Low-dose deferasirox treatment in allogeneic hematopoietic cell transplantation survivors: Evaluation of iron overload by measuring liver iron concentration and non-transferrin-bound iron

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Iron overload is a common complication of allogeneic hematopoietic cell transplantation (HCT); however, its management remains to be studied. We retrospectively analyzed the efficacy and safety of low-dose deferasirox treatment in four HCT survivors with iron overload and measured serum ferritin levels, liver iron concentrations (LIC), and non-transferrin-bound iron (NTBI) levels. Patients who had become transfusion-independent after HCT were treated using 10 mg/kg/day deferasirox. Their median age was 36.5 years (range, 27–39), and they had survived a median of 66 months (range, 27–101) after HCT. After a median of 23.5 months (range, 16–34) of deferasirox treatment, serum ferritin levels, LIC, and NTBI levels decreased in all patients, and NTBI decreased in three patients. The median ferritin levels, LIC, and NTBI levels decreased from 6135 (range, 3720–10,500) to 1782 ng/mL (range, 775–6840), 24.6 (range, 9.6–43.0) to 7.8 mg/g (range, 2.8–42.3), and 1.26 (range, 0.89–2.09) to 0.82 μmol/L (range, 0.64–1.54), respectively. Abnormal liver function tests improved in all patients after deferasirox treatment. On the other hand, all patients experienced an increase in serum creatinine levels. In conclusion, treatment with low-dose deferasirox might be an effective alternative for allogeneic HCT survivors with iron overload. (Journal of Hematopoietic Cell Transplantation 5 (4): 148–154, 2016.)

Introduction

Allogeneic hematopoietic cell transplantation (HCT) recipients are at a risk of developing iron overload owing to red blood cell (RBC) transfusions both during the initial treatment of the disease and during the transplantation period. Iron overload is a common complication of allogeneic HCT, and it has been associated with liver dysfunction and with an increased risk of late infections after allogeneic HCT.¹⁻⁶ Although published consensus guidelines recommend screening HCT survivors for iron overload,¹ the clinical impact and management of this overload has not been well studied.

Deferasirox is a once-daily, orally administered iron chelator, and it is frequently used to reduce iron burdens in patients who require long-term transfusions for congenital and acquired disorders.⁸⁻¹⁰ However, studies regarding its efficacy in allogeneic HCT survivors with iron overload have been limited, and its optimal dose has not yet been determined.¹¹⁻¹²

Iron burden estimation is currently based on serum ferritin levels, but in allogeneic HCT recipients, many confounding factors, such as inflammation, ineffective erythropoiesis, and liver disease, can also be related to ferritin overestimation.¹³⁻¹⁶ Additional diagnostic testing, such as a liver biopsy or measuring liver iron concentrations (LIC) using magnetic reso-

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nance imaging (MRI) or a superconducting quantum interference device (SQUID), may be indicated if treatment is being considered for suspected iron overload. The noninvasive measurement of LIC using the R2 MRI technique is highly sensitive and specific compared to a liver biopsy. Non-transferrin-bound iron (NTBI), which increases in patients with iron overload, is a marker of iron toxicity, and several studies have demonstrated that NTBI is a good index for iron overload in patients with thalassemia. In a previous study, we assessed the quantification of iron burden in 122 allogeneic HCT survivors by determining NTBI levels.

To evaluate the efficacy and safety of low-dose deferasirox treatment in allogeneic HCT survivors with iron overload, we retrospectively analyzed deferasirox treatment in four allogeneic HCT survivors, measuring not only serum ferritin levels but also LIC and NTBI levels.

Materials and Methods

We retrospectively analyzed four allogeneic HCT survivors who were treated with deferasirox treatment owing to iron overload between January 2009 and December 2010 and had been followed-up at the Japanese Red Cross Nagoya First Hospital. Iron overload was defined as serum ferritin levels of >1000 ng/mL because more iron-related liver function test (LFT) abnormalities have been observed in patients with this serum ferritin level, without any other suspected causes for the elevated levels, such as infections.

