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Literature review

Assessment of Bone Marrow Failure Syndrome Management Outcome in Pediatrics – Saudi Perspective

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Abstract: Bone Marrow Failure Syndrome (BMFS) is a rare yet severe condition affecting pediatric populations, characterized by a reduced production of hematopoietic lineages leading to pancytopenia. This article explores the multifaceted nature of BMFS in children, its diverse etiologies, treatment modalities, and outcomes, with a particular focus on the Saudi Arabian context. BMFS encompasses both inherited and acquired forms, often presenting diagnostic challenges due to its heterogeneity. Inherited BMFS accounts for 30% of cases and includes rare conditions like Fanconi Anemia and Schwachman-Diamond Syndrome, where treatment approaches vary depending on severity. Acquired BMFS, constituting 70% of cases, may exhibit complete recovery or require prolonged treatment with immunosuppressants. Hematopoietic Stem Cell Transplantation (HSCT) remains a primary treatment option, with outcomes influenced by factors such as donor type and graft success. Saudi Arabia, despite its high-income status, has faced limited data availability on BMFS outcomes, but the number of HSCT procedures performed in the country is steadily increasing. Survival rates in HSCT patients vary based on factors such as donor match and the underlying cause of BMFS. Additionally, the risk of secondary malignancies is relatively high in BMFS patients, adding complexity to long-term management. While Saudi studies indicate survival rates comparable to international standards, challenges in the assessment of BMFS outcomes persist, given the condition's rarity and diversity. This article underscores the importance of continued research and data collection to enhance our understanding and management of BMFS in the pediatric population, both in Saudi Arabia and globally.

Keywords: Bone Marrow Failure Syndrome, Pediatric Population, Hematopoietic Stem Cell Transplantation, Etiology and Treatment, Saudi Arabia

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Introduction

Bone marrow failure syndrome (BMFS) in the pediatric population is among the uncommon health issues, affecting only a small number of children each year. However, the condition is severe posing treatment challenges. Despite the best treatment, adverse outcomes are not rare in the condition. Moreover, it results in reduced life expectancy almost in all cases. Nonetheless, many children can expect close to normal life for a long.

BMF is a condition characterized by reduced production of one or more hematopoietic lineages, depending on the cause. This results in reduced production of one or another kind of blood cells or even leads to pancytopenia. Though not in all, BMFS leads to pancytopenia in many cases, especially if the condition is inherited. Hence, in the case of inherited bone marrow failure syndrome (IBMFS), the treatment of choice is almost always hematopoietic stem cell transplantation (HSCT). In the case of acquired BMF, many cases (up to 30%) may resolve either spontaneously or with the help of conservative treatment.[1] Nonetheless, those who develop severe aplastic anemia (SAA) require bone marrow transplantation. The optimal choice of the donor in most cases is matched sibling if possible.[2] However, in most

cases, this option is not present, and thus donor is usually HLA matched individual outside the family, which affects the treatment outcomes adversely.

As one can understand that assessing the outcomes of BMF poses significant challenges. The first challenge is the heterogeneity of the condition. It is a condition that occurs for many reasons, and in many cases, the cause remains unidentified. Additionally, outcomes also depend on the choice of treatment. Even in the case of bone marrow transplantation, outcomes depend on the donor's choice.[2] Another significant challenge in assessing BMFS outcomes in the pediatric population is the limited availability of global and Saudi studies data. Further, most studies have sample sizes as the conditions are among rare disorders. Despite numerous challenges in assessing outcomes of BMFS in the pediatric population, we look at the various aspects to develop a better understanding.

