Efficacy and Safety of Iron Chelation Therapy After Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Thalassemia Patients: A Retrospective Observational Study

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Background: Studies on the increased body iron load in patients with thalassemia major have thoroughly demonstrated the problems caused by iron overload. In patients who undergo hematopoietic stem cell transplantation (HSCT) as curative therapy, iron overload continues long after transplantation. There are few pediatric studies on chelation therapy in the posttransplant period. In this study, we present the outcomes of our patients who received posttransplant oral chelation therapy.

Patients and Methods: This retrospective observational study evaluated the outcomes of pediatric patients with thalassemia major who used oral chelation therapy after allogeneic HSCT at the Akdeniz University Pediatric Bone Marrow Unit between January 2008 and October 2019.

Results: Deferasirox therapy was initiated in 58 pediatric patients who underwent HSCT for thalassemia. Pretreatment mean serum ferritin was 2166 ± 1038 ng/mL. Treatment was initiated at a mean of 12 ± 6.7 months after transplantation and continued for a mean of 15.7 ± 11.5 months. At treatment discontinuation, the mean serum ferritin was 693 ± 405 ng/mL and the mean reduction was −1472.75 ± 1121.09 ng/mL ($P < 0.001$ vs. posttreatment). Serum ferritin was below 500 ng/mL in 52% of the patients at treatment discontinuation. Manageable side effects such as nausea, vomiting, liver enzyme elevation, and proteinuria were observed in 17% of the patients, while one patient developed ototoxicity.

Conclusions: Deferasirox therapy effectively reduces iron overload in the posttransplant period. Studies evaluating the effects of early treatment on the graft may help to establish guidelines for posttransplant chelation therapy. Clear guidelines are needed regarding when to initiate and discontinue treatment.

Key Words: posttransplant chelation, hematopoietic stem cell transplantation, pediatric patient, thalassemia major

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Beta-thalassemia major (β-TM) is the most common hereditary hemoglobinopathy worldwide. Overall, 17% of the global population is affected by β-TM. Approximately 300,000 babies are born with β-TM each year.[1]

In transfusion-dependent thalassemia patients, the excess iron that accumulates in the body causes organ damage, leading to severe morbidity and mortality. Standard treatment for β-TM involves regular blood transfusion, iron overload reduction, and splenectomy if necessary. In transfusion-dependent thalassemia patients, the excess iron that accumulates in the body causes organ damage, leading to severe morbidity and mortality.

Gene therapy and many other novel alternative treatment approaches (targeting α/β chain equilibrium, ineffective erythropoiesis, and iron absorbance mechanisms) are currently being investigated. At present, however, the most commonly applicable curative treatment that is affordable in most countries is hematopoietic stem cell transplantation (HSCT).[2–5] According to the literature, > 5000 β-TM patients have undergone HSCT.[5–8] HSCT is commonly performed in β-TM patients in Turkey.[6,7,9,10] According to the records of the European Group for Blood and Marrow Transplantation (EBMT) from the years 2000 to 2010, 14% of the patients who underwent transplantation due to hemoglobinopathy were in Turkey.[7]

HSCT should be performed as early as possible to increase the success of transplantation and reduce long-term transplant complications.[5] With age, organ dysfunction caused by iron overload results in a higher risk of transplant complications and mortality; therefore, fewer transplantations are performed in adults.[1] Current experience shows that overall survival after HSCT is over 90%, and thalassemia-free survival is around 85%.[2,4,5,8] Clinical experience with HSCT in thalassemia patients is steadily growing.

With increased disease-free survival rates after HSCT, the focus has shifted to monitoring these patients for long-term complications.[11,12] Compared with the long-term complications expected with medical treatment, patients who undergo HSCT have lower rates of complications other than infertility and have similar quality of life to the normal population.[9,13]

Numerous studies on the relationship between pretransplantation iron overload and HSCT have demonstrated that excess iron in the body is associated with lower overall survival and a higher incidence of transplant-related mortality.[14–19]

Even if patients become transfusion-independent after transplantation, their hepatic iron load decreases very gradually, remaining high for up to 5 years and continuing to cause organ damage posttransplant.[20–23] Patients with iron overload who undergo HSCT were shown to have liver dysfunction and progression to cirrhosis, even years after transplantation.[24]

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Phlebotomy can be done once or twice a week to reduce iron load. However, this invasive procedure is not appropriate for patients with cardiac dysfunction. Another option is chelation therapy, which is not administered in hospital and is known to be effective in lowering ferritin in patients with thalassemia. Deferasirox (DFX) is an oral chelator that has been used safely in patients with thalassemia since 2005.

This study aimed to evaluate the efficacy and safety of oral chelation therapy after HSCT in our β-TM patients.

