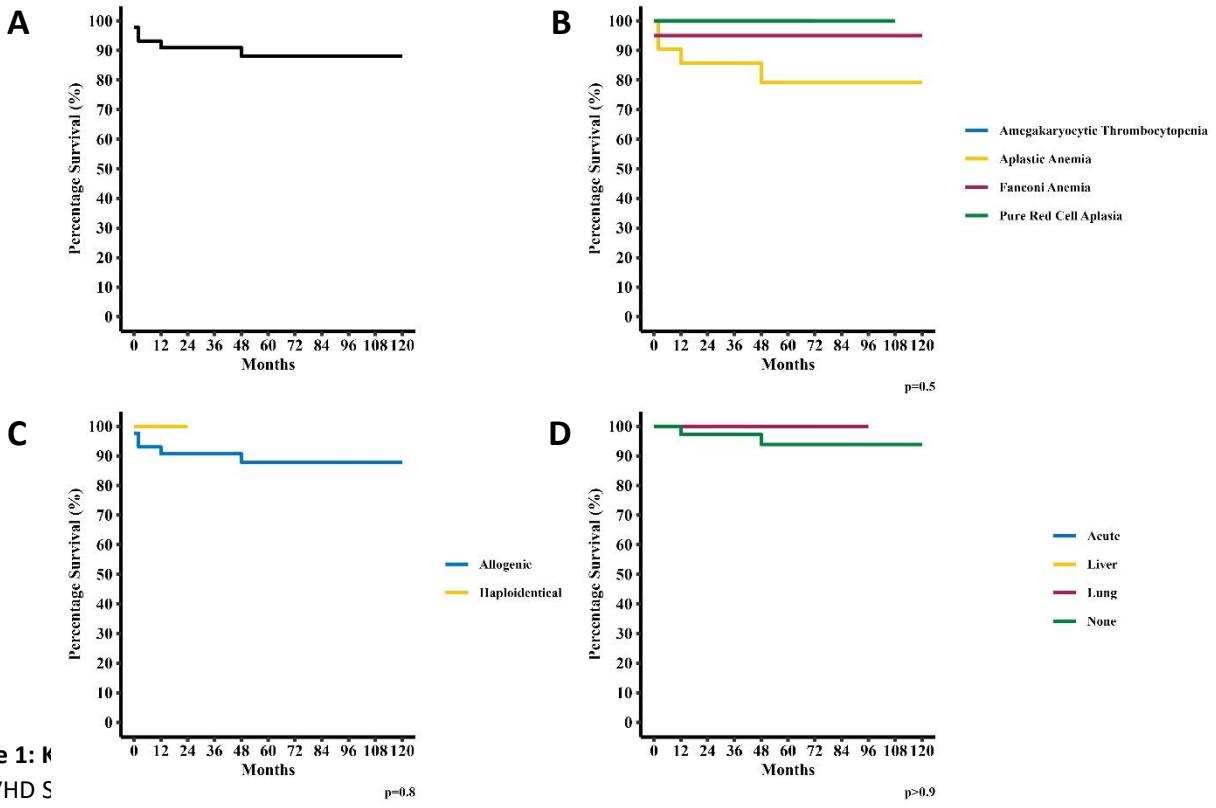

Figure 1: K ion, **D)** GVHD S

Table 1: Demographic and clinical characteristics of included patients

Characteristic	**N = 46**[1]
Disease	
Amegakaryocytic Thrombocytopenia	1 (2.2%)
Aplastic Anemia	23 (50%)
Fanconi Anemia	20 (43%)
Pure Red Cell Aplasia	2 (4.3%)
Age (Years), Mean (SD)	8.7 (3.5)
GVHD Status	
Acute	2 (4.3%)
Chronic Liver GVHD	1 (2.17%)
Chronic Lung GVHD	1 (2.17%)
None	38 (82.6%)
Passed	4 (8.9%)
CD34*10^6, Mean (SD)	3.64 (2.25)
CMV Reactivation	
Negative	33 (73%)
Passed	2 (4.4%)
Positive	10 (22%)
Day of Engraftment, Mean (SD)	15.70 (2.29)
BMT	
Allogenic	44 (95.7%)
Haploidentical	2 (4.3%)
[1] n (%); Mean (SD)	