Etiology, Treatment, and Outcomes

BMFS is a heterogeneous disorder, and outcomes would significantly depend on the etiological factors. It is vital to understand that BMFS occurs due to a range of inherited and acquired health conditions. In many cases, the cause of BMFS even remains undenied (idiopathic), causing much distress to the patient and parents. Studies suggest that about 30% of BMF cases in the pediatric population occur due to inherited disorders and another 70% due to acquired health conditions.[3]

Studies show that BMFS has a triphasic peak, with the first peak at 2 to 5 years, another 20 to 25 years, and then after 65 years of age.[3] In the pediatric population, about one-third of cases are due to inherited disorders. Most of these disorders are rare, and their prevalence does not seem to have much relation to geographies and ethnicities. Among the inherited causes are conditions like Congenital Amegakaryocytic Thrombocytopenia, Fanconi Anemia, Telomere Biology Disorder, Diamond Blackfan Anemia, Schachman Diamond Syndrome, and Severe Congenital Neutropenia.[2] Among them, the most common is Fanconi anemia affecting 1 to 5 children out of a million. It appears that in about 75% of cases of inherited BMFS, the cause remains unidentified.[3] When it comes to the Saudi experience, a Saudi study by AlMozain et al. analyzed 183 (155 adults and 28 pediatric) patients with myelodysplastic syndrome (MDS) and found that the cause of BMFS could not be identified in half of the pediatric cases.[4] Hence, it is pretty evident that the cause of BMFS remains unidentified in most cases in Saudi.

In the pediatric population, 70% of BMFS are due to inherited disorders like Idiopathic Aplastic Anemia, Infections (hepatitis A, B, C, CMV, HIV, EBV, Fungal, Tuberculosis), radiation, drugs and toxins, autoimmune disorders (SLE and RA). However, the most relevant cause is bone marrow infiltration due to conditions like leukemia, myelodysplastic syndrome, and metaplastic malignancy.[2] Among cancers, leukemia is the most common but still among rare disorders. In 15 years period from 1999-2013, 8712 cases were reported, and thus estimated burden in the pediatric population was less than 2 in 100,000.[5] BMFS due to other causes like infections or aplastic anemia, or autoimmune disorders is also rare.[6] It means that if we consider that inherited and acquired BMFS are rare events, there are only a few hundred cases of BMFS occurring in Saudi Arabia every year.

When considering outcomes of BMFS, much would depend on whether the condition was inherited or acquired and the kind of treatment used. When it comes to inherited, which makes up 30% of cases of BMFS in the pediatric population, many with severe cytopenia are treated with bone marrow transplant or hematopoietic stem cell transplantation (HSCT). However, it depends on the condition's severity and if the inherited disorder was identified.

Among inherited conditions, Fanconi Anemia (FA) is most common, often diagnosed between 5 to 10 years, with varied clinical presentation. The risk of bone marrow (BM) failure in the conditions is 50-90%. It means that most would need HSCT. In the Schwachman-Diamond Syndrome (SDS) case, only about 20-33% develop BM failure and thus have a much better prognosis and outcomes. Thus, as one can see, not all patients living with inherited BMFS require HSCT, and many have good outcomes with conservative treatment and can

even expect prolonged remission, or they may benefit from other treatments like blood transfusion, steroids, and so on.[7]

In the case of acquired BMFS, one-third can expect a complete recovery, and many others would require prolonged treatment with androgens, immunosuppressants, and other medications.[2], [8] It means that less than half of those living with acquired BMFS would require HSCT. This means that a few hundred children need HSCT in Saudi every year. Thus, when assessing BMFS management outcomes in pediatrics, it would be wise to focus on HSCT outcomes, as it remains the primary treatment in those who develop BMFS.