PATIENTS AND METHODS

This study included β-TM patients who underwent allogeneic HSCT in a single center in Turkey (Department of Pediatric Hematology and Oncology, Akdeniz University Faculty of Medicine). DFX was approved for use in Turkey in March 2008. Data pertaining to 120 allogeneic HSCT procedures performed on 113 patients between March 2008 and October 2019 were screened for the study group. The data were reviewed retrospectively from patient charts and electronic records. Data obtained up to November 2020 were included in the analysis. Patients with signs of liver graft-versus-host disease (GVHD) or hepatitis B/C infection were excluded. Hepatitis B and C infections were among the exclusion criteria because of the possible impact on liver function tests. However, no patients were excluded based on this criterion.

In matched sibling donor and matched related donor transplants, a myeloablative regimen (busulfan/cyclophosphamide) was used, whereas a reduced-toxicity conditioning regimen (treosulfan/fludarabine/thiotepa) was used for matched unrelated donor transplants.[8,25] Protocol 26, the conditioning regimen recommended by the Pesaro group for class 3 patients, was used.[1] All patients who underwent allogeneic HSCT received prophylactic antimicrobial prophylaxis.

Antithymocyte globulin was added to the conditioning regimen to reduce the risk of graft rejection and GVHD. Cyclosporine and short methotrexate were administered as GVHD prophylaxis. DFX was not initiated until immunosuppressive therapy was discontinued.

Of 113 patients who underwent allogeneic HSCT due to β-TM, 18 had autologous reconstitution. A second HSCT was performed in 3 of these patients.

Of the 113 screened patients, 72 used posttransplant oral chelation therapy. Fifty-five of the patients were excluded from the study. The reasons for the exclusion of these patients from the study were as follows; 15 patients with autologous reconstitution, 5 patients who underwent phlebotomy after HSCT, 15 nonsurviving patients had not received chelation therapy after HSCT, and 6 patients with grade 3 to 4 GVHD, 14 patients who did not use oral chelation therapy regularly were excluded from the study.

Sixteen patients died due to transplant complications (infection in 9, acute GVHD in 3, sinusoidal obstructive syndrome in 1, and chronic GVHD in 2 patients). Among the patients receiving chelation therapy, only 1 patient died due to infection after the second transplantation.

There were 72 surviving patients who received oral chelation therapy after transplantation. Of these, 58 continued posttransplant follow-up in our hospital. The regular chelation use of the patients was made by questioning the patient and the parent separately at each visit and using the prescription drug tracking system. Fourteen patients who were followed up in other centers and referred to our center for HSCT were referred back to their centers with a follow-up and treatment plan after they discontinued immunosuppressive therapy due to social obligations (eg, lack of accommodation, work obligation, etc.). These patients visited our center at intervals of 6 to 12 months for follow-up. Although all of these patients survived, they were excluded from this study due to the lack of postchelation data. The patients with HSCT came to follow-up examinations twice a week until immunosuppressive therapy was discontinued; after discontinuation, visits were extended to once a week, every 2 weeks, once a month, once every 3 months, once every 6 months, and once a year, with more frequent visits if needed. Patients who adhered to this follow-up schedule were included.

Cardiac T2* magnetic resonance imaging (MRI) and liver R2 MRI (liver iron concentration [LIC]) measurements are the best indicators of body iron load, but unfortunately, these examinations are not accessible in every time in our center. For that reason, body iron load was evaluated using serum ferritin, T2*-weighted MRI-assessed LIC when possible, and liver biopsy in the pretransplant period, while only serum ferritin was evaluated in the posttransplant period. Cardiac T2* MRI was not performed in 35 of the patients because they were 10 years of age or younger. Therefore, a comparison of serum ferritin values was used in our study to demonstrate the effectiveness of chelator use in reducing iron load.

Pretransplant ferritin values and posttransplant ferritin values before initiation of oral chelation therapy and at discontinuation were recorded. Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST]) and renal function tests (creatinine) values were examined. The patients' drug, dose, and duration of treatment, drug-related adverse events, and HSCT-related data were also recorded.

Ethics Statement

The study was approved by the Akdeniz University Medical Faculty Clinical Research Ethics Committee (KAEK-863).

Statistical Analysis

χ^2 test was used for parametric analyses and Mann-Whitney test for nonparametric analyses. Paired-samples *t* tests were used to analyze differences between pretreatment and posttreatment laboratory parameters and compare posttreatment serum ferritin levels with pretreatment and pretransplant values to evaluate reduction of body iron overload. A value of $P < 0.05$ was accepted as significant. Data analysis was performed using SPSS Statistics, version 23.0 for Windows (IBM Corp., Armonk, NY).

RESULTS

Patient Distribution and Baseline Demographics

Of 113 patients transplanted between March 2008 and October 2019, 72 patients received oral chelation therapy, and 58 of these patients with regular follow-up and no missing data were included in the analysis (Fig. 1).

Twelve (20%) of the patients had matched unrelated donors and received the reduced-toxicity conditioning regimen. For the other patients, the conditioning regimen was selected according to their Pesaro classification. Three patients underwent second transplantation.

