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LETTER TO THE EDITOR

Efficacy and safety of oral deferasirox treatment for transfusional iron overload in pure red cell aplasia patients after allogeneic stem cell transplantation

Ryo Shimizu[1,2] · Masahiro Takeuchi[1] · Emiko Sakaida[1] · Chikako Ohwada[1] · Masako Toyosaki[3] · Shinichiro Machida[3] · Makoto Onizuka[3] · Katsuhiro Shono[4] · Masahiro Onoda[4] · Takeshi Saito[5] · Shingo Yano[5] · Masatsugu Tanaka[6,7] · Shin Fujisawa[6] · Takehiko Mori[8] · Kensuke Usuki[9] · Satoshi Takahashi[10] · Heiwa Kanamori[7] · Chiaki Nakaseko[1,11] · Shinichiro Okamoto[8]

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Dear Editor,

Pure red cell aplasia (PRCA) is a major complication after major ABO-incompatible allogeneic hematopoietic stem cell transplantation (allo-SCT), and the incidence rate was reported as 7.5% [1–4]. In general, patients with PRCA require repeated red blood cell (RBC) transfusions, which results in iron overload and organ dysfunction [5, 6]. Although iron-chelating therapy with deferasirox is a treatment option for iron overload, the tolerability and outcome of deferasirox in patients with PRCA after allo-SCT are unclear. Therefore, we conducted a retrospective multicenter study to evaluate the safety and efficacy of deferasirox.

We enrolled 313 patients who underwent major and bidirectional ABO-incompatible allo-SCT from 2008 to 2012, and 23 patients (7.3%) developed PRCA (Supplementary Tables S1 and S2). The median follow-up period of surviving patients with PRCA was 25 months (range 6–65). The overall survival of these patients was not significantly lower than that of the control group (Fig. 1a, $P = 0.96$). Of these, 10 received deferasirox (Supplementary Table S3). The median initial dose was 8.0 mg/kg/day, which is lower than the recommended initial dose (20 mg/kg/day) (Fig. 1b). The median maintenance dose and duration were 11.8 mg/kg/day and 162 days, respectively. With careful monitoring, all except one could maintain and escalate the dose of deferasirox after administration. At the time of the last RBC transfusion, the median serum ferritin levels in deferasirox-treated patients significantly improved compared with those in untreated patients (1566 vs. 2739 ng/mL; $P = 0.037$, Fig. 1c). In the deferasirox group, the value of serum ferritin was significantly decreased with the treatment (median − 768.1 ng/mL; $P = 0.047$, Fig. 1d).

Three patients developed organ dysfunctions due to iron overload, two had liver dysfunction, and one had multi-organ dysfunction including liver, heart, and hematopoietic

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✉ Masahiro Takeuchi
m-takeuchi@faculty.chiba-u.jp

