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Case Report

DEFERASIROX USE AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRIC PATIENTS WITH β-THALASSEMIA MAJOR: Preliminary Results

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□ *There are limited data on the posttransplantation pharmacological treatment of iron overload in ex-thalassemic patients and the current approach is phlebotomy. The authors chelated 2 ex-thalassemic patients after hematopoietic stem cell transplantation with deferasirox for 6 and 24 months. Although serum ferritin levels decreased, cardiac and hepatic iron load, measured by T2* magnetic resonance imaging (MRI), showed decrease in iron overload in these organs. The drug was tolerated well by both patients and no adverse effect on donor hematopoiesis was observed. This preliminary study demonstrates that deferasirox is well tolerated in these patients and will be a good potential therapy when more data have been obtained from larger studies.*

Keywords bone marrow transplant, iron overload, thalassemia

β-Thalassemia major (β-TM) is an inherited hemoglobin disorder resulting in chronic hemolytic anemia. Regular blood transfusions are necessary in these patients to supress extramedullary hematopoesis and cardiac decompensation caused by the marked anemia [1]. The lack of physiological mechanisms to eliminate excessive iron leads to its deposition in tissues. The use of iron chelators is the mainstay of treatment in β-TM patients in order to ameliorate the inevitable complications of iron overload due to regular

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transfusions; however, the definitive cure for β-TM is hematopoietic stem cell transplantation (HSCT) [2].

It has been shown in several studies that iron levels begin to rise during conditioning therapy before transplantation and peak at around the day of HSCT, which may be attributed to the cytotoxic therapy inducing marrow damage releasing iron pools and increasing free iron levels [3, 4].

The adverse impact of high pretransplantation serum feritin levels has been studied extensively in patients with thalassemia. Higher transplant related mortality has been reported in patients with class 3 status (patients with portal fibrosis, hepatomegaly, and inadequate iron chelation) [5].

Recent studies have demonstrated negative impact of hyperferritinemia on survival of patients with hematological malignancies undergoing HSCT, as well [6, 7]. Iron overload has been attributed to increased incidence of acute graft-versus-host disease (GVHD) and blood stream infection rates in adult patients with hematological malignancies who underwent myeloablative conditioning [7].

Appropriate chelation in patients with β-TM prior to HSCT is important for improving thalassemia-free survival and decreasing transplant-related mortality. However, there are limited data on the posttransplantation pharmacological treatment of iron overload in these patients and the current approach is phlebotomy [3]. Here, we present successful iron chelation with deferasirox after HSCT in 2 patients with β-TM who had improvement in cardiac iron overload as measured by T2* magnetic resonance imaging (MRI).

CASE 1

A 12-year-old boy with β-TM was under regular packed red cell transfusions and iron chelation with subcutaneous desferoxamine 5 times a week, 40 mg/kg/day, since 4 and 24 months old, respectively (Table 1). HSCT was applied from human leukocyte antigen (HLA)-matched male sibling while pretransplant status was Class 2 (irregular chelation and hepatic fibrosis). The patient received intravenous desferoxamine (30 mg/kg/day) for 30 days prior to HSCT, since serum ferritin was 4568 ng/mL and could achieve a pretransplantation serum ferritin of 3549 ng/mL. The patient was conditioned with busulfex (12.8 mg/kg), cyclophosphamide (200 mg/kg), and antithymocyte globulin (ATG) (30 mg/kg) and GVHD prophylaxis consisted of methotrexate (10 mg/m^2/dose) on days +1, +3, +6 and cyclosporin A (CsA) (1.5 mg/kg/dose intravenous [IV] twice a day). The patient received peripheral stem cells of 7.5 × 108/kg mononuclear cells, 6 × 106/kg CD34+ cells from his HLA 6/6–matched brother. Neutrophil and platelet engraftments were achieved by +13th and +34th day of HSCT, respectively, and CsA was ceased after tapering by the end of the first year.

TABLE 1 Clinical Characteristics of the Patients

	Case 1	Case 2
β-Thalassemia mutation	Cd 39(C→T)/Cd 44(−C)	Cds 8/9(+G)/Cds 8/9(+G)
Age at HSCT (year), gender	12, Male	8, Female
Age of first transfusion	4 months old	7 months old
Number of transfusions in the last 1 year	0	0
Splenectomy	—	—
Hepatitis C	—	—
Chelations prior to HSCT	Desferoxamine	Desferoxamine alone between 2 and 7 years of age. Combined treatment with desferoxamine and deferiprone for 1 year up to HSCT

Note. HSCT = hematopoetic stem cell transplantation.

After HSCT, patient refused both phlebotomy and desferoxamine subcutaneous use and at the +11th month of transplantaion, deferasirox was initiated (20 mg/kg/day, oral [PO]) with cardiac T2* MRI value of 15.38 ms and serum ferritin level of 5275 ng/mL. The T2* value was measured as 16.2 ms and serum ferritin 3248 ng/ml by the 24th month of initiation of deferasirox (Table 2).