All patients were treated with deferasirox during the post-transplant period. The patients had never received iron-chelating therapy, and they did not have any of the following contraindications for deferasirox: (1) hypersensitivity to deferasirox, (2) severe renal impairment, (3) poor performance status, and (4) progressive malignant disorder. Deferasirox was initiated orally at a dose of 10 mg/kg/day in three patients. In the other patient (patient 2), the starting dose was 20 mg/kg/day; however, the dose was reduced to 10 mg/kg/day after 6 months of initial treatment by her physician and not due to adverse effects.

Serum ferritin levels were periodically monitored, and deferasirox treatment was continued until the levels decreased to <500 ng/mL. LIC was estimated using the R2 MRI technique (FerriScan®; Resonance Health, Perth, Australia; reference range, 0.17–1.8 mg/g dry tissue) before and after deferasirox treatment. The plasma of the patients was frozen and sent to Asahikawa Medical University, and NTBI levels (averages of healthy donors: males, 0.206±0.091; females, 0.212±0.095 μmol/L) were measured as previously described. LFTs were periodically performed and compared before and after deferasirox treatment; these included aspartate aminotransferase (AST; reference range, 7–38 IU/L), alanine aminotransferase (ALT; reference range, 4–34 IU/L), lactate dehydrogenase (LDH; reference range, 119–229 IU/L), gamma-glutamyl transpeptidase (γ-GTP; reference range, 10–47 IU/L), and alkaline phosphatase (ALP; reference range, 103–335 IU/L). We also monitored serum creatinine (reference range, 0.50–0.80 mg/dL) levels and considered deferasirox cessation or dose reduction if the creatinine levels increased over the baseline levels. We obtained data on the number of RBC units that had been transfused since the initial diagnosis of underlying hematological disorders from the blood bank of the Japanese Red Cross Nagoya First Hospital and from the institutions where the patients had been transfused. Patients who had current symptoms or signs of chronic graft-versus-host disease (GVHD) were diagnosed as having active chronic GVHD.

This study was approved by the Japanese Red Cross Nagoya First Hospital’s Institutional Review Board. Informed consent was obtained from all individual participants included in the study, in accordance with the Declaration of Helsinki.

Results

Patient characteristics

Patient and transplantation characteristics are summarized in Table 1. The median age at the initiation of deferasirox treatment was 36.5 years (range, 27–39 years); three patients were female and the other one was male. The median time from allogeneic HCT to the initiation of deferasirox treatment was 66 months (range, 27–101 months). Primary diagnoses included aplastic anemia (n = 3) and myelodysplastic syndromes (n = 1). All patients had undergone bone marrow transplantation from an unrelated donor after a myeloablative conditioning regimen. Only one patient had received transplantation from a serologically HLA-mismatched (DR1 locus) donor, while others received transplantations from HLA-matched donors. GVHD prophylaxis comprised of a combination of short-term methotrexate and tacrolimus (n = 3) or cyclosporine (n = 1). Two patients had a history of grade II–IV acute GVHD. All patients had active chronic GVHD at the time of initiating deferasirox treatment (extensive type; n = 3, limited type; n = 1), and two patients were receiving
immunosuppressive treatment with oral tacrolimus.

The median number of packed RBC units transfused during the pre- and post-HCT periods was 126 (range, 100–140 units) and 12 units (range, 8–48 units), respectively, and that transfused during the total period was 147 units (range, 128–150 units). All patients were transfusion-independent at the initiation of deferasirox treatment. None had any evidence of viral hepatitis. No patients had distinctive clinical heart failure, which was evaluated by echocardiography or measurement of brain natriuretic peptide, at the time of initiating deferasirox treatment (data not shown).

