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Increased Hepatic Iron Content Predicts Poor Survival in Patients With Iron Overload Who Underwent Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Transfusional iron overload remains a serious problem in alloHSCT setting. Liver is among the most common organs that iron accumulate. The degree of hepatic iron content might be associated with poorer survival in alloHSCT recipients.

Aim: Iron overload results in increased infection, venous-oclusive disease and hepatic dysfunction in allogeneic hematopoietic stem cell transplant (alloHSCT) recipients. Liver is one of the most common sites of iron overload. **Patients and Methods:** A total of 50 alloHSCT recipients that underwent liver biopsy in Erciyes Stem Cell Transplantation Hospital, Erciyes University, between 2004 and 2011 were enrolled in the study. The liver biopsy specimens have been obtained from the archives of Erciyes University, Department of Pathology and stainned for iron content. **Results:** The mean age was found 34 ± 11 years. For median overall survival (OS); 53 months (min-max: 41-65) in patients with grade 0, 55 months (min-max: 47-64) in patients with grade 1, in patients with grade 2 patients 25.4 months (11.5-39.4), grade 3 patients 29.3 months (min-max: 12.3-46.3) and grade 4 patients 2.6 months (min-max: 2.0-3.3). Overall survival was correlated with the degree of liver iron content and it was statistically significant in Kaplan-Meier analysis ($P < .001$). Disease-free survival was found (DFS); grade 0 patients 47.1 months (min-max: 32.0-62.0), grade 1 patients 36.9 months (min-max: 21.0-65.0), grade 2 patients 23.5 months (min-max: 12.0-59.0), grade 3 patients 27.4 months (min-max: 5.3-59.3) and grade 4 patients 2.6 months (min-max: 2.0-3.0). For DFS; it was negatively correlated with the degree of liver iron content nevertheless; it was not was statistically significant in Kaplan-Meier analysis ($P = .093$).Hepatic iron overload might be associated with poor survival in patients with transfusional iron overload that underwent alloHSCT. **Conclusion:** Hepatic iron content might be associated with poorer prognosis in patients with iron overload that underwent alloHSCT.

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Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is considered as a curative treatment for many patients with malignant and nonmalignant hematological disorders. alloHSCT recipients are at risk of developing transfusional iron overload (IO) because they have large red blood cell transfusions during the initial treatment of their disease and during the period of allogeneic transplantation. Iron overload is considered to be a common complication of Hematopoietic Stem Cell Transplantation (HCT), and published consensus guidelines recommend screening for it in HCT survivors.[1] Iron overload has been reported to have a relationship with liver dysfunction and to increase the risk of infections late after alloHSCT.[2-5] However, the IO on survivors after allogeneic HCT, and its clinical effect needs larger prospective studies to establish reliable data.

The estimation of iron overload is currently on the basis of serum ferritin levels, but in hematopoietic stem cell transplantation (HSCT) recipients, many confounding factors such as

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inflammation, ineffective erythropoiesis, and liver disease can be related to ferritin overestimation.[6,7] In the present literature, nontransferrin-bound iron, which is increased during IO, is considered to be a marker of iron toxicity.[8-13]

Complications related to IO might increase transplant-related mortality in allogeneic stem cell transplant patients.[14] These complications are post-transplant liver dysfunction,[15] mucositis,[16] bacterial, fungal, and viral infections,[17-19] acute graft versus host disease (GVHD),[20,21] and sinusoidal obstruction syndrome (SOS).[7,22] IO might also present an exacerbation of hepatic GVHD after alloHSCT,[23] so a liver biopsy might be useful for differential diagnosis in these circumstances. In many studies, iron has been shown to be important in innate and adaptive immune responses in patients with hereditary hemochromatosis and nontransplant transfusional IO. The underlying mechanism is that IO can lead to defective chemotaxis and phagocytosis by neutrophils and macrophages, decreased natural killer cell activity, and a decrease in the number and altered function of CD41-positive ($CD41^+$) and CD81 T^+ cells.[24,25] We studied the liver iron content (LIC) of alloHSCT recipients who underwent transcutaneous liver biopsy because of established diagnosis of post-transplant complications such as GVHD, liver IO, and SOS.

Patients and Methods

A total of 50 alloHSCT recipients with transfusional IO who underwent liver biopsy were enrolled in the study. The file records were evaluated retrospectively. All patient data in the pre- and post-transplant period including abnormality in liver function test, veno-occlusive disease, sepsis, cytomegalovirus or other viral infections, acute respiratory distress syndrome, GVHD, transplant-related mortality, disease-free survival (DFS), and overall survival (OS). Platelet engraftment was defined as: the day on which platelet count exceeded 20,000/mm^3 and neutrophil engraftment; or the day on which neutrophil count exceeded 500/mm^3 for at least 3 days consecutively. All patient data were obtained from the patient files by the same physicians. The study was approved by the ethics committee of Erciyes University (approval number: 2014/226).

The Definition of LIC

The paraffin-embedded liver tissue samples were taken from the archives of Department of Pathology. The sections were stained with Prussian blue for hemosiderin-stainable granules. Samples were evaluated by the same pathologist. Histologic grades or scores were assigned for iron (score, 0-4). Many iron-grading systems are now available and have been reviewed in detail.[26,27] Grade 1 has been reported for any quantitative amount of iron granule deposition within scattered hepatocytes in the acinar zone. Grade 2 was reported for granules present at × 100 and present in >50% of hepatocytes; grade 3, to discrete granules seen at × 20 in zone 1 or panacinar, with a zonal gradient across the acini; and grade 4, to blue granules seen by the naked eye and microscopically present within hepatocytes, with little or no gradient present. Scattered Kupffer cells; sinusoidal, portal tract connective tissue; and bile duct epithelial staining, unless involving hepatocytes, were considered nonspecific and scored as either 0 or 1.

Statistical Analysis

The Shapiro–Wilk test was used, and histogram and q-q plots were examined to assess data normality. To compare the differences among groups, the Kruskal–Wallis H test was applied. The Siegel–Castellan test was performed for multiple comparisons. Data were expressed as frequencies and percentages, mean and standard deviation or median and interquartile range. To compute the survival probabilities of LIC grades and compare each other, Kaplan–Meier curves were constructed and a Log-rank test was applied. To identify the risk factors in survival, Cox proportional hazards regression analyses were applied. For each factor, hazard ratios (HRs) were calculated with 95% confidence intervals (CIs) for OS and for DFS. To identify the independent