CASE 2

An 8-year-old girl with Class 2 (irregular chelation and minimal hepatic fibrosis) β-TM was under chronic transfusion program and was initated chelation with desferoxamine (35 mg/kg/day). In addition to desferoxamine, the patient had been started on oral chelator deferiprone 20 mg/kg/dose, 4 times a day (tid), 4 times a week for 12 months prior to HSCT. By combined therapy, serum ferritin level decreased from 3710 to 2829 ng/ml just

TABLE 2 Serum Ferritin and MRI Findings Under Deferasirox Treatment

	Case 1		Case 2	
	Value when chelation initiated	Follow-up measurement (24th month of deferasirox use)	Value when chelation initiated	Follow-up measurement (6th month of deferasirox use)
Serum ferritin (ng/mL)	5275	3248	2312	1365
Cardiac T2* MRI (ms)	15.38	16.20	22	25.20
Hepatic T2* MRI (ms)	—	—	2.65	5.00

Note. MRI = magnetic resonance imaging.

prior to transplantation. HSCT was performed from her HLA 6/6–matched mother after conditioning with busulfex (12.8 mg/kg), cyclophosphamide (200 mg/kg), and antithymocyte globulin (ATG) (40 mg/kg). GVHD prophylaxis was done with methotrexate and CsA, similar to Case 1, and received peripheral stem cells of 4×10^8/kg mononuclear cells, 6×10^6/kg CD34+. Neutrophil and platelet engraftments were achieved by the +12 and 19th posttransplantation days. The patient experienced a complicated early posttransplant course and suffered from mucormycosis prior to neutrophil engraftment and managed with amphotericin B, severe sinusoidal obstruction syndrome, and graft-versus-host disease. At posttransplant 27th month, the patient was started on deferasirox (25 mg/kg/day, PO), with a cardiac T2* value of 22 ms and serum ferritin level of 2312 ng/mL. The cardiac T2* MRI was repeated by the 6th month of drug initiation and revealed an increase in T2* to a level of 25.2 ms and the corresponding serum ferritin level was measured as 1365 ng/mL. The hepatic T2* MRI was also obtained prior to deferasirox and revealed 2.65 ms and by the 6th month of chelation hepatic T2* increased to 5 ms.

The clinical data, serum ferritin and cardiac and hepatic MRI are summarized in Tables 1 and 2.

Unfortunately, they do not have T2* measurements prior to HSCT, since validated T2* MRI was not available in our center at that time. The irregular chelation of both patients related to the compliance problems was responsible for the Class 2 status, prior to HSCT, and deferasirox was not a labeled drug in the country while these patients underwent transplantation. Both of the patients refused subcutaneous desferoxamine use for iron chelation during the post-HSCT period and the phlebotomy schedule was not feasible, related to the refusal of Case 1 and vascular access problems in Case 2.

Deferasirox was a labeled drug for use in the patients for transfusion-related hemosiderosis, when these patients were initiated deferasirox therapy. Parental informed consents and patients' consents were obtained prior to initiation of deferasirox. Both patients underwent audiological and ophtalmological evaluations, renal function tests including serum creatinine, urine protein/creatinine ratio, and glomerular filtration rates, and liver function tests before initiation of deferasirox. No contraindication for the use of deferasirox was identified. Both patients were free of graft-versus-host disease at the initiation of deferasirox and were not under immunosupressive treatment. In both patients T2* MRI was performed using the multiecho T2* approach. In Case 2, hepatic T2* MRI was also performed before and by the 6th month of chelation. During the follow-up, both patients sustained graft and did not develop any adverse reaction that may be attributed to deferasirox therapy. The patients were screened monthly for hematological indices and renal functions. Audiological and ophtalmological evaluations were repeated every 6 months. Neither of the patients received any

concomitant medication at the initiation and during the follow-up period of deferasirox therapy.

DISCUSSION

Hematopoietic stem cell transplantation remains the only curative treatment for patients with β-TM. Current results of transplantation in patients aged less than 17 years from matched related donors offer 80% to 87% cure rates according to risk classes.

The high pretransplantation levels of serum ferritin have negative impact on the transplantion related mortality in patients with β-TM and effective chelation prior to HSCT contributes to better outcomes. On the other hand, it has been reported that hepatic iron and serum ferritin levels may be raised for several years after transplantation [8, 9]. In a study of 76 survivors of allogeneic and autologous HSCT who were at least 1 year post transplant, it was found that 88% of the patients had high serum ferritin levels and in half of these patients accompanying impaired liver functions were unexplainable by other causes, including viral hepatitis, venoocclusive disease, or GVHD, suggesting that iron overload may be an important contributing factor to liver disease in the stable posttransplant setting. Additionally, in the same study, improvement in liver function tests was observed in 10 patients following venesection therapy [8].