Table 1. Clinical features and outcome of deferasirox treatment for iron overload after allogeneic HCT

| Patient characteristics and clinical features | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|-----------------------------------------------|-----------|-----------|-----------|-----------|
| **Age/sex**                                  | 36/Female | 37/Female | 27/Female | 39/Male   |
| **Diagnosis**                                | AA        | AA        | AA        | MDS       |
| **Time since HCT, months**                   | 79        | 101       | 53        | 27        |
| **Conditioning regimen**                     | CY 200 mg/kg | CY 200 mg/kg | CY 200 mg/kg | CY 120 mg/kg |
|                                               | + TBI 5 Gy | + TLI 5 Gy | + TLI 5 Gy | + TBI 12 Gy |
| **Donor**                                    | Unrelated | Unrelated | Unrelated | Unrelated |
| **Graft source**                             | BM        | BM        | BM        | BM        |
| **HLA disparity**                            | Match     | Match     | Mismatch  | Match     |
| **GVHD prophylaxis**                         | sMTX+Tac  | sMTX+CsA  | sMTX+Tac  | sMTX+Tac  |
| **Acute GVHD**                               | None      | None      | Grade I   | Grade II  |
| **Chronic GVHD**                             | Extensive | Extensive | Extensive | Limited   |
| **Immunosuppressants during DFX treatment**   | None      | None      | Tac       | Tac       |
| **RBC transfusion from diagnosis, units**    | 150       | 148       | 146       | 128       |
| **DFX treatment**                            |           |           |           |           |
| **Dose, mg/kg**                              | 10        | 20→10     | 10        | 10→4     |
| **Duration, months**                         | 24        | 34        | 16        | 23        |
| **Data at DFX treatment initiation**         |           |           |           |           |
| **Ferritin, ng/mL**                          | 10500     | 8530      | 3720      | 3740      |
| **LIC, mg/g dry tissue**                     | 12.8      | >43.0     | 36.4      | 9.6       |
| **NTBI, μmol/L**                             | 2.09      | 0.89      | 1.12      | 1.40      |
| **AST, IU/L**                                | 108       | 65        | 37        | 47        |
| **ALT, IU/L**                                | 116       | 53        | 34        | 93        |
| **LDH, IU/L**                                | 204       | 180       | 157       | 208       |
| **γ-GTP, IU/L**                              | 51        | 36        | 24        | 102       |
| **ALP, IU/L**                                | 421       | 261       | 210       | 307       |
| **Creatinine, mg/dL**                        | 0.54      | 0.70      | 0.57      | 0.68      |
| **Hemoglobin, g/dL**                         | 14.6      | 14.1      | 14.1      | 15.7      |
| **Data after DFX treatment**                 |           |           |           |           |
| **Ferritin, ng/mL**                          | 1220      | 6840      | 2344      | 775       |
| **LIC, mg/g dry tissue**                     | 2.8       | 42.3      | 12.0      | 3.6       |
| **NTBI, μmol/L**                             | 0.81      | 1.54      | 0.82      | 0.64      |
| **AST, IU/L**                                | 21        | 28        | 24        | 19        |
| **ALT, IU/L**                                | 29        | 32        | 21        | 17        |
| **LDH, IU/L**                                | 269       | 180       | 156       | 189       |
| **γ-GTP, IU/L**                              | 36        | 26        | 25        | 123       |
| **ALP, IU/L**                                | 670       | 301       | 266       | 312       |
| **Creatinine, mg/dL**                        | 0.87      | 0.88      | 0.63      | 0.84      |
| **Hemoglobin, g/dL**                         | 14.0      | 14.5      | 13.3      | 16.4      |

HCT, hematopoietic cell transplantation; AA, aplastic anemia; MDS, myelodysplastic syndromes; CY, cyclophosphamide; TLI, total lymphoid irradiation; TBI, total body irradiation; BM, bone marrow; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; sMTX, short-term methotrexate; Tac, tacrolimus; CsA, cyclosporine A; DFX, deferasirox; RBC, red blood cell; LIC, liver iron concentration; NTBI, non-transferrin-bound iron; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase
Efficacy of deferasirox

