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A Prospective Study of Iron Overload Management in Allogeneic Hematopoietic Cell Transplantation Survivors

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We report the results of a single-center, prospective evaluation for iron overload and subsequent treatment in 147 adult allogeneic hematopoietic cell transplantation (HCT) recipients who survived beyond 1 year after transplantation. Patients were screened by serum ferritin level; those with ferritin >1000 ng/mL underwent liver R2 magnetic resonance imaging to estimate liver iron concentration (LIC; normal ≤1.8 mg/g). Patients with significant iron overload (defined as LIC ≥5 mg/g), based on physician and patient preference, were offered observation only, phlebotomy, or enrollment in a pilot study of deferasirox. Sixteen patients had significant iron overload. Their median age was 51 years (range, 29-64 years), and they had survived a median of 21 months (range, 12-114 months). All 16 patients were transfusion-independent at study enrollment. Five patients received no treatment (median LIC, 6.4 mg/g; range, 5.1-28.3 mg/g), 8 underwent phlebotomy (median LIC, 13.1 mg/g; range, 7.8-43.0 mg/g), and 3 received daily deferasirox 20 mg/kg/day orally for 6 months (LIC, 6.3, 9.0, and 19.9 mg/g). Two patients had abnormal liver function tests, and 1 patient each had cirrhosis and unexplained congestive heart failure; all 4 of these patients underwent phlebotomy. Follow-up serum ferritin concentrations decreased spontaneously in 4 patients in the observation-only arm. Phlebotomy was generally well tolerated. Deferasirox also was well tolerated and led to decreased LIC after 6 months of therapy in all 3 patients. Phlebotomy is feasible in the majority of allogeneic HCT recipients who have survived for ≥1 year after HCT and have significant iron overload. Although the number of subjects is small, deferasirox may be a safe and effective alternative for allogeneic HCT survivors with iron overload who cannot undergo phlebotomy.

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INTRODUCTION

Transfusion-related iron overload occurs in 30%-60% of allogeneic hematopoietic cell transplantation (HCT) recipients [1-3]. Post-HCT iron overload has been associated with such early complications as infections and hepatic sinusoidal obstruction syndrome [2,4,5]. Iron overload increases the risk of hepatic fibrosis and cardiomyopathy in long-term pediatric transplantation survivors with thalassemia who become transfusion- independent after HCT but continue to have a high body iron burden [6,7]. The natural history of iron overload and its impact on late organ dysfunction in adult long-term HCT survivors remain unclear. Based on experience in children with hemoglobinopathies, adult allogeneic HCT survivors with persistently elevated body iron levels may be at risk for developing hepatic and cardiac dysfunction.

The management of posttransplantation iron overload in adult HCT survivors has not been well studied. Although long-term follow-up guidelines recommend screening with serum ferritin measurements at 1 year post-HCT [8], there are no clear-cut criteria for when and how to treat iron overload. Treatment options include phlebotomy and iron chelation therapy. Phlebotomy can be considered the treatment of choice because of its safety and efficacy, but it may not be feasible in patients with coexisting anemia. Deferoxamine is also feasible, relatively safe, and efficacious for treating post-HCT iron overload, but it is

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inconvenient to administer [2]. Deferasirox is a recently introduced oral iron chelator with efficacy similar to deferoxamine [9,10]; its safety profile in HCT recipients has not been established, however. To determine the optimal management of iron overload after transplantation, we prospectively evaluated the management of iron overload in allogeneic HCT recipients who had survived for 1 year or more after transplantation.

METHODS

Patients

Adult allogeneic HCT recipients (aged ≥18 years) who had survived ≥1 year after HCT at the University of Minnesota Blood and Marrow Transplant Program were prospectively evaluated for iron overload (Figure 1). Patients were evaluated primarily for a pilot study to assess the feasibility and safety of deferasirox in this population. Patients were initially screened with serum ferritin measurements; those with serum ferritin level >1000 ng/mL underwent R2 magnetic resonance imaging (MRI) of the liver to estimate liver iron concentration (LIC; normal range, 0.17-1.8 mg/g dry tissue) [11-13]. Patients with significant iron overload, defined as LIC ≥5 mg/g on liver R2 MRI, were assigned to the observation arm or the treatment arm based on physician and patient preference. Among patients assigned to the treatment arm, phlebotomy was the treatment of choice; patients who could not undergo phlebotomy because of anemia (hemoglobin <11 g/dL) or refused phlebotomy were given the option to enroll in a pilot study to evaluate the feasibility of deferasirox in HCT survivors.

