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Successful T Cell Replete Haploidentical Peripheral Blood Hematopoietic Stem Cell Transplantation in a Young Girl with Diamond Blackfan Anemia

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Case Report

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Abstract

Only curative therapy for DBA is haematopoietic stem cell transplantation (HSCT). Most published cases have used matched related and unrelated donor HSCT. We report a 5 years old girl who diagnosed with DBA at the age of 6 months and transfusion dependent. She underwent 5/10 human leucocyte antigen haploidentical mismatch related T cell replete HSCT utilizing a myeloablative conditioning regimen including intravenous busulfan (total dose of 12.8 mg/kg), fludarabine (total dose of 160mg/m^2), thiotepa (10mg/kg single dose) and rabbit anti thymocyte globulin (ATG) (total dose of 6 mg/kg). Post-transplant cyclophosphamide on day+3 and +4 with tacrolimus and mycophenolate mofetil were used as GVHD prophylaxis. Her neutrophil engrafted on day+ 15. On day+78 she had steroid refractory grade III acute gut GVHD which was not responsive to adequate doses of etanercept, mesenchymal stem cells, basiliximab and infliximab also, but eventually it responded to equine ATG and oral methotrexate. Her immunosuppression was weaned off very slowly. At 23 months of follow up she had full donor chimerism with hemoglobin of 15.2g/dl, reticulocytes of 1% and complete immune reconstitution. Haploidentical HSCT could represent an effective option for cure in patient with DBA.

Keywords: DBA; Haploidentical; Stem cell transplant

Abbreviations: DBA: Diamond-Blackfan anemia; HSCT: Haematopoietic Stem Cell Transplantation; ATG: Anti Thymocyte Globulin; HLA: Human Leukocyte Antigen; PBSC: Peripheral Blood Stem Cell; TLI : Total Lymphoid Irradiation.

Introduction

Diamond-Blackfan anemia (DBA) is a rare inherited bone marrow failure syndrome (congenital hypoplastic anemia) that usually presents in infancy and childhood.

The reported incidence of DBA is 5-10 per one million births [1]. The exact mechanism is unclear, but a defect in one of the early steps in erythropoiesis has been proposed. In about 15-20% of affected children, there is a defect within *RPS19 gene* (ribosomal protein S19) [1]. Corticosteroids remain the mainstay of treatment and approximately 80% of patients responds, however, only 20% of patients achieve complete remission. Some 40% require long term therapy with steroids, which can have significant adverse effects, and a further 40% remain transfusion-dependent and at risk for complications due to iron overload [2,3]. The only curative treatment for DBA is allogeneic hematopoietic stem cell transplant (allo-HSCT), which is offered to the patients who become unresponsive or intolerant to drug therapy or chronic transfusion dependent. Furthermore, allogeneic matched sibling HSCT has already been reported with significant better overall survival (OS) than alternative donor HSCT in patients with DBA [4-7]. Subsequently Mughisimia, et al. [8] reported even improved OS in matched unrelated HSCT also. Haploidentical HSCT is scarcely reported in children with DBA.

Case

A 5-year-old girl presented at other hospital at the age of six months with progressive pallor. She was diagnosed with DBA on the basis of peripheral blood showing macrocytic anemia and reticulocytopenia with normocellular bone marrow showing erythroblastopenia. She was given a trial of steroids for 3 months but did not respond. She was then started on regular blood transfusion. Iron chelation was started only in the third year of life with oral Deferasirox when her serum ferritin level was found to be more than 1300 ng/ml. Furthermore, this girl is referred to our center for possible allo-HSCT treatment in view of his transfusion-dependent DBA with hyperferritinemia. The diagnosis was reconfirmed at our center. Except hypertelorism and epicanthal folds she did not have any dysmorphic features. We could not do erythrocyte adenosine deaminase level and *RPS19* genetic studies. T2*MRI showed mild iron over load in liver and heart. She had ferritin of 2500 ng/ml at the time of HSCT. This girl had no siblings so parents opted for haploidentical HSCT after meticulous discussion. Father was chosen as donor. He had Normal complete blood count but we could not perform genetic studies. She was initially treated for class I and II HLA antibody (mean fluorescence index of 20000 each) with weekly bortezomib (dose 1.3 mg/m^2 for 4 doses, Bortetrust, Panacea biotech Ltd), weekly rituximab (375mg/m^2 for 4 doses) with biweekly plasmapheresis for 4 cycles. Repeat HLA antibody titer could not be performed. One month prior to HSCT she received one cycle of fludarabine (total dose of 180mg/m^2) and dexamethasone for additional immunosuppression to prevent rejection. Finally, she underwent 5/10 human leukocyte antigen (HLA) mismatch related haploidentical T cell replete granulocyte colony-stimulating factor primed peripheral blood stem cell (PBSC) HSCT from ABO compatible father utilizing a myeloablative conditioning regimen including intravenous busulfan (total dose of 520mg/m^2), fludarabine (total dose of 175 mg/m^2), thiotepa (10mg/kg single dose) and rabbit anti thymocyte globulin(ATG- Thymoglobulin, Sanofi-Genzyme, Canada) (total dose of 4.5 mg/kg). Post-transplant cyclophosphamide (PTCy) 50mg/kg on day+3 and +4 with tacrolimus and mycophenolate mofetil were used as GVHD prophylaxis. Total infused CD34+ stem cell dose was 27 x 10^6/kg of recipient. She tolerated the conditioning regimen and bone marrow infusion well. Her neutrophil and platelet engrafted on day+ 15 and day+10 respectively. Chimerism analysis post HSCT (on day+28, +60, +100 and +365) revealed full donor chimerism. On day+78 she had steroid refractory grade III acute gut GVHD which was not responsive to adequate doses of etanercept, mesenchymal stem cells, basiliximab and infliximab, but eventually it responded to equine ATG (Atgam; Pfizer Pharmacia & Upjohn company, Michigan 49001, USA)(10mg/kg/day for 7 days) and oral methotrexate (10mg/m^2 weekly). Her immunosuppression was weaned off very slowly. At 23months of follow up she had full donor molecular chimerism with hemoglobin of 15.2g/dl, reticulocyte count 1%, WBC 8600/mm^3, Platelets 4.5 lakhs/mm^{3}and complete immune reconstitution. Thus, this case of haploidentical HSCT represents an effective option for cure in patients with DBA.