1 Department of Hematology, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba 260-8677, Japan

2 Department of Hematology, Asahi General Hospital, Asahi, Japan

3 Department of Hematology and Oncology, School of Medicine, Tokai University, Isehara, Japan

4 Department of Internal Medicine, Chiba Aoba Municipal Hospital, Chiba, Japan

5 Division of Clinical Oncology and Hematology, Jikei University School of Medicine, Tokyo, Japan

6 Department of Hematology, Yokohama City University Medical Center, Yokohama, Japan

7 Department of Hematology, Kanagawa Cancer Center, Yokohama, Japan

8 Division of Hematology, Department of Medicine, School of Medicine, Keio University, Tokyo, Japan

9 Department of Hematology, NTT Medical Center, Tokyo, Japan

10 Division of Molecular Therapy, The Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

11 Department of Hematology, School of Medicine, International University of Health and Welfare, Narita, Japan

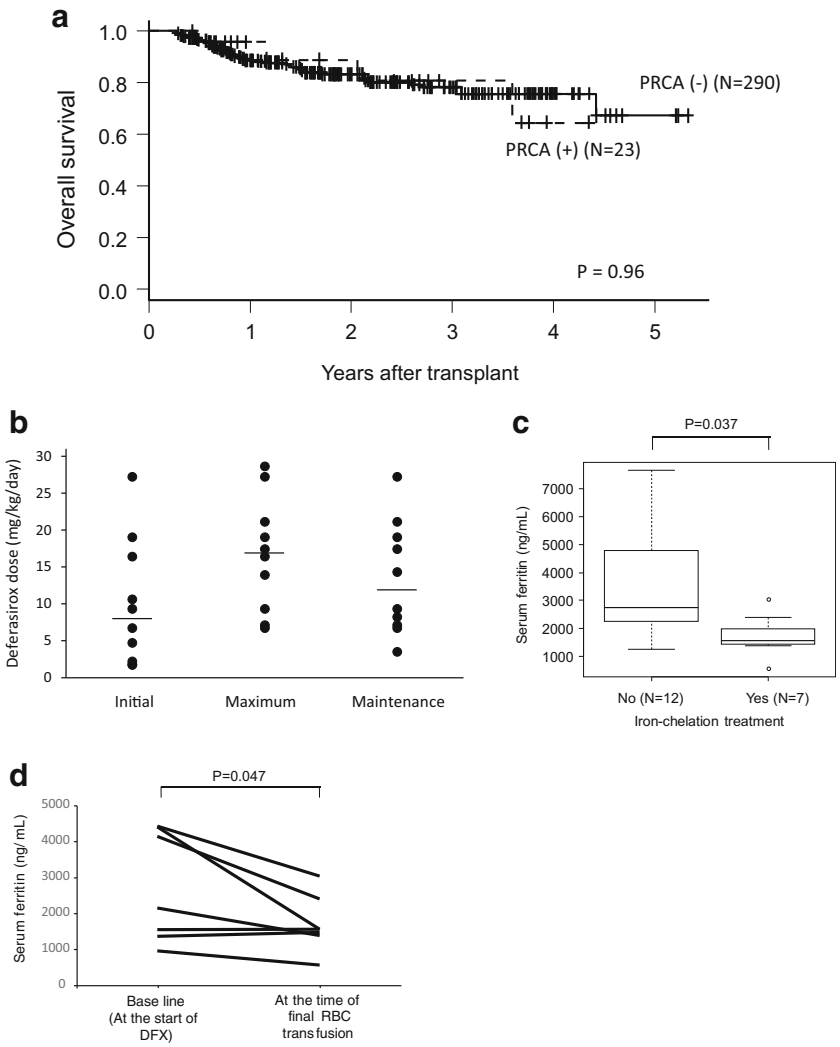

Fig. 1 Survival and deferasirox treatment in patients with pure red cell aplasia after allogeneic hematopoietic stem cell transplantation. **a** The overall survival for patients with and without pure red cell aplasia (PRCA). At 2 years after transplant, the overall survival was 88.6% (95% CI 60.7–97.1%) for the PRCA group and 83.1% (95%CI 77.5–87.4%) for the non-PRCA group ($P = 0.96$). **b** The median dose of deferasirox in patients with PRCA after allogeneic stem cell transplantation. The median of the initial dose, maximum dose, and maintenance dose of deferasirox were 8.0, 16.9, and 11.8 mg/kg/day, respectively. **c** Serum ferritin levels of patients at the final red blood cell transfusion with and without deferasirox treatment. **d** Serum ferritin levels of patients administered deferasirox, at the beginning of the deferasirox and the final transfusion

disturbance. While two continued deferasirox until improvement of organ dysfunction, the other discontinued because of adverse events. Six of 10 patients who received deferasirox developed mild to moderate adverse events: elevation of the serum creatinine level in 3, mild gastrointestinal symptoms in two, and grade 3 skin rash in one. Although two patients discontinued deferasirox treatment due to adverse events, the others continued with or without dose reduction.

The safety profile of deferasirox was similar to previous experiences of allo-SCT recipients [7–9]. Skin rash and elevation of serum creatinine levels were major adverse events occurring with dose dependence [10]. From these findings, low-dose administration of deferasirox is recommended to prevent discontinuation due to adverse events.

To the best of our knowledge, this is the first retrospective study of the use of deferasirox in patients with PRCA after allo-SCT. Low-dose administration of deferasirox is safe and feasible in patients with PRCA after allo-SCT. We suggest that the continuous administration of deferasirox resulted in a negative iron balance and the improvement of organ dysfunctions. Most patients with PRCA after allo-SCT spontaneously resolve and can discontinue RBC transfusion someday. Thus, even if patients can only take a lower dose of deferasirox, we anticipate an improvement of iron overload by continuing for an extended period.

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Author contributions R.S, M.T., and C.N. designed the research. R.S. and M.T. collected and analyzed patients' clinical data and performed statistical analysis. R.S., M.T., E.S., C.O., M.T., S.M., M.O., K.S., M.O., T.S., S.Y., M.T. S.F., T.M., K.U., S.T., H.K., C.N., and S.O. were responsible for patient care and stem cell transplantation. R.S., M.T., E.S., and C.N. wrote the manuscript. All authors reviewed the draft manuscript and approved the final version of the manuscript for submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethical committee of the Graduate School of Medicine, Chiba University, Chiba, Japan (accession no. 564). This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained in the form of opt-out on the website.

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