There is no clear mechanism for the iron overload seen in the transplantation period that may be due to transfusions or related to the conditioning regimens causing marrow damage leading to increased free iron available. Iron continues to be a problem during posttransplantation period, even may be much more than untransplanted patients, because it may increase the risk of transplantation-related mortality through increasing the risk of infection, GVHD, and sinusoidal obstruction syndrome. It has been reported that iron load and hepatitis C infection are independent risk factors for progression of liver fibrosis during post-HSCT period and coexistence of both multiplies the risk [10].

Currently, the common approach for the treatment of iron overload during post-HSCT period for patients with β-TM is phlebotomy. In a previous study, 48 patients with Class 2 or 3 β-TM underwent phlebotomy for a period of 4.5 $\pm$ 1.5 years (range, 2–7 years) following HSCT because of the persistently high serum ferritin levels by the 2nd year. Phlebotomy was found to be safe and effective in reducing serum ferritin and liver iron concentrations and has become a widely applicable treatment for posttransplantation iron chelation in patients with β-TM [11]. In another study, it has been shown that subclinical left ventricular diastolic dysfunction and impaired left ventricular contractility in patients with β-TM may be reversed by phlebotomy initiated after HSCT [12].

In a small sample size of 18 ex-thalasemic patients, it has been reported that serum ferritin, transferrin saturation and liver iron decreased with desferoxamine chelation of 5 to 20 months during posttransplantation period and desferoxamine use for this purpose has been claimed to be a safe and effective alternative to phlebotomy [13]. A patient with sideroblastic anemia has been reported to be put on phlebotomy and deferiprone plus desferoxamine combined treatment after HSCT and was reported to have a decline in serum ferritin and liver iron burden during the follow-up period [14]. The usual treatment for iron overload after HSCT in patients with β-TM is phlebotomy [3,11,15]; however, there are limited data on the pharmacological chelation of iron during the posttransplantation period, including the safety, optimal dose, time for initiation of treatment, and duration of therapy [3].

In the present preliminary study there was improvement in liver iron concentration (LIC) measured by T2$*$ MRI by the 6th month of treatment in Case 2. Additionally, cardiac T2* values indicating the cardiac iron load improved in both patients and a drop in serum ferritin levels were obtained (Table 2). The patients did not exhibit any adverse events that may be attributed to deferasirox. The usual recommended dose of deferasirox for negative iron balance in patients with β-TM is 30 to 35 mg/kg/day. In our 2 posttransplant patients, considering the safety issues, lower doses (20 and 25 mg/kg/day) were used, since these patients became free of transfusion and would require lower doses of chelation drug. However, the decline in serum ferritin and iron load in tissues at this dose was slow. Although it is prudent to start with lower doses in these patients given the lack of safety data, we have no idea in this population what the right dose should be. Dose increments, as tolerated, would be reasonable given the slow decline seen in our cases.

Patients with thalassemia usually have compliance problems to the use of subcutaneous desferoxamin injections even during the pretransplantation period and it may be much more difficult to convince them to use desferoxamine after transplantation. Additionally, desferoxamine supports the growth of *Zygomycetes*, because it acts as xenosiderophore, delivering iron to iron-uptaking molecules of these species [16]. On the other hand, deferasirox has recently been reported to be beneficial in mucormycosis in both human and animal models [17, 18]. These patients are prone to infections during posttransplantation period related to immunosuppressive treatments. Case 2 developed mucormycosis soon after transplantation, preceeding the neutrophil engraftment and long before deferasirox initiation. Case 2 also developed sinusoidal obstruction syndrome and this may also be related to the high pretransplantation serum ferritin levels (19).

Nausea, vomiting, diarrhea, rash, dyspepsia, upper abdominal pain, nephrotoxicity, and hepatotoxicity are among the reported side effects of deferasirox [20]. During the follow-up with monthly visits, neither of the

patients developed such an adverse reaction. Serum creatine and alanine aminotransferease (ALT) did not exceed upper limit of normal and serum creatinine did not show an increase more than 33% of the baseline value.

Deferasirox may also be an easier way of chelation in these patients because of the once-daily and oral use of the drug. In conclusion, our experience in use of deferasirox in pediatric patients with β-TM suggests that deferasirox, as a well-tolerated chelation option, may be useful for patients who cannot tolerate phlebotomy. To our knowledge as being the first data in written literature on use of deferasirox for chelation after HSCT in patients with β-TM, the results of the present study seem to be promising for patients who are for some reason inconvenient for phlebotomy or disagree with the reinitiation of desferoxamine. Currently, a prospective study is going on with deferasirox (20 mg/kg/day) use after 3 to 6 months in transplanted adult patients with transfusional iron overload (21). A prospective, well-designed, multicenter study has been planned for pediatric patients, and our institution has enrolled with a pioneering role and this prospective study may further increase our understanding of the safety and efficacy of deferasirox for posttransplantation period use.

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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