A report of haploidentical allogeneic haematopoietic stem cell transplantation for inherited bone marrow failure in Sri Lanka

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Abstract

Bone marrow failure (BMF) in children can be idiopathic (70-80%) or inherited. Haematopoietic stem cell transplantation (HSCT) is the only cure for both causes.

Allogeneic HSCT requires a suitable donor. Many children will not have a HLA matched sibling or unrelated donor. A haploidentical donor is available for all children as each parent will have at minimum a 50% HLA match.

This report of a 7-year old girl with BMF treated with a haplo-HSCT, the first in Sri Lanka, highlights the importance of developing a haploidentical HSCT programme as a potential cure for a disease with a dismal outcome.

Introduction

Aplastic anaemia (AA) is defined by pancytopenia with a hypocellular bone marrow, in the absence of fibrosis or an abnormal infiltrate [1]. Most cases (70-80%) are idiopathic, the rest are mainly inherited bone marrow failure syndromes (IBMFs).

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare IBMFs, which results from mutations in c-MPL, the gene that codes for the thrombopoietin receptor [2]. About 50% of patients progress to AA by 5 years of age.

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the sole curative option for both IBMFs and acquired AA (aAA) in children [3].

We report the case of a 7-year old girl with CAMT that progressed to severe AA, successfully treated with a haploidentical allogeneic HSCT (haplo-HSCT), the first such reported case from Sri Lanka.

Case presentation

A 7-year old girl, third child of non-consanguineous healthy parents, presented at the age of 1 year 4 months, with spontaneous ecchymoses and severe thrombocytopenia. She had a normocellular bone marrow with marked reduction of megakaryopoiesis. Initially managed as immune thrombocytopenia, with suboptimal response to corticosteroids and dapsone, two years later she developed pancytopenia with a markedly hypocellular marrow that fulfilled the criteria for severe AA. No somatic features of IBMFs were identified and had a negative chromosome fragility test. Karyotype revealed 46, XX, inv [9] (p11q13), a normal variant. Two pathogenic mutations in the MPL gene at exon 3 and 8 were identified by next generation sequencing(compound heterozygous). A diagnosis of severe AA due to CAMT was made.

Few life threatening bleeding episodes, including a subdural haemorrhage, further complicated with platelet refractoriness due to high titre HLA antibodies prompted urgent definitive treatment. A matched sibling donor (MSD) was not available, therefore a matched unrelated donor (MUD) transplant from an Indian donor was planned. However, it was impossible to import donor stem cells from overseas due to the COVID pandemic. Considering the life-threatening nature of her illness, a haplo-HSCT (5/10 HLA match) from her 42-year-old father was offered.

To mitigate the risk of graft rejection due to high titre donor specific antibodies (DSAs) of 9827MFI, 5 plasma exchanges and 4 doses of 0.4g/Kg immunoglobulin alternatively and a single Rituximab dose (375mg/m^2) was instituted immediately before conditioning.

Conditioning was done with rabbit anti thymocyte globulin (ATG) 4.5mg/kg, thiotepa 10mg/kg, 5 daily doses of fludarabine (Flu) 30mg/m^2each, 2 days of cyclophosphamide (Cy) 14.5mg/kg and total body irradiation 2Gy single fraction on Day-1.

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Granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSC) were harvested and 6.1×10^6/kg of CD34 positive cells were transfused.

Graft versus host disease (GVHD) prophylaxis was with cyclophosphamide 50mg/kg/d on D+3 and D+4 (PTCy), and tacrolimus, titrated to achieve adequate plasma levels.

Her post-transplant period was complicated with severe cytokine release syndrome (CRS) with high fever, generalized erythematous skin rash, splenomegaly, deranged liver transaminases (AST 307.9u/l and ALT 557.3u/l) and serum ferritin of 269,500ng/ml. Methyl-prednisolone 30mg/kg intravenous × 3 days was administered with diuretics, antibiotics and fluid restriction. Steroids were tailed off after clinical and biochemical parameters normalized.

Haematological recovery of neutrophils and platelets occurred on D+11 and D+14 respectively. Currently, 6 months post-transplant, she remains clinically well, free of GVHD with a normal blood count and 99.5% donor chimerism.

Discussion

IBMFs typically have characteristic physical anomalies, however, these can be very subtle or even absent. CAMT is a rare autosomal recessive disorder, presenting in infancy and not usually associated with somatic abnormalities [4]. About 50% of patients develop AA by 5 years of age. The initial presentation with isolated thrombocytopenia, absent megakaryocytes in a normocellular bone marrow, followed by progressive marrow failure together with compound heterozygosity for 2 pathogenic mutations in MPL gene is diagnostic of CAMT in our patient.

Allo-HSCT, which has been routinely practiced in developed countries for many decades, is the only curative option for both IBMFs and aAA in children [3]. However, the first allo-HSCT performed in Sri Lanka was as recently as 2014, for a child with thalassaemia major [5]. The experience in allo-HSCTs for BMFS in Sri Lanka is very limited, and that too only with HLA matched donors (HLA-MDs).

Alternative donor HSCT is an option for AA when HLA-MDs are unavailable. However, risks of graft rejection, infectious complications and GVHD are higher than with HLA-MDs [6] More intensive conditioning, as in our patient, is required to minimize rejection and GVHD [7].

Several studies have reported encouraging results with haplo-HSCT, especially in children. A review of 375 patients reported rejection rates of 6%, grade II-IV GVHD of 23% and 1 year survival of 80% [8].

DSAs are associated with a ten-fold increased risk of graft failure in haplo-HSCT[4]. Various protocols for reduction of DSA mediated graft rejection are published [4], however, there is no robust evidence to suggest that any one is superior to another. The DSA titre performed after 3 cycles of PE in our patient showed a significant reduction from 9827MFI to 4600MFI.

A study of 75 patients who, like our patient, received G-CSF mobilized, T-cell replete haploidentical PBSCs showed that CRS is common and severe CRS is associated with high transplant related mortality, poor overall survival, and delayed neutrophil recovery [9]. CRS is a systemic inflammatory response syndrome related to aberrant immune activation or immune hyperstimulation, giving rise to increased cytokine levels and inflammation [10]. IL-6 is a key mediator of CRS in haplo-HCT, therefore, monoclonal anti-IL-6 receptor antibody tocilizumab appears to be effective. It was fortuitous our patient responded to high dose corticosteroids.

Even if facilities and finances are available for allo-HSCT, only about 30% of patients have a MSD. There is no marrow donor registry in Sri Lanka. A MUD maybe available from an international donor registry. The cost of acquiring stem cells from an Indian registry donor is SLR 2,500,000 and is far more from any other country. Therefore, many children with BMF will not have a HLA matched donor and be forced to face the inevitable. A haploidentical donor is available for all children, as each parent will have at minimum a 50% HLA match

This report, the first in Sri Lanka, highlights the importance of developing a haploidentical HSCT programme as a cost effective, potential cure for a disease with a dismal outcome.

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