Changes in the various examination data before and after deferasirox treatment are summarized in Table 1, and a representative clinical course is shown in Figure 1. The median duration of deferasirox treatment was 23.5 months (range, 16–34 months). All patients experienced a decrease in serum ferritin levels; the median serum ferritin level decreased from 6135 (range, 3720–10500 ng/mL) to 1782 ng/mL (range, 775–6840 ng/mL) (Figure 2a). LIC also decreased in all patients from a median of 24.6 (range, 9.6–43.0 mg/g) to 7.8 mg/g (range, 2.8–42.3 mg/g) (Figure 2b). NTBI levels decreased in three patients and did not decrease in one (patient 2) who had high serum ferritin level and LIC even after deferasirox treatment (Figure 2c). AST and ALT levels decreased from a median of 56 (range, 37–108 IU/L) to 23 IU/L (range, 19–28 IU/L) and from a median of 73 (range, 34–116 IU/L) to 25 IU/L (range, 17–32 IU/L), respectively; they both normalized in all patients (Figure 2d and e).

Deferasirox treatment did not exacerbate chronic GVHD in four patients. Two patients on immunosuppressant therapy had achieved dose reduction (patient 3) or cessation (patient 4) of tacrolimus, respectively.

Toxicities of deferasirox

All four patients experienced an increase in serum creatinine levels, and the median creatinine level increased from 0.58 (range, 0.54–0.70 mg/dL) to 0.86 mg/dL (range, 0.63–0.88 mg/dL) (Figure 2f). In case of one patient (patient 4), serum creatinine levels increased from 0.68 to 1.21 mg/dL at six months after the initiation of deferasirox treatment, which required the cessation of the drug. After two months, his creatinine levels recovered, and deferasirox was subsequently reinitiated with a reduction in dose from 10 to 4 mg/kg/day, without any further treatment interruptions. This patient achieved an effective reduction in serum ferritin levels (from 3740 to 775 ng/mL), LIC (from 9.6 to 3.6 mg/g), and NTBI levels (from 1.40 to 0.64 µmol/L).

There were no other distinct side-effects, such as gastrointestinal disturbances, skin rash, liver dysfunction, or complications related to visual and auditory senses, during deferasirox treatment.

Discussion

There have been limited studies concerning treatment with deferasirox for iron overload after allogeneic HCT. In a prospective study on the management of iron overload in allogeneic HCT survivors, Majhail et al reported that deferasirox decreased serum ferritin levels and LIC after six months of treatment in three patients.11 In a retrospective study of deferasirox with or without phlebotomy in 23 allogeneic HCT survivors, Sivgin et al reported significant decreases in serum ferritin and ALT levels.12 Our study, even with the small number of patients, suggested that low-dose deferasirox treatment appeared to be well-tolerated and effective in adult allogeneic HCT survivors with iron overload. This efficacy was demonstrated by decreases in not only serum ferritin levels but also in LIC and NTBI levels. Moreover, the decrease in the iron overload.
Deferasirox at a dose of 20–30 mg/kg/day has been recommended for regularly transfused patients, and 20 or 30 mg/kg/day deferasirox had been prescribed for allogeneic HCT survivors. In this study, as all patients were RBC transfusion-independent, three patients received an initial dose of 10 mg/kg/day; in case of the other patient (patient 2), the dose was reduced from 20 to 10 mg/kg/day early in the course of the treatment based on the decision of her physician, not due to adverse effects. Treatment with 10 mg/kg/day deferasirox effectively reduced the iron burden; furthermore, 4 mg/kg/day deferasirox was also effective in one patient (patient 4). Two clinical prospective studies have recently demonstrated the efficacy and safety of deferasirox treatment for allogeneic HCT survivors. Vallejo et al reported that deferasirox treatment for a median 45.7 weeks significantly reduced serum ferritin and LIC level in the overall population. In this study, dose increase was required in only 16.7% of the patients. Jaekel et al also reported a steady decline in serum ferritin after a median of 330.5 days of deferasirox treatment at a median dose of 7.5 mg/kg/day. Taken together, these results suggested the efficacy of low-dose deferasirox treatment for allogeneic HCT survivors with iron overload.