Median overall survival was not reached as shown in **Figure 2A**. 1-year and 3-year overall survival probability was 91%, while 5-years survival probability was 88%, as shown in **Table 2.** Overall survival did not show any significant difference based on the log-rank test across disease groups as shown in **Figure 2B and Table 2**, with 1-year and 3-year survival probability of 86% in severe aplastic anemia, 95% for Fanconi anemia, while pure red cell aplasia and

Amegakaryocytic thrombocytopenia showed 100% 1-year, 3-years, and 5-years overall survival probability. Overall survival did not show any significant difference across transplantation type and GVHD status, as shown in **Figure 2C**

Table 2: Survival analysis measures at 1/3/5 years.

Overall Survival (OS)	**1-Year**	**3-Years**	**5-Years**	**Log-rank P-value**
Overall	91%	91%	88%	
Disease				0.5
Amegakaryocytic Thrombocytopenia	100%	100%	100%	
Severe Aplastic Anemia	86%	86%	79%	
Fanconi Anemia	95% (86%, 100%)	95% (86%, 100%)	95%	
Pure Red Cell Aplasia	100%	100%	100%	
Transplantation Type				0.76
Allogenic	91%	91%	88%	
Haploidentical	100%	Not Reached	Not Reached	

Haploidentical transplantation showed 100% 1-year survival probability, and 3-year and 5-year survival was not reached. While matched sibling transplantation showed 91% 1-year and 3-year survival and 88% 5-year survival.
A significant difference was seen between CMV reactivation groups and disease type in which 80% of patients with CMV reactive groups had aplastic anemia (p-value=0.011) as shown in Table 3. In addition, patients with reactive CMV had a significantly lower age (median: 5.0 vs. 11.0, p-value=0.009). CD34 levels were partially significantly higher in patients with CMV reactivation (median: $4.0 * 10^{6}$ vs. $2.7 * 10^{6}$, p-value=0.057) as shown in **Table 3**.
Regarding the OS time and OS status, there are significant differences in OS time between the CMV positive and CMV negative, the median time for OS time in CMV negative 0% (p-value=0.001) was more than the median time OS for CMV positive 30% (p-value 0.012) with statistically significant differences as shown in table 3.

Table 3: Demographic and clinical factors associated with CMV reactivation.

Characteristic	Negative, N = 32*	Positive, N = 10*	p-value
Disease			0.011[1]
Amegakaryocytic Thrombocytopenia	0 (0%)	1 (10%)	
Aplastic Anemia	11 (34%)	8 (80%)	
Fanconi Anemia	19 (59%)	1 (10%)	
Pure Red Cell Aplasia	2 (6.3%)	0 (0%)	
Age	11.0 (7.8, 12.0)	5.0 (3.3, 5.8)	0.009[1]
GVHD Status			0.001[2]
Acute	0 (0%)	1 (10%)	
Liver	1 (3.1%)	0 (0%)	
None	30 (94%)	5 (50%)	
PASSED	0 (0%)	4 (40%)	
Skin, Liver, Eyes	1 (3.1%)	0 (0%)	
CD34 * 10^6	2.70 (2.00, 3.80)	4.00 (3.20, 6.00)	0.057[2]
Day of Engraftment	15.00 (14.50, 16.50)	16.00 (15.00, 17.00)	0.6[2]
BMT			0.5[1]
Allogenic	32 (100%)	9 (90%)	
Haploidentical	0 (0%)	1 (10%)	
OS Time	78 (48, 120)	36 (8, 48)	<0.001[2]
OS Status	0 (0%)	3 (30%)	0.012[1]

* n (%); Median (IQR)

[1] Chi-squared test

[2] Welch Two Sample t-test

Discussion

In the present study, we provide insights into the outcomes of matched sibling bone marrow transplantation in pediatric patients with various hematological disorders, including Fanconi anemia, severe aplastic anemia, pure red cell aplasia, and congenital amegakaryocytic thrombocytopenia. Bone marrow transplantation is a critical treatment option for these disorders, and this study aimed to explore the impact of different factors on transplantation outcomes.