When it comes to hematopoietic stem cell transplantation (HSCT) outcomes in Saudi, there is a paucity of data. Moreover, it is worth understanding that Saudi is a high-income nation, which means that many cases of BMFS are treated abroad. Nonetheless, things are fast changing in Saudi, and the first HSCT was done in 1984 in the nation. Fortunately, now most HSCT procedures are done in the nation, and thus the number of HSCTs done in the nations has constantly been rising. Studies show that about four medical centers located in Riyadh, Jeddah, and Dammam are carrying out more than 90% of all HSCT in Saudi. Consequently, data shows that between 2008 and 2016, the total number of HSCT procedures done in Saudi in Pediatrics ranged from 120 to 160 cases.[9]

It would be correct to say that inherited BMFS outcomes in severe cases are significantly proportional to HSCT outcomes. The success of HSCT significantly depends on the underlying cause and graft source. Studies show that the 10-year survival rates of HSCT are moderately good at 83%, 73%, 68%, and 51% for each consecutive decade. Hence, one can see that despite the amazing results, the life expectancy of those living with BMFS is much less than that of healthy adults. Here, the survival rate would be much higher with sibling-matched donors. Studies show that survival for 40 years is extremely high and almost close to 100% in those who do not require ongoing steroid use. However, this rate declines to 50% if immunosuppressant therapy is needed.[3], [7] However, some studies show that in the case of unrelated donor transplantation, long-term survival is 30-40%.[7]

Thus, as one can see, outcomes depend on the underlying cause of BMFS, as some conditions may resurge, and in others, one may experience prolonged remission. Furthermore, much depends on the graft's success. Thus, for example, a study in HSCT patients demonstrated that a 5-year survival rate was 83% or higher in graft failure-free patients. Graft rejection rates increase considerably in the case of HLA-mismatched HSCT. Even in the case of a graft match, one-third of the patients may expect some graft-versus-host disease.[10] Similarly, a study using data from 563 Aplastic Anaemia (AA) children showed that long-term survivability was as high as 91% in the case of HLA-matched family donors.[11] Studies also suggest that outcomes are worst in patients with unidentified BMFS causes.[12]

Though there are few Saudi studies reporting outcomes in patients diagnosed with BMFS, nonetheless, most data suggest that short-term and long-term survivability rates in Saudi are quite similar to that reported in the US and Europe. A study by Lujain Talib et al. from Jeddah, SA, reported that two-year survivability in HSCT patients was 96.6%. However, outcomes are much worse in those who require Paediatric Intensive Care Unit (PICU) admissions. They found that about one-fourth of all patients who have undergone HSCT do need PICU admission, and in such patients, 2-year survivability is reduced to 58%.[13]

Apart from survivability in individual conditions causing BMFS, or considering the outcomes of HSCT, another critical factor to consider is the risk of malignancies. It appears that the risk of secondary malignancies in those affected by various disorders causing BMFS or those who have undergone HSCT is relatively high. For example, studies suggest that those living with FA have a risk of developing solid tumors between 28% to 40% in the long run, that is, in 15-20 years, which may also affect the disease or treatment outcomes.[7]

Conclusion

To sum up, BMFS is a condition that occurs due to numerous reasons, and thus predicting outcomes is quite challenging. Generally, outcomes would depend on the etiology of the

condition. For example, FA has a worse outcome among inherited conditions than SDS. Additionally, for those with unidentified inherited BMFS, the prognosis is worse. But, regretfully, studies show that in the case of inherited BMFS, the cause remains unidentified in the majority of the cases. It means that most of those living with BMFS would ultimately need HSCT.

Studies suggest that 70% of the BMFS cases are acquired even in the pediatric population, with many conditions benefiting from conservative treatment. Among acquired conditions, malignancies are challenging to treat. Many patients with secondary BMFs, would also need HSCT.

It means that perhaps half of all cases of BMFS would ultimately need HSCT. Therefore, outcomes in those living with BMFS significantly depend on the outcomes of HSCT. In the case of HLA-matched family donors, long-term outcomes of HSCT are pretty good, with long-term survivability of greater than 80%. However, in the case of the non-family donor or unmatched donor, the outcomes are much worse, with long-term survivability of about 30-40%. Additionally, early PICU admissions post-HSCT could be regarded as predictive factors.

Finally, it is worth understanding that even with excellent conservative treatment outcomes or with good HSCT outcomes, those living with BMFS are at significant risk of developing secondary malignancies. In the long run, almost every second long-term survivor may be affected by malignancies.

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