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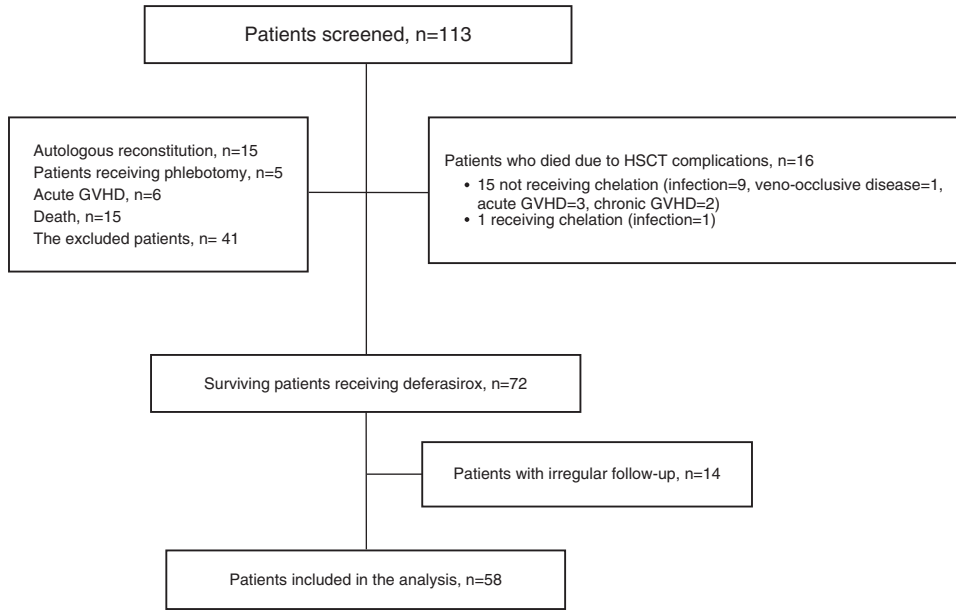


FIGURE 1. Study flow chart showing numbers of screened, excluded, and included patients. GVHD indicates graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.

The mean age of the patients who received oral chelator therapy was 9.1 ± 4.2 years (median: 9.4 y, range: 1.7 to 18 y). Details of the patients' transplantations are presented in Table 1.

TABLE 1. Demographic and Clinical Characteristics of Thalassemia Major Patients Who Underwent Hematogenic Stem Cell Transplantation

Characteristics	n (%)
N	58
Age (y)	
Mean ± SD	9.1 ± 4.2
Sex	
Male	27 (46.6)
Female	31 (53.4)
Pretransplantation serum ferritin (ng/mL)	
Median (range)	1753 (774-5109)
Pesaro Classification	
Class I	4 (7)
Class II	43 (73)
Class III	12 (20)
Graft source	
Bone marrow	34 (58.6)
Peripheral stem cell	19 (32.8)
Cord blood+bone marrow	5 (8.6)
Donor status	
MSD	42 (72.4)
MPD	3 (5.2)
MRD	1 (1.7)
MUD	12 (20.7)
HLA status	
6/6	8 (13.8)
10/10	49 (84.5)
9/10	1 (1.7)
Transplant status	
Full chimeric	48 (82.8)
Stabile mixed chimeric	10 (17.2)

MPD indicates matched parent donor; MRD, matched related donor; MSD, matched sibling donor; MUD, matched unrelated donor.

All patients used DFX as an oral chelator. One patient was switched from DFX to deferiprone due to DFX-related ototoxicity. Chelation therapy was initiated in patients who had no signs of active GVHD, were no longer receiving immunosuppressive therapy, and had serum ferritin level > 1000 ng/mL

DFX was initiated at an initial dose of 10 to 20 mg/kg/d. The dose received by the patients for pretransplantation chelation was the primary consideration, and treatment was given at a dose ~10 mg/kg/d lower than this dose. The dose was rounded according to the appropriate formulation of the drug (125/250/500 mg). The most frequently used dose was 20 mg/kg/d. The dose was gradually increased by 5 to 10 mg/kg/d based on treatment response and adverse effects. A patient with a ferritin value of 4009 before starting chelation therapy was increased to 40 mg/kg/d. The mean DFX dose was 23.6 ± 5.6 mg/kg/d (mode: 20 mg/kg/d).

Efficacy of Iron Chelation Therapy

The median pretransplant serum ferritin level of the patients was 1753 ng/mL (range: 774 to 5109 ng/mL). Chelation therapy was initiated at a mean of 12 ± 6.7 months (median: 9.7 mo, range: 5.8 to 36.6 mo) after transplantation, and the mean treatment duration was 15.7 ± 11.5 months (median: 12.2 mo, range: 0.5 to 53 mo). At the time of data analysis, 8 patients were continuing treatment. Their mean treatment duration was 11 ± 9.98 months and the median was 6.65 months (range: 3.77 to 30.77 mo).