Gastrointestinal disturbances and rashes are reportedly the most common adverse events in patients treated with deferasirox. In our study, these were not observed; one of the causes for this could be the low doses of deferasirox. Mild and non-progressive increases in serum creatinine levels also have been reported in 36%–38% patients treated with deferasirox. Recent studies of deferasirox treatment after allogeneic HCT also reported that the most common adverse event

Figure 2. Changes in (a) serum ferritin, (b) LIC, (c) NTBI, (d) AST, (e) ALT, and (f) serum creatinine after deferasirox treatment for iron overload in allogeneic HCT survivors.

DFX, deferasirox; LIC, liver iron concentration; NTBI, non-transferrin-bound iron; AST, aspartate aminotransferase; ALT, alanine aminotransferase
was increased serum creatinine. In our study, all patients showed an increase in serum creatinine levels despite the fact that lower deferasirox doses were used, and one patient required deferasirox cessation and dose reduction later. Two patients were being treated with a calcineurin inhibitor, which can also trigger renal dysfunction, for chronic GVHD. The combination of deferasirox with the inhibitor may have synergistically worked in increasing the risk of renal dysfunction. The safety and feasibility of their concurrent use thus requires further evaluation.

In allogeneic HCT survivors, although there was a moderate correlation between the serum ferritin level and number of transfused RBC units, many confounding factors can also be related to ferritin overestimation. Therefore, iron burden estimation based on the serum ferritin levels is not completely appropriate in allogeneic HCT recipients. In addition, other diagnostic testing, such as measuring LIC or NTBI, has not yet been easily available in clinical practice. Therefore, further studies are warranted to determine which patients have true iron overload and will benefit from iron chelation therapy after allogeneic HCT.

Iron overload can contribute to the etiology of liver dysfunction, but it can also mimic the exacerbation of hepatic GVHD; this may result in an unnecessary continuation or intensification of immunosuppressive therapy. Elevated pre-transplant serum ferritin levels have been reported to exacerbate acute GVHD, but there have been no studies on the relationship between iron overload in post-transplantation and in chronic GVHD. One patient in this study (patient 1) underwent a liver biopsy before the initiation of deferasirox treatment; the biopsy demonstrated hemosiderosis and hepatic GVHD. Her liver dysfunction resolved with a decrease in serum ferritin levels, LIC, and NTBI levels (Figure 1). Deferasirox may improve the liver dysfunction caused by iron overload that coexists with hepatic GVHD.

Phlebotomy is a safe, effective treatment for iron overload among children with thalassemia who have undergone allogeneic HCT. Previous studies also have reported on the safety and feasibility of phlebotomy for adult allogeneic HCT survivors with iron overload. There have however been no prospective trials comparing deferasirox with phlebotomy for the treatment of iron overload after allogeneic HCT; therefore, further studies are warranted.

In conclusion, although only a small number of patients were retrospectively analyzed in this study, our study indicated that low-dose deferasirox treatment might be effective alternative for allogeneic HCT survivors with iron overload. Further studies are warranted to confirm the safety and efficacy of deferasirox, to determine optimal therapeutic objectives, and to make a comparison with phlebotomy.

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Authorship

TG and KM designed the study. TG performed the study, analyzed the data and wrote the paper. KI, KS, and YK contributed the measurement of NTBI. SK, NK, EY, DK, AS, SK, YO, and MI collected the data and performed the study.

Conflict of interest disclosure

KI and YK received research funding from Shino-Test Corporation for a collaborative research project with Shino-Test Corporation. YK also received research funding from Novartis Pharma K. K. The remaining authors declare no competing financial interests.

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