The study protocol was approved by the Institutional Review Board, and all participants provided informed consent before enrollment. The deferasirox pilot study was registered at www.clinicaltrials.gov (NCT00602446).

Adult recipients of both myeloablative and nonmyeloablative conditioning regimens were eligible. Patients with any contraindication for MRI and those with relapse or progression of underlying disease were excluded. Additional eligibility criteria for patients considered for the deferasirox pilot study included: (1) Eastern Cooperative Oncology Group performance status of 0-2 and life expectancy ≥6 months, (2) adequate renal function (serum creatinine ≤ 1.6 mg/dL and creatinine clearance of ≥ 60 mL/min on 2 occasions within 30 days of enrollment), (3) adequate hematopoietic reserve (absolute neutrophil count $\geq 1.0 \times 10^9$/L, hemoglobin ≥8.0 g/dL, and platelet count $\geq 50 \times 10^9$/L), (4) adequate hepatic function (serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT] <5 times the upper limit of normal), (5) absence of active infection or uncontrolled graft-versus-host disease (GVHD), (6) not pregnant or breast feeding and able to use contraception, and (7) absence of deferasirox therapy within 12 months of study enrollment.

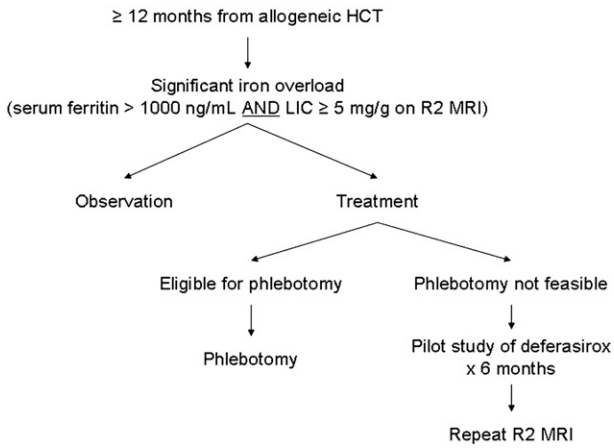

Figure 1. Treatment schema. Assignment to observation or treatment was determined by physician and patient preference. Patients in the treatment arm could enroll in a pilot study of deferasirox if they could not undergo phlebotomy because of anemia (hemoglobin <11 g/dL) or they refused phlebotomy.

A total of 147 patients were screened for this study between January 2008 and August 2009 (Figure 2). This number included 56 patients who had been enrolled in an earlier study evaluating the prevalence of iron overload in adult allogeneic HCT survivors [1]. Of the 147 patients, 124 were screen failures; these included patients with a serum ferritin concentration of ≤1000 ng/mL and patients in whom serum ferritin level was not measured because of patient or transplant physician refusal for study participation. In addition, patients who had received <10 red blood cell (RBC) transfusions since the diagnosis of their hematologic disorder were not asked to participate in this study. Twenty-three patients had a serum ferritin concentration >1000 ng/mL and all of these patients had iron overload (LIC >1.8 mg/g on liver R2 MRI), 16 with significant iron overload (LIC ≥5 mg/g).

Study Evaluations

MRI measurement of LIC was based on the imaging of proton transverse relaxation rates (R2) within the liver using a 1.5-T MRI machine (MAGNETOM Avanto; Siemens, Malvern, PA). This noninvasive R2 MRI technique (FerriScan; Resonance Health, Perth, Australia) has proven highly sensitive and specific for estimating LIC in studies comparing it with liver biopsy and biomagnetic liver susceptometry using a superconducting quantum interference device [11-13].

After baseline ferritin measurement and liver MRI, patients in the observation and phlebotomy arms underwent follow-up evaluation at the discretion of their transplant physician. Patients enrolled in the