Successful treatment with deferasirox in a patient with secondary hemochromatosis following allogeneic stem cell transplantation for acute lymphoblastic leukemia

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A 41-year-old Japanese man with Philadelphia chromosome-positive acute lymphoblastic leukemia received allogeneic hematopoietic stem cell transplantation (allo-HSCT) from a human leukocyte antigen (HLA)-matched unrelated donor at molecular complete remission. Although bone marrow engraftment was successful, he required frequent red blood cell transfusions due to pure red cell aplasia following transplantation. He developed a high ferritinemia (4960 ng/ml) and secondary hemochromatosis and was treated with deferasirox for iron overload following allo-HSCT. After 10 months of iron chelation therapy, the serum ferritin level decreased to 575 ng/ml, serum aminotransferases returned to normal values, and magnetic resonance imaging revealed improvements in abnormal findings in the liver. Liver dysfunction after allo-HSCT was initially considered to be chronic graft-versus-host disease but actually occurred due to hepatic hemochromatosis. These results suggested that iron-chelating therapy with deferasirox is useful for patients presenting with iron overload following allo-HSCT. (Journal of Hematopoietic Cell Transplantation Vol. 1 No. 1; 33–36, 2012)

Iron overload is a relatively common complication induced by serial red blood cell (RBC) transfusions in patients with chronic anemia and/or hematologic malignancies. Recent studies have suggested that pretransplant iron overload is an important predictor of outcome in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT).1 Other studies suggest that posttransplant iron overload is also a prognostic factor in these patients.2 The oral iron chelator, deferasirox, is widely used for the treatment of transfusional iron overload.3 The present report describes a case of a patient with posttransplant iron overload who was successfully treated with deferasirox, resulting in a decrease in serum ferritin level and improvement of hepatic hemochromatosis.

A 41-year-old Japanese man was diagnosed with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in December 2001. He received chemotherapy combined with imatinib and obtained a hematological complete remission (CR). After several courses of consolidation chemotherapy, he underwent allo-HSCT from a human leukocyte antigen (HLA)-matched unrelated donor in August 2002. There was a minor ABO incompatibility (donor: O, recipient: A). Molecular CR, as assessed by reverse-transcriptase polymerase chain reaction, was obtained at transplantation. The conditioning regimen consisted of thiotepa (200 mg/m² for 2 days), cyclophosphamide (2,250 mg/m² for 2 days), and total body irradiation (12.5 Gy in five fractions). He received prophylaxis against graft-versus-host disease (GVHD) with short-term methotrexate (10 mg/m² on day 1, and 7 mg/m² on days 3 and 6) and tacrolimus (0.03 mg/kg as a continuous infusion). The bone marrow engraftment was successful, and complete chimerism was confirmed on day 19 following allo-HSCT. He developed grade I acute GVHD on day 12, but symptoms improved by day 22. The patient was discharged on day 76 without acute GVHD.

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The patient developed pure red cell aplasia (PRCA) by day 107 and received a total of 82 Japanese units of RBC transfusion from transplantation until resolution of PRCA on day 253. He was initiated on iron-chelating therapy with deferoxamine (500 mg/day, subcutaneous injection) for transfusion-related iron overload (serum ferritin level 5100 ng/ml) from day 148 to 253. The last RBC transfusion was on day 253 after transplantation, and serum ferritin was 2200 ng/ml at that time. Tacrolimus was tapered and discontinued on day 84, as the patient had no signs of GVHD. His aminotransferase levels continued to gradually increase, but following the introduction of iron-chelating therapy with deferoxamine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels decreased from 125 and 212 U/L to 30 and 35 U/L, respectively. However, they increased again after cessation of iron-chelating therapy without any signs of underlying chronic GVHD.

In October 2007 (62 months after allo-HSCT), the patient’s serum ferritin level was 4960 ng/ml, serum AST level was 103 U/L, and serum ALT level was 197 U/L. He was not receiving any immunosuppressive medications or medications to treat liver dysfunction (e.g., ursodeoxycholic acid or stronger neo-minophagen C) at that point. He was diagnosed with secondary hemochromatosis on the basis of elevated serum ferritin level and abnormal findings on magnetic resonance imaging (MRI) of the liver and spleen (Fig. 1). Hepatitis viruses and/or use of any hepatotoxic drugs were excluded by laboratory testing and clinical history. Liver dysfunction due to chronic GVHD was not suggested because of the absence of characteristic findings (e.g., sicca syndrome, skin lesions). Although liver biopsy was recommended, the patient refused to undergo this procedure.