Median serum ferritin level before chelation was 1829 ng/mL (range: 1015 to 6120 ng/mL, mean ± SD: 2166 ± 1038 ng/mL) and at treatment discontinuation was 589 ng/mL (range: 170 to 2058 ng/mL, mean ± SD: 693 ± 405 ng/mL). Serum ferritin level fell below 500 ng/mL in 54% (27) of the 50 patients whose chelation therapy was discontinued (treatment is ongoing in 8 patients). The other 23 patients did not fully adhere to DFX therapy. For these patients who did not take their medication or took it irregularly, DFX therapy was discontinued without reduction of serum ferritin to below 500 ng/dL. The effectiveness

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TABLE 2. The Relationship Between Ferritin Levels and Treatment Adherence

	Nonadherent	Adherent	Continuing Treatment	*P**
Ferritin at end of chelation (ng/mL)				0.379
Mean ± SD	1066.35 ± 1073.76	−1775.55 ± 1167.43	−774.15 ± 571.34	
Median (range)	−932 (1283 to −3279.5)	−1416 (−4718 to −464)	−619.35 (−194 to −166.5)	
Change in ferritin with treatment (ng/mL)				0.438
Mean ± SD	1301.75 ± 1026.51	−1869 ± 1201.24	−626.95 ± 208.87	
Median (range)	−1058 (591 to −3934)	−1475 (−678.4 to −5795)	−602 (−370 to −966)	
Treatment duration (mo)				0.325
Mean ± SD	15.67 ± 12.71	17.14 ± 11.03	11 ± 9.97	
Median (range)	12.70 (0.47-52.97)	13.9 (5.23-45.87)	6.6 (3.77-30.77)	

*χ^2 test.

of chelation therapy according to treatment adherence is presented in Table 2.

The mean reduction in serum ferritin with chelation therapy was −1472.75 ± 1121.09 ng/mL ($P < 0.001$ vs. posttreatment). When compared with pretransplant serum ferritin levels, the reduction achieved with treatment was mean −1356.19 ± 1127.62 ng/mL and was statistically significant ($P < 0.001$ vs. pretransplant) (Table 3).

Safety of Iron Chelation Therapy

Adverse Events

No side effects were observed in 83% (n = 49) of our patients. Of the 10 patients who experienced side effects, 2 patients reported multiple adverse events (nausea/vomiting and elevated liver enzymes or proteinuria and elevated liver enzymes). The other 8 patients had proteinuria (n = 2), elevated liver enzymes (n = 4), rash (n = 1), or ototoxicity (n = 1). The patient who developed ototoxicity was switched from DFX to deferiprone (details below). For the other patients, treatment was continued with dose modification.

TABLE 3. Laboratory and Clinical Data in Patients Undergoing Chelation Therapy With Deferasirox

Characteristics	n (%)
Pretransplantation serum ferritin (ng/mL)	
Mean ± SD	2052.75 ± 986.15
Median (range)	1753 (774-5109)
Pretreatment serum ferritin (ng/mL)	
Mean ± SD	2166 ± 1038
Median (range)	1829 (1015-6120)
Posttreatment serum ferritin (ng/mL)	
Mean ± SD	693 ± 405
Median (range)	589 (170-2058)
Time of deferasirox initiation, posttransplant (mo)	
Mean ± SD	12.14 ± 6.77
Median (range)	9.7 (5.8-36.6)
Duration of chelation therapy (mo)	
Mean ± SD	15.68 ± 12.23
Median (range)	12.2 (0.47-52.97)
Chelation-related adverse events	
None	47 (81)
Elevated liver enzymes	6 (10.3)*
Proteinuria	3 (5.2)*
Skin rash	1 (1.7)
Ototoxicity	1 (1.7)
Multisystem	2 (3.4)*
Chelation treatment status	
Ongoing	8 (13.8)
Discontinued	50 (86.2)

*Multiple adverse events were observed in 2 patients (nausea/vomiting and elevated liver enzymes in 1 patient, proteinuria and elevated liver enzymes in 1 patient).

When chelation therapy was initiated in the patient who developed ototoxicity, their ferritin level was 4009 mg/mL. We initiated DFX at 20 mg/kg/d. Due to the slow reduction in ferritin value during clinical follow-up, the drug dose was gradually increased by 5 mg/kg/d at 9, 21, and 30 months. At 40 months, ferritin level was 2508 mg/dL, and the DFX dose was increased to 40 mg/kg/d. A hearing test performed at 52 months revealed 5% hearing loss was detected in the right ear. The patient's ferritin level was 904 mg/dL, and chelation therapy was discontinued. Two months later, ferritin level was measured as 904 mg/mL. The patient showed complete chimerism after transplantation and was switched to deferiprone at 54 months. After using deferiprone for 6 months, ferritin level was measured as 435 mg/mL, and chelation therapy was discontinued. A follow-up hearing test indicated 100% hearing in both ears.

