original research report

T2* MRI changes in the heart and liver of ex-thalassemic patients after hematopoietic stem cell transplantation

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BACKGROUND: Non-invasive methods like MRI-based techniques have been considered recently for assessment of liver and heart status in patients with thalassemia major (TM). The purpose of this study is to examine the alterations of hepatic and myocardial T2* MRI values in TM patients after hematopoietic stem cell transplantation (HSCT) just before starting chelation therapy.

PROCEDURE: The study included fifty-two TM patients with mean age of 7.6 years who were referred to our center for HSCT. Before HSCT, patients underwent liver biopsy to determine fibrosis stage based on the Lucarelli classification. Hepatic and myocardial T2* values before and 6 months after transplantation were measured and analyzed.

RESULTS: There was not a statistically significant increase in myocardial T2* values after HSCT (p-value = 0.35). Hepatic T2* values significantly decreased after HSCT (p-value <0.001), showing the liver status has been worsened. In subgroup analysis, post-HSCT hepatic T2* values (adjusted for baseline values) were significantly higher in patients with graft-versus-host disease (GvHD) compared to non-GvHD patients (p-value = 0.04).

CONCLUSIONS: The issue of iron overload is still remained as the main problem in ex-thalassemic patients after HSCT. We found T2* MRI technique a quite beneficial method for following up the patients after transplantation. Obviously, planning large controlled trials associated with liver biopsy results after transplantation is required.

KEYWORDS: Thalassemia major; T2* MRI; Hematopoietic stem cell transplantation

INTRODUCTION

Thalassemia major (TM) is still one of the most prevalent hematologic inherited disorders.[1,2] Nowadays, considering the high probability of event-free survival (80%) reported for HSCT,[3] it has been settled as the only curative treatment for TM patients.[4] The aim of treatment with HSCT is to rectify the ineffective endogenous erythropoiesis with allogenic substitute.[3] One of the main problems for ex-thalassemic patients after transplantation is excessive iron overload which may results in different tissue injuries in future mainly in the heart and liver.[5–12] On the other hand, this iron overload has probably affected many outcomes which graft-versus-host disease (GvHD) occurrence is one of them. While some articles expressed that iron overload raises the rate of graft-versus-host disease (GvHD) occurrence in ex-thalassemic patients,[5,6] it has been recently showed that iron overload can reduce the incidence of GvHD[7] by its immunosuppressive effect.[8–12] Although non-invasive methods like measuring serum ferritin level has been utilized as a detector for iron overload, ferritin values can be easily influenced by simple events such as inflammation and infections.[13] It is worthy to mention that

liver biopsy is not desired after a successful transplantation because of being invasive, inconvenience and having complications. On the other hand, it should not be neglected that cardiac biopsy is completely dangerous and impossible. All the above discussed reasons resulted in utilizing MRI-based methods[14–17] in which T2* MRI technique has earned more attention than the other methods because of its high efficiency in estimation of iron overload either in the heart or liver.[18–21] However, there are few studies investigating the application of MRI-based methods for assessment of iron overload post-HSCT.[22,23]

This study attempted to investigate the status of iron overload in the heart and liver in ex-thalassemic patients, using noninvasive method after HSCT and immediately before starting chelation therapy. In this study, we aimed to find answers to the following questions: Is the situation getting worse or better? What is the role of GvHD on this state?

PATIENTS AND METHODS

Patient characteristics

The target population was HSCT candidates with TM (aged < 15) who were referred to the Hematology-Oncology Research Center and Stem Cell Transplantation (HORCSCT) from March 2009 to April 2012. The Institutional Review Board and Ethics Committee approved the study protocol which was in accordance with the principles of the Declaration of Helsinki. The parents of children with TM signed an informed consent to participate in the study based on the exclusion and inclusion criteria. The diagnosis of TM had already been confirmed in the referral medical centers by hemoglobin electrophoresis or mutation analysis. Patients with cardiac disease, AIDS, HBV, HCV or progressive cirrhosis were excluded from the study. It is worthy to mention that all patients underwent echocardiography and EKG. Moreover, a cardiac consultation was arranged before transplantation. For categorizing the patients and determination of Lucarelli classification, liver biopsy samples were taken from all patients. No patient underwent liver biopsy after HSCT due to invasiveness and intolerability. Regarding the iron overload in the heart and liver, T2* MRI values and serum ferritin level were measured in all patients before HSCT and 6 months after transplantation just before starting iron chelation therapy.

Transplant preparation and procedure

Patients and their relatives were checked to find HLA-A, HLA-B, and HLA-*DR* matched donors by low-resolution molecular typing. The sources of progenitors were peripheral blood stem cell (PBSC), bone marrow stem cell (BMSC), or cord blood. Marrow was harvested from iliac crests when the donor was under general anesthesia and directly infused into the recipients without further manipulation. The peripheral blood stem cells were mobilized by granulocyte colony-stimulating factor (G-CSF), using 5 μg/kg for 4 days.

Conditioning regimens and GvHD prophylaxis

The conditioning regimens in class I-II thalassemia patients included busulfan (3.5 mg/kg/day from day −8 for four consecutive days), cyclophosphamide (50 mg/kg/day IV from day −4 for four consecutive days) and rabbit antithymocyte globulin (Thymoglobin, 1.25 mg/kg IV two consecutive days before transplantation). All class III patients with thalassemia received conditioning regimen of busulfan (3.5 mg/kg/day from day −9 for four consecutive days) and cyclophosphamide (40 mg/kg/day IV from day −5 for four consecutive days).

Regarding GvHD prophylaxis, cyclosporine (1.5 mg/kg daily, IV, on day −2, and then 3 mg/kg on day +7) in combination with a short-course treatment with methotrexate (10 mg/m^2 on days +1 and 6 mg/m^2 on days +3,+6, and +11) was administered for patients. Cyclosporine continued orally for 6–7 months after HSCT and discontinued in the absence of GvHD.

Supportive care

Regarding supportive care, all the patients were hospitalized in protective isolation with hyperalimentation. Acyclovir and fluconazole were given as prophylaxis for the prevention of viral or fungal infections and trimethoprim–sulfamethoxazole was administrated to prevent Pneumocystis jiroveci. To check CMV infections, quantitative PCR or CMV PP65 antigen assay was performed twice weekly. All patients received phenytoin as prophylaxis for busulfan- induced seizures.

Follow-up

Based on Short Tandem Repeat (STR) typing, hematopoietic chimerism monitoring was performed on days 15, 30, 60, 90, and 180 after HSCT. After discharge, all patients were followed up in the post- HSCT clinic weekly during the first month, then every 2 weeks by day 100 after HSCT, and thereafter it was conducted on an individual case basis.