First Ever Pediatric Allogeneic Hematopoietic Stem Cell Transplantation In A Transfusion Dependent Thalassemia Patient In Bangladesh- A Case Report With 17 Months Post-Transplant Follow Up

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Abstract:

Background: Hematopoietic stem cell transplantation (HSCT) is the mainstay of treatment for many disease conditions. The first allogeneic HSCT was done by E. Donnall Thomas which was reported in the New England Journal of Medicine in September 1957. In that study six patients of Acute Leukemia were treated with radiation and chemotherapy followed by intravenous infusion of marrow from a normal donor where only two patients were engrafted but all died within 100 days of transplantation. In 1979 Thomas applied allogeneic HSCT earlier in the course of acute leukemia and reported a 50% cure rate in AML patients transplanted after first remission. In Bangladesh there was no scope of HSCT for thalassemia patients. The first ever pediatric allogeneic HSCT in a transfusion dependent thalassemia patient was performed in BMT center of CMH Dhaka on 30 November 2021. Here the case is reported with 17 months post-transplant follow up.

Case Report: Arfin a 3 years 11 months old boy first reported in November 2018 with the history of repeated blood transfusion since 6 months of age and was diagnosed as a case of Hb-E Beta thalassemia. On initial presentation he had hepatomegaly, splenomegaly, stunting, high serum ferritin level, and high liver iron concentration and was treated with regular irradiated and filtered PRBC with multiple iron chelating agents. On 30 November 2021 allogeneic HSCT of that patient was successfully completed. Donor was his elder brother who was Hb-E trait and had 10/10 HLA full matches. In April 2023 after 17 months during post-transplant follow up his Hb was 10.3 gm/dl, serum ferritin level was normal, had normal growth and required no further blood transfusion after transplantation.

Conclusion: In transfusion dependent thalassemia patients allogeneic HSCT is curative. This is the first and successful case of allogeneic HSCT in thalassemia patients in Bangladesh.

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Introduction:

Bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT) is the mainstay of treatment for many disease conditions. The first human bone marrow transplantation was done of a patient with aplastic anemia in 1939.[1] The first allogeneic HSCT was done by E. Donnall Thomas which was reported in the New England Journal of Medicine on September 1957.[2] The first Autologous BMT in a 28-years old male patient with AML was done on 1976.[3] In transfusion dependent thalassemia patient allogeneic hematopoietic stem cell (HSC) transplantation is the mainstay of treatment.[4] It was a matter of debate in '80s and early '90s.[5] In thalassemia major patient HSC transplantation causes replacement of the ineffective erythropoiesis with allogeneic healthy bone marrow which helps in effective erythropoiesis and prevent hemolysis and correct anemia.[6,7] This also prevent transfusion related complications and hazards of iron overload. HSCT

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results in disease free survival probabilities of 90%, 84% and 78% respectively for Pesaro class 1, 2 and 3 patients.[8] In Bangladesh, Combined Military Hospital(CMH) Dhaka successfully completed an allogeneic HSCT of a transfusion dependent thalassemia patient on 30 November 2021.

Case summary:

Master Arfin 2nd issue of non-consanguineous parents initially reported to us in November 2018 at 3 years 11 months of age with history of repeated blood transfusion (BT) for 6 months of age. He was diagnosed as a case of Hb E-Beta Thalassemia and was being treated conventionally with BT and chelating agents. His milestones of development were age appropriate. His father was of Beta Thalassemia trait, mother and elder brother were of Hb-E trait. The child was on regular BT initially every two months interval up to 2 years of age which gradually reduced to 20 - 25 days interval and amount of BT also increased to 170 ml/kg/year. He was on regular chelating agents including desferrioxamine, deferasirox along with gamma chain inducer hydroxyurea. On examination he was cooperative, pale, weight was on 10th centile of CDC growth chart and HAZ was -2.2. He had hepatomegaly and splenomegaly. Liver was palpable by 3cm from the right costal margin and the spleen was palpable by 3 cm from the left costal margin along its long axis. On investigation his HB was7.2gm/dl, serum ferritin level was 2000 ng/ml. So as per pesaro risk classification the child was class II for Transplantation. We treated the patient with regular irradiated, filtered PRBC transfusion, Injection Desferrioxamine was given initially as IV infusion 5 days per week then as ferritin level was increasing (2700ng/ml) and Liver Iron Concentration (LIC) was (on 30 July 2019) 24.7 mg/g dry tissue of liver, subcutaneous desferrioxamine was given 5 days per week along with oral deferasirox and deferiprone. Hydroxyurea was also given along with other supportive treatment. His treatment was continued and kept under regular follow up as we had to defer the transplantation due to covid-19 pandemic. After three years in November 2021 at his 6 years 11 months of age we could finally prepare him for allogeneic Hematopoietic stem cell transplantation (HSCT). His HSCT was done in BMT center of combined military hospital (CMH) Dhaka. On pre-transplant physical examination the child was cooperative, pale, weight was 19.4kg, height 111cm, weight for age was on 10th centile of CDC growth chart, he was stunted, HAZ was -2.2, Liver was not Palpable, spleen was 2cm from left costal margin along its long axis. On investigation Hb was 6.9 gm/dl, serum ferritin level was 1202 ng/ml, LIC was 9.4mg/gm dry weight of liver and no portal fibrosis on fibro scan. So, after treatment as per Pesaro risk classification the child became class-I for Transplantation. Donor was his elder brother who was Hb-E trait and had full 10/10 HLA match. His bone marrow conditioning started on 12 November 2021 with Fludarabine, Busulphan, ATG and Cyclophosphamide for 15 days as per protocol. Bone marrow Stem cells were collected from donor on 30 November 2021 and stem cell infusion given on the same day. The patient was on regular close follow up and monitoring including physical examination, vital parameters and biochemical parameters. Blood picture was regularly monitored and engraftment started from 11th post transplant day. To prevent GVHD Cyclosporine- A and Methotrexate were given and to prevent infection antibiotic, antifungal and antiviral were given as per protocol. Gradually his cell count came to normal and hemoglobin level increased to 10gm/dl then the child was discharged and kept under regular follow up. During post-transplant follow up on June 2022 his hemoglobin was 9.5gm/dl, on December 2022 Hb was 10gm/dl, on April 2023 after 17 months of transplantation his Hb was 10.3gm/dl, serum ferritin level was 90ng/ml, liver and spleen were not palpable, weight was 21 kg, weight for age was on 10th centile of CDC growth chart, height was 121 cm, height for age was on 10th centile of CDC growth chart and he required no blood transfusion after transplantation. Chimerism study was done on day 30 and day 90 after translation and donor cell population was found 82% and 91% respectively.

Discussion:

The HSC transplantation for transfusion dependent thalassemia patient was pioneered by the Pesaro group.[9-12] It is now practiced worldwide as the curative option for this disease. Thalassemia has been transformed from a deadly disease of childhood to a chronic disease of adulthood due to the massive development of medical treatment and effective chelating agents with increase in survival and quality of life.[13] An Italian study revealed that mean direct cost of medical therapy for thalassemia is approximately 15000 euro/year/patient.[14] In India the cost is about 1000 USD/patient/year[15] and in Bangladesh

the cost is about 1600- 3900 USD/patient/year.[16] If we take the amount into consideration the actual cost of medical treatment is also very high. The cost of allogeneic HSCT in India is about 15,000- 45,000 USD[17] and in Bangladesh the cost reduced by 30- 40%, as such HSC transplantation remains as cornerstone of curative treatment. Incremental cost per year gained with use of HSCT as compared with transfusion and chelation was USD 986 in case of matched related donor (MRD) and USD 2579 in case of a matched unrelated donor transplantation.[18] Main challenge of HSC transplantation is only one third of patients have HLA identical sibling in family.[19] Mismatched donor transplantation trails are also very minimum.[20] HSC transplantation for a matched unrelated donor is also studied with satisfactory results which is almost similar with sibling donor in pediatric and adult patient.[21‘] In a study after allogeneic HSCT the probability of moderate or severe chronic GVHD in thalassemia patients was 8 and 2% respectively.[22] In Pesaro class 1 patients the probability of overall survival, thalassemia-free survival and rejection are 90, 87 and 3% respectively.[23,24] In case of Pesaro class 2 patients the probability of overall survival rate, thalassemia-free survival and rejection are 87, 85 and 3% respectively.[23,2.4] In case of Pesaro class 3 patients the probability of overall survival is 79% but probability of rejection is 30%.[25]

Conclusion: In transfusion dependent thalassemia patients allogeneic HSCT is the curative treatment. Hemoglobin level rises and remains to normal level, requires no BT after 17 months of transplantation and the patient has normal growth and development. This is the first and successful case of allogeneic HSCT of thalassemia patients in Bangladesh which will remain as a milestone and will serve as twilight for other patients and also for the health care providers to improve HSCT in Bangladesh.

Conflict of Interest:
We declare no conflict of interest.

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