Laboratory Parameters

Mean pretreatment and posttreatment serum creatinine levels were 0.33 ± 0.11 mg/dL (median: 0.30 mg/dL, range: 0.20 to 0.70 mg/dL) and 0.41 ± 0.17 mg/dL (median: 0.40 mg/dL, range: 0.20 to 1.2 mg/dL), respectively, which was a statistically significantly change (Table 4). Creatinine level increased 33% above baseline in 12 patients (20.6%). However, this did not cause a change in medication. A patient with a creatinine level of 1.2 mg/dL had proteinuria in a spot urine sample, but no significant proteinuria was detected in a 24-hour urine sample. None of the patients had persistent creatinine elevation. In a patient with a creatinine level of 1.2, the DFX dose was continued at a lower dose after a 2-week interruption, and no further elevation was observed during follow-up.

Mean pretreatment and posttreatment serum ALT levels were 40.22 ± 32.50 IU/L (median: 29 IU/L, range: 9 to 168 IU/L) and 28.93 ± 25.84 IU/L (median: 21 IU/L, range: 9 to 144 IU/L). For serum AST, these values were 39.77 ± 19.39 IU/L (median: 34 IU/L, range: 14 to 92 IU/L) and 31.61 ± 20.68 IU/L (median: 27 IU/L, range: 8 to 111 IU/L). These changes were also significant (Table 4).

Elevation in liver enzymes was only significant in 1 patient whose maximum AST level was 3.5 times over baseline and 3 times over the normal upper limit of the laboratory. Maximum ALT elevation was 6.5 times over baseline and 2.9 times over the normal upper limit. Treatment was not discontinued due to elevated liver enzymes in any of the patients. Although proteinuria was detected in

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TABLE 4. Pretreatment to Posttreatment Changes in Iron and Laboratory Parameters in Pediatric Beta-thalassemia Major Patients Treated With Deferasirox After Allogeneic HSCT

Parameters	Mean ± SD	95% CI (Lower Limit, Upper Limit)	*t*	*P**
Change in serum ferritin (ng/mL)				
Posttreatment−pretreatment	−1472.75 ± 1121.09	−1767.53, −1177.98	−10.0	< 0.001
Posttreatment−pre-HSCT	−1356.19 ± 1127.62	−1652.68, −1059.70	−9.16	< 0.001
Change in AST (U/L)				
Posttreatment−pretreatment	−8.29 ± 25.64	−15.04, −1.55	−2.46	0.017
Change in ALT (U/L)				
Posttreatment−pretreatment	−10.10 ± 35.82	−19.52, −0.68	−2.14	0.036
Change in creatinine (mg/dL)				
Posttreatment−pretreatment	0.07 ± 0.17	0.03, 0.11	3.35	0.001

*Paired-samples *t* test.
ALT indicates alanine transaminase; AST, aspartate transaminase; CI, confidence interval; HSCT, hematopoietic stem cell transplantation.

spot urine evaluation, 24-hour urine revealed no significant proteinuria, and DFX therapy was continued.

Table 4 shows the changes in the patients' serum ferritin, AST, ALT, and the creatinine levels measured at the start of DFX therapy and at discontinuation.

DISCUSSION

Today, HSCT is widely used as a curative intervention for thalassemia patients. Many studies have investigated the impact of pretransplant iron overload on outcome after HSCT. Although data regarding the effects of pre-HSCT iron overload on GVHD are contradictory, it has been shown that iron overload predisposes to fungal infections and causes hepatic sinusoidal obstruction syndrome, liver dysfunction, late endocrinopathy (hypothyroidism, parathyroid failure, diabetes mellitus), and cardiac damage.[19,25–31] Meyer and colleagues investigated the prognostic effect of posttransplant iron overload in 290 patients who underwent myeloablative allogeneic HSCT. Their study showed that ferritin level peaked in the first 1 to 3 months after transplantation followed by a gradual decline, and they determined that hyperferritinemia had an adverse impact on 5-year overall survival, independent of GVHD and transfusion need.[32]

After a successful transplant, even if there is no additional increase in iron burden, the existing iron remains "frozen" and causes damage in the long term.[20,33] Prospective studies have shown that iron overload continues to cause progressive liver dysfunction, cirrhosis, and cardiac dysfunction long after HSCT in some patients.[24] Therefore, posttransplant iron overload should be considered a potential cause of morbidity and mortality due to additional comorbidities caused in the long term (over decades). Large epidemiological population-based studies and follow-up in patients with hemoglobinopathy have shown that high transferrin saturation is associated with increased morbidity and mortality, providing evidence for the need to assess and reduce iron load after HSCT.[33]

Patients with iron overload due to chronic transfusion now survive into their 50s.[34] Today, the overall survival rate with HSCT has reached 95%, and the thalassemia-free survival rate is up to 85%. The focus has now shifted to long-term complications in these patients. To prevent long-term complications after transplantation, the need for chelation therapy should be evaluated in all patients.[11,31,35]