Once-daily oral deferasirox was initiated at a dose of 20 mg/kg/day (initial dose: 10 mg/kg) in November 2008 (73 months after allo-HSCT). His serum ferritin level decreased to 575 ng/ml, AST level decreased to 31 U/L and ALT level decreased to 36 U/L by November 2009 (12 months after iron-chelating therapy). Abdominal MRI in November 2009 (85 months after allo-HSCT) revealed improvement of hepatic hemochromatosis after treatment (Fig. 1). Although transient elevation of serum creatinine was seen, no other adverse reaction was detected during deferasirox treatment. The patient remains in remission for Ph+ ALL and has been free of iron overload and liver dysfunction for 2 years despite

Figure. 1. Clinical course
T1-weighted magnetic resonance image (MRI) shows decreased signal in the liver and spleen, a finding that is consistent with iron overload. Following iron-chelating therapy, MRI-based abnormalities improve in the liver but not in the spleen.
the discontinuation of iron-chelating therapy in October 2009 (84 months after allo-HSCT).

Transfusion-related iron overload occurs in 30% of allo-HSCT recipients and increases the risk of infection, sinusoidal obstructive syndrome, and hepatic dysfunction after transplantation. Kaloyannidis et al. reported that desferrioxamine administration after allo-HSCT may improve disease-free survival. Although there are relatively few reports indicating that the oral iron chelator, deferasirox, is useful for transfusional iron overload following allo-HSCT, the present patient was successfully treated with deferasirox, resulting in a decrease in serum ferritin levels and a decrease in hepatic iron overload evaluated by serum aminotransferase levels and MRI. In the present patient, elevation of serum ferritin after discontinuation of RBC transfusion suggests that treatment with deferoxamine was insufficient to protect against transfusional iron overload and/or increased gastrointestinal absorption of iron. Liver dysfunction after allo-HSCT was initially considered to be due to chronic GVHD in this case, but subsequent data suggested that hepatic hemochromatosis was the true cause. Kamble et al. reported that iron overload can be mistaken for GVHD exacerbation, resulting in unnecessary continuation or intensification of immunosuppressive therapy and reported that routine screening with serum ferritin and the evaluation of hepatic iron overload with MRI can identify a subgroup of patients who may benefit from oral chelating agents. Recently, Majhail et al. described a prospective study of iron overload and subsequent treatment in 147 allo-HSCT recipients who survived beyond 1 year after transplantation. They reported that deferasirox may be a safe and effective alternative for allo-HSCT survivors with iron overload who cannot undergo phlebotomy.

Iron chelation with phlebotomy or deferoxamine has long been used for the management of iron overload. Phlebotomy is a simple and effective approach to remove excessive tissue iron. However, its use is limited to patients with good graft function and venous access, and patients treated via this strategy may require erythropoietin support. The use of deferoxamine in the HSCT patients is complicated by the very short half-life of this drug, thereby requiring frequent and/or prolonged infusions. In addition, the ability of deferoxamine to release iron to bacteria and fungi is thought to be problematic in patients with underlying immunodeficiency. Deferasirox may be a useful treatment modality in these patients but can also be associated with adverse effects, such as gastrointestinal events, skin rash, and renal dysfunction. Thus, its use requires a careful consideration of the appropriate indications for the drug, identification of appropriate candidates to receive this agent, and a therapeutic strategy to prevent or address drug-related adverse effects.

In conclusion, routine screening of serum ferritin and evaluation of hepatic iron overload with MRI may be useful to identify patients who may benefit from oral chelating therapy. Further study of deferasirox in a larger patient population is required to definitively determine its utility for the control posttransplant iron overload.

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Authors’ contributions

AN wrote the manuscript; AN, MT, TT, and MK collected data; AM, YI and HK reviewed the manuscript.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

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