Discussion

Allo-HSCT is the only available curative treatment for DBA. The first successful allo-HSCT treatment of patient with DBA was done four decades ago [9]. That patient died but showed the path that DBA is a transplantable disease. Since the initial case, more patients were transplanted and 3 major registries worldwide reported overall survival (OS) anywhere between 75-80% [4,6,7,10]. HSCT from HLA-matched sibling donors, have been reported significant better OS than alternative donor (72 -88 v/s 14-39%) [4,6,7]. A better survival rate in unrelated donor bone marrow recipients was reported in the Japanese DBA registry series [8]. We could opt for haploidentical HSCT because this patient had no siblings.

We did not choose cord blood (CB) HSCT because many authors reported a worse outcome in unrelated CB transplant while the results of related CB HSCT were comparable with outcomes obtained with other hematopoietic stem cell sources [5,8,11]. Majority of patients received busulfan, cyclophosphamide and ATG based myeloablative conditioning. Only Mughisimia, et al.[8] reported one children who underwent haploidentical peripheral blood stem cell (PBSC) HSCT utilizing fludarabine, cyclophosphamide, ATG and total lymphoid irradiation (TLI) conditioning but that patient died at day+100 due to sepsis. We also used myeloablative fludarabine, busulfan based conditioning in our patient because this patient had less years of iron exposure without significant organ toxicity. We discouraged TLI based conditioning regimen because radiation based regimen has been associated with more chances of malignancies after HSCT and even patients with DBA per se are more prone to malignancies [12]. Due to more advancement in HLA typing technique and supportive care a recent Italian registry had shown no significant difference in OS between matched related and matched unrelated donor [10]. Based on the DBA International Clinical Consensus Conference, patients with DBA, may be considered for transplant prior to age 10 years, whether steroid-responsive or transfusion-dependent, if an HLA-matched related donor is available. Two largest registries worldwide [4,10] had clearly shown that if the age is less than 9 years, OS is significantly better. On the other hand, the indications for HSCT for a patient without a matched related donor were limited and reserved only for those who had bi- or trilineage cytopenia and/or the evolution to myelodysplasia or leukemia [2]. Though our patient did not have any of these features at the time of HSCT, tremendous improvement in unrelated donor/ haploidentical transplantation currently as well as the documented very high risk of severe iron overload in chronically transfused DBA patients made us think that this haploidentical HSCT approach could be offered as front-line therapy if a HLA-matched donor is not available [3,8,13]. In general, as in patients with thalassemia, DBA patients also had improved outcomes when transplantation was performed at a younger age, before multiple transfusions lead toiron overload or the development of significant allo-sensitization [2,13,14]. Roggero, et al. [3] described that due to an unknown biological mechanism DBA patients had more early severe iron overload than regularly chelated thalassemia patients. Recent Italian registry [10] had reported worse outcome with high ferritin level though not statistically significant. Our patient also had ferritin level of 2500ng/ml at the time of HSCT and could be the another reason we opted for HSCT early. Italian registry [10] has reported 25 % of grade III-IV acute graft versus host disease post HSCT in children with DBA. Our patient also had steroid refractory grade III acute GVHD possibly due to very high CD3+ T lymphocytes with a big stem cell dose. We could have avoided that severe GVHD by manipulating CD3+ T cell dose. Fortunately, this GVHD responded well to oral methotrexate and ATG combination.

To conclude, our case report highlighted that haploidentical HSCT is a reasonable alternative for cure in young patients with DBA who are steroid refractory and/or chronically transfusion dependent if either related or unrelated donors are not available.

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