In a study by the Pesaro group, 22% of β-TM patients with progressive hepatic fibrosis before transplantation developed cirrhosis in the posttransplant period.[24] The Pesaro group also demonstrated that phlebotomy (6 mL/kg) performed every 2 weeks after transplantation reduced the iron load.[21] In another study, repeated biopsies showed that phlebotomy or chelation therapy reduced iron load and induced regression of liver cirrhosis.[36] In cases where a rapid reduction in iron load is desired or chelation therapy cannot be initiated due to drug toxicity, phlebotomy is an effective and low-cost interventional treatment method that is performed every 2 weeks. Phlebotomy can also be performed with smaller volumes, especially for patients with cardiac dysfunction.

Inati and colleagues conducted a prospective randomized controlled trial evaluating the efficacy of phlebotomy and DFX in 26 children who underwent transplantation due to thalassemia major and had serum ferritin levels 500 mg/mL or higher and LIC of 3 mg Fe/g dry weight (dw). This was the first pediatric study evaluating iron load with LIC in the post-HSCT period, and the results demonstrated that DFX was more effective than phlebotomy in reducing iron load.[37] Nevertheless, the parents of 13 of 14 patients in the phlebotomy arm wanted to switch to the DFX arm due to anxiety and difficulty in finding vascular access during the phlebotomy process.

We also performed phlebotomy on 5 of our patients before they started using oral chelator treatment. Forty-five (77.6%) of our patients were transplanted from matched related donors, and 32 (71%) of these donors had thalassemia minor. Therefore, 71% of our patients exhibited moderate anemia consistent with the thalassemia minor phenotype in the posttransplant period. This is why we did not consider phlebotomy a suitable option in these patients. Because they were receiving oral chelation therapy before transplantation, none of our patients accepted chelation therapy with phlebotomy after transplantation.

Yesilipek and colleagues evaluated the efficacy and safety of DFX in 26 pediatric patients with hyperferritinemia (serum ferritin >1000 μg/L; cardiac MRI T2* <20 ms, or LIC ≥ 5 mg/g dw) who underwent transplantation due to thalassemia in their 52-week prospective, randomized, multicenter study. They showed that ferritin and LIC values decreased significantly, and cardiac T2*MRI measurements increased above 20 ms in all patients with DFX.[6] The studies of DFX in post-HSCT survivors with iron overload are summarized in Table 5.

As thalassemia patients usually undergo HSCT in childhood, the efficacy of chelation with DFX in adults has generally been investigated in patients undergoing HSCT for malignancy, and significant decreases in serum ferritin and LIC have been demonstrated.[37,38,40,42]

In previous studies and guidelines, DFX was started after has discontinued immunosuppressive therapy and has

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TABLE 5. Management of Iron Overload With DFX in HSCT Recipients

References	Patients/Study Dates/ Study Design	Iron Overload/DFX Timing and Dose	Study Period	Comments
Sivgin et al[38]	23 adult patients Between May 2008 and April 2010 Retrospective study	Iron overload: ferritin ≥ 1000 ng/mL DFX initiation: 115 d (66-134) after HSCT DFX dose: 20-30 mg/kg/d	Treatment duration: median 94 d (72-122 d)	In the posttransplant setting, significantly reduced iron parameters; 13% of patients had side effects
Majhail et al[39]*	3 adult patients Between January 2008 and August 2009 Prospective study	Evidence of iron overload: ferritin ≥ 1000 ng/mL, LIC ≥ 5 mg/g) DFX initiation: 12 mo after HSCT DFX dose: 20 mg/kg/d	Treatment duration: 6 mo	Well tolerated and decreased LIC in all patients
Vallejo et al[40]*	30 adult patients were enrolled and 22 completed the study Between January 2008 and August 2009 Prospective study	Evidence of iron overload: ferritin ≥ 780 ng/mL, LIC ≥ 5 mg/g) DFX initiation: 6 mo after HSCT DFX dose: 10-30 mg/kg/d	Treatment duration: median 45.7 wk (range: 7.9-57.9 wk) Treatment was interrupted if ferritin levels ≤ 400 ng/mL	No drug-related serious adverse events; significant reduction in ferritin and LIC
Jaekel et al[41]*	76 adults were recruited and 46 completed the study Between 24 April 2008 and 29 June 2012 Prospective study	Evidence of iron overload: ferritin ≥ 1000 ng/mL DFX initiation: 12 mo after HSCT DFX dose: 10-20 mg/kg/d	Treatment duration: 1 y Treatment was interrupted if ferritin levels ≤ 500 ng/mL	Negative iron balance in 84% of patients; serum blood creatinine increased in 26.5% of recipients with a manageable safety profile, even in patients receiving cyclosporine
Inati et al[37]*	26 pediatric patients Prospective, randomized	Evidence of iron overload: median ferritin: 999 ng/mL (503-5884 ng/mL) DFX dose: 10-20 mg/kg/d	Treatment duration: 1 y Treatment was interrupted if ferritin levels ≤ 300 ng/mL	Well tolerated and decreased LIC in all patients
Yesilipek et al[6]*	26 pediatric patients Prospective, randomized	Evidence of iron overload: ferritin > 1000 µg/L, cardiac MRI T2* <20 ms or LIC: ≥ 5 mg/g) DFX dose: 10-20 mg/kg/d	Treatment duration: 52 wk Treatment was interrupted if ferritin levels ≤ 300 ng/mL	No drug-related serious adverse events; significant reduction in ferritin and LIC