Our cohort included 46 patients of the pediatric age group, and the hematological disorders in the cohort revealed that severe aplastic anemia was the most prevalent (50%), followed by Fanconi anemia (43%), pure red cell aplasia (4.3%), and CAMT (2.2%). This distribution aligns with the known prevalence of these conditions and emphasizes the importance of bone marrow transplantation in their management. Hematopoietic stem cell transplantation (HSCT) is a medical procedure that entails the intravenous infusion of hematopoietic stem cells to restore the production of blood cells in individuals who have impaired bone marrow function. [1]

In this study, we evaluated the type of transplantation performed, with the majority of patients (96%) undergoing matched sibling bone marrow transplantation. Matched sibling transplantation involves using bone marrow from a healthy donor, and this approach is commonly used in cases where a suitable donor is available. [2] Interestingly, two patients (4.3%) received a haploidentical bone marrow transplant, which involves using bone marrow from a half-matched donor, typically a parent or sibling. Haploidentical transplantation is a newer approach that started recently for patients with severe aplastic anemia and offers an option for patients who lack fully matched donors. However, given the small sample size, further investigation is required to determine the comparative efficacy of matched sibling and haploidentical transplantations in this cohort.[3]

The ultimate goal of haploidentical-HSCT is to balance host-versus-graft and graft-versus-host reactions while preserving immune responses against infections. The strategy has been pursued to achieve this: supplementing a T cell-depleted graft with controlled alloreactive or pathogen-specific T cells in vivo t cell depletion by the use of post-transplant cyclophosphamide. [4], [5]

A major obstacle in managing children with hematological disorders such as acquired severe aplastic anemia (SAA) lies in distinguishing whether the condition is acquired, or a result of inherited disorders related to immune dysregulation or inherited bone marrow failure syndromes (IBMFS). [6] SAA patients who have acquired the condition or have non-Fanconi anemia inherited bone marrow failure syndromes (IBMFS) and matched related donors (MRD) generally undergo a standardized hematopoietic stem cell transplantation (HSCT) conditioning regimen. [7]

The results of matched sibling HSCT have shown continuous improvement due to advancements in high-resolution HLA typing, conditioning regimen selection, and supportive care measures. Additionally, significant progress in graft manipulation techniques and graft-versus-host disease (GVHD) prophylaxis has led to outcomes with alternative donors that are now comparable to those achieved with HLA-identical siblings and fully matched volunteers. [8], [9]

Our study also assessed CD34 levels, a marker for hematopoietic stem cells in the graft. The mean CD34 level in the donor bone marrow was 3.62 (2.25). CD34 levels are indicative of the quality of the stem cell graft, with higher levels generally associated with better transplantation outcomes. A study by Yokoyama et al.

The study's strength lies in its focus on pediatric patients and the exploration of various factors that can influence bone marrow transplantation outcomes. However, it is essential to acknowledge some limitations. The small sample size may limit the generalizability of the findings, and larger studies involving multi-center collaborations could strengthen the evidence further. Additionally, the retrospective nature of the study could introduce biases in data collection and analysis.

The only curative therapy for inherited and acquired bone marrow failure is HSCT therapy depending on the available donor for transplantation. In acquired and inherited bone marrow failure syndromes (IBMFS), a matched and