*Supported by Novartis Pharmaceuticals.
DFX indicates deferasirox; HSCT, hematopoietic stem cell transplantation; LIC, liver iron concentration; MRI, magnetic resonance imaging.

no signs of GVHD. In the study of 16 pediatric thalassemia patients conducted by Li et al,[43] deferoxsamine chelation therapy was initiated at 3 months, and no graft failure was observed. Based on this study, they recommended starting chelation therapy in patients with the high hepatic iron load as early in the posttransplant period as possible, immediately after recovery from early complications. However, there are no studies in the literature in which DFX chelation therapy was initiated this early in the pediatric age group.[43]

Jaekel et al[41] evaluated the effect of DFX use on serum cyclosporine levels in patients receiving posttransplant DFX therapy and showed that blood cyclosporine levels were not affected, and no adjustment of cyclosporine dose was required. Patients with acute GVHD were not included in the study, but chronic GVHD was detected in 45% of the patients during treatment, and only 1 patient was reported to have DFX discontinued due to GVHD.

A study in which DFX therapy was used during the administration of the conditioning regimen demonstrated a reduction in labile plasma iron shortly after transplantation, and the early initiation of DFX therapy was reported to be safe.[44,45]

Previous studies have not specified a clear cutoff value for the discontinuation of chelation therapy. Sivgin et al[42] reported in retrospective study that serum ferritin level decreased from a median concentration of 2636 ng/mL (range: 721 to 7572 ng/mL) to 1143 ng/mL (range: 366 to 2961 ng/mL) over a median of 94 days (range: 72 to 122 d), while Inati et al[37] reported a decrease from a median of 999 ng/mL (range: 503 to 5.884 ng/mL) to 515 ng/mL (range: 139 to 4000 ng/mL) over a follow-up period of 1 year. In a study by Yeşilipek et al,[6] ferritin levels were under 500 µg/L in only 33% of patients after 52 weeks of treatment. Most prospective studies on this topic have been conducted with industry support and were terminated when the planned study period was completed.[6,37,39,41,44] In these studies, a ferritin level below 300, 400, or 500 mg/mL was sought for discontinuation of chelation therapy. Although a clear threshold is not specified in the EBMT recommendations, we can conclude from the literature that the general consensus is to reduce ferritin to 500 mg/mL or lower. Assessing whether the ferritin level has been lowered to the target level is advisable before discontinuing treatment.

While reviewing our study data, we noted that high serum ferritin levels were detected in our patients before initiating chelation therapy, but we waited for termination of immunosuppressive therapy to start DFX. For this reason, the timing of DFX initiation in our study was at a mean

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of 12 ± 6.7 months posttransplant, and the mean duration of chelation therapy was 23.6 ± 11.5 months. These periods are consistent with those reported by Marjhail et al[39] and fairly similar to those reported by Sivgin et al.[38] At discontinuation of treatment, the mean serum ferritin level in our patients was 693 ± 405 ng/mL and serum ferritin levels fell <500 ng/mL in 54% of 50 patients (excluding 8 patients whose treatment is ongoing).

Our results are consistent with the literature and demonstrate that DFX therapy effectively and safely reduces serum ferritin levels. In the pretransplant period, only 20% of our patients were class III according to the Pesaro classification. This led us to suspect that although drug adherence was actually good in most patients in the pretransplant period, it may have decreased after transplantation. If chelation therapy had been initiated in the early posttransplant period, when the patients had more frequent follow-up visits at the hospital, it may have been possible to decrease their ferritin levels even further.

We believe that iron load assessment and initiation of chelation therapy during the closer follow-up of the early posttransplant period will facilitate the effective reduction of ferritin to normal levels. In thalassemia patients who are transfusion-independent, starting chelation treatment at a stage where even the post-HSCT prophylactic drugs have been discontinued may have decreased the patients' compliance in terms of drug therapy.

Nearly all studies on the use of DFX demonstrated moderate but manageable adverse effects (nausea, vomiting, moderate elevation of creatinine, and liver enzymes) and reports of severe adverse effects are extremely rare.[6,37,38,40–42] We discontinued DFX due to ototoxicity in 1 of our patients. However, this may be related to the chelation therapy previously used by the patient.