unaffected by the same disease (according to the genetic testing done) sibling is the ideal donor, but another matched and unaffected family donor may also be appropriate.
When a matched sibling donor is not available, haploidentical transplantation would be considered especially in acquired SAA as an upfront choice or after immune suppressive therapy failure, and results from such transplants may be suboptimal as a result of more frequent complications such as rejection and graft vs. host disease (GVHD). For acquired SAA, immune suppressive therapy IST might be used as first-line therapy, but HSCT is the 1st choice if there is a matched sibling donor, In our study the OS in HSCT (around 79%) is comparable to the OS in different studies where 5-year overall survival of children with acquired SAA varies from 73 to 100% under different treatments. [10,11].
In patients with acquired SAA who didn't have an HLA-matched sibling, medical treatment with IST or haploidentical transplant is considered, though HSCT with a matched unrelated donor MUD has increasingly been considered for upfront-first line HSCT with improving outcomes and lower risk for GVHD. Alternate donor transplants are not available in Jordan. A search and work of the marrow registry for a MUD should be initiated without delay,
In general, myeloablative conditioning is used for AA, and reduced-intensity conditioning is recommended for IBMFS as discussed in the conditioning section above, Bone marrow is the recommended stem cell source for both acquired and inherited bone marrow failure due to a proven survival advantage and reduced risk of development of GVHD, 100% (all our transplant cases done by bone marrow stem cell source) In HSCT, the rate of development of chronic GVHD is 4.3% using bone marrow in our study vs. 22–27% with peripheral blood stem cells seen in other studies using the peripheral stem cells (PBSC) [12,13] .
Additionally, Bacigalupo et al. reported improved survival advantage (90% vs. 76%) using bone marrow as the source of stem cells with no difference in rates of engraftment (approximately 90% regardless of stem cell source) [13, 14]. Also, the European Group for Blood and Marrow Transplantation (EBMT) analysis showed that in both matched donors and MUD transplants, the use of peripheral blood as the source of stem cells was the strongest negative predictor of survival [31]. In terms of stem cell sources for HSCT in IBMFS, a clear association with the rate of GVHD has not been seen in FA, however use of PBSC was associated with a significantly higher risk of secondary cancer, therefore Bone marrow is also the preferred stem cell source for FA and is also recommended for the remaining IBMFS [15, 16].

GVHD where observed in 8.7% of our patients and regarding GVHD prophylaxis is an essential measure to decrease mortality and morbidity, as the occurrence of GVHD in non-malignant transplants is the main leading cause of long-term morbidity, mortality, and overall quality of life, and may lead to even more significant toxicity in patients with IBMFS. according to our study, 2 patients died from chronic GVHD. standard post-transplant GVHD prophylaxis for acquired SAA includes cyclosporin and short-course methotrexate, which was shown to be superior to Cyclosporin alone, and when combined with early timing of transplant and an ATG-containing preparative regimen in matched sibling HSCT, Storb reported a 95% engraftment rate and 90% 2 y OS [17,18].

Our findings showed that CMV reactivation was associated with higher CD34 levels. The reactivation of CMV represents a significant infectious factor contributing to illness and death following allogeneic hematopoietic stem cell transplantation (HSCT) [20]. Tiera et al. study showed that reactivation of CMV remains a concern as a risk factor for unfavorable post-transplant results and does not appear to provide any safeguard against the recurrence of hematologic diseases. Possibly, CMV could have a preference for infecting early myeloid progenitor cells or encouraging the transformation of infected pluripotent CD34+ cells into myeloid-lineage subsets that facilitate latency [21].
In general, the rates of graft rejection have dramatically improved in acquired SAA with improved supportive care and conditioning regimens and reduced waiting time before proceeding to HSCT and therefore, less exposure to blood products from multiple donors prior to transplant. For IBMFS, what is reported in the literature is limited to small and primarily retrospective reviews of specific inherited conditions and thus reflection and generalizations are difficult to make. In our data for patients with FA, where recipients of matched related donor HSCT have survival rates above

95% at median follow up times of 1– 5 y which is better than what is reported in the EBMT study of the period 2000–2009 reported 78% and 65% OS at 5-year post-transplant for MSD and MUD, respectively. [19]

In patients with IBMFS, we didn't perform haploidentical transplantation which is only performed for our patients with acquired SAA with 100% success rate for the patient transplanted less than one year ago as its new approach started in our center hope to make more cases with long OS and best outcome.

Conclusion:

Significant improvements have been made in the use of hematopoietic stem cell transplantation to treat both acquired and inherited bone marrow failure. Outcomes for matched sibling HSCT for inherited and acquired BMF syndromes are good, and HSCT is the treatment of choice for BMF patients who have available matched related donors.

In our study, the outcomes of bone marrow transplantation in pediatric patients with hematological disorders were not significantly influenced by the disease type or transplantation type. The study highlights the need for larger, multi-center investigations to corroborate these findings.

Funding

This study has not received funding from any source.

Conflict of interests

All authors declare no conflict of interest.

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