There is no consensus in the literature regarding the timing and methods of treatment for iron overload reduction in HSCT patients. Sivgin and colleagues initiated chelation therapy regardless of GVHD status. In fact, 85% of patients with GVHD were diagnosed after chelation therapy was initiated, and they continued immunosuppressive and chelation treatments together.[38] The authors concluded that oral DFX therapy is safe and effective in the posttransplant setting, with or without phlebotomy. In the study of 16 pediatric thalassemia patients conducted by Li et al,[43] deferoxamine chelation therapy was initiated at 3 months, and no graft failure was observed. Based on this study, they recommended starting chelation therapy in patients with the high hepatic iron load as early in the posttransplant period as possible, immediately after recovery from early complications. However, there are no studies in the literature in which DFX chelation therapy was initiated this early in the pediatric age group.[43]

The EBMT, Center for International Blood and Marrow Transplant Research, and American Society for Blood and Marrow Transplantation have recommended screening by serum ferritin level measurement at posttransplant 1 year to protect patients from late adverse effects.[17,35] Marjhail et al[17] stated that if transplantation was not performed due to a transfusion-related disease, the iron reduction can be postponed until 1 or 2 years. However, it is emphasized that in thalassemia patients, especially those with persistent post-HSCT liver dysfunction, iron overload must be considered, and patients should be evaluated earlier to assess the need for chelation therapy.[23]

In a multicenter phase II study evaluating the efficacy and safety of DFX, Yesilipek et al[6] initiated post-HSCT chelation therapy with DFX 3 months after discontinuing immunosuppressive therapy and reported that starting DFX as early as posttransplant 6 months was safe in patients whose immunosuppressive therapy was discontinued.

The EBMT 2019 guidelines referred to in this study state that DFX therapy can be initiated at a dose of 20 mg/kg/d starting as early as 6 months but make no restriction related to immunosuppressive therapy.[6]

Based on our study data, we can recommend that after discontinuing posttransplant immunosuppressive therapy, patients without signs of nephrotoxicity who have a ferritin level of > 1000 mg/dL, cardiac T2* MRI < 20 ms, and LIC ≥ 5 mg/g dw can safely be treated starting at a dose of 10 to 20 mg/kg/d and that treatment should continue until their ferritin falls <500 mg/mL.

We see that varying DFX doses such as 10, 20, or 30 mg/kg/d have been used in previous studies. However, the evidence indicates that a dose of 20 mg/kg/d is sufficient for effective treatment.[6,37,38,40,41] Film-coated tablets are now safely used in the treatment of thalassemia patients. Although there is no study evaluating the use of this formulation in posttransplant patients, we believe it can be used at a dose of 7 to 14 mg/kg/d.

In the follow-up of our thalassemia patients, we monitored body iron load with serum ferritin level, and cardiac T2* MRI evaluation was also performed when it was possible to do so in our hospital. LIC measurement is not a method we can utilize in routine practice. In our center, we evaluate patients' iron load using ferritin level, which is the most appropriate test applicable in our daily practice. However, when transplantation is planned, we evaluate patients for the presence of hepatic fibrosis by liver biopsy according to the Pesaro classification in the pretransplant preparation period. Based on this evaluation, 55 (93%) of our patients were low-risk (class I to II). In posttransplant follow-up, we did not perform T2* MRI and LIC evaluation because it was not available in our hospital.

Despite the fact that T2* MRI and LIC measurements were not performed regularly for all patients, we believe our results are valuable for many centers with similar conditions. Nevertheless, centers should try to improve access to T2* MRI and liver R2 MRI (LIC) methods, which are the gold standard for monitoring body iron load.[46,47]

CONCLUSIONS

For thalassemia patients who undergo HSCT, long-term complications and quality of life have become more important than survival. Reducing the iron load to normal levels should be a priority in these patients to avoid posttransplant complications associated with iron toxicity in the long term.[5,20,34]

Although there is consensus on the effective and safe use of oral chelation therapy, there are no definitive criteria for treatment initiation and discontinuation.[6,10,33,37,38,48] The decision to initiate chelation therapy is made using a personalized treatment approach based on factors such as the patient's transplant-related clinical condition, continued transfusion dependence, and ability to tolerate chelation therapy.[45]

In conclusion, there is a need for well-designed prospective, randomized, controlled studies evaluating the effects of early and late initiation of chelation therapy with DFX film-coated tablets and water-soluble tablet forms on graft and GVHD, immunosuppressive therapy and other

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drug interactions, drug toxicity, and chelator efficacy. The results of these studies may form the basis for the creation of a detailed chelation treatment algorithm.

Study Limitations

This was a retrospective, observational study. Not performing T2*-weighted MRI and LIC evaluations of the patients in the post-HSCT period and evaluating iron load based on serum ferritin levels is a weakness of this study. Another limitation was that there was no standardized assessment of the causes of drug nonadherence. For this reason, we could not make a detailed objective evaluation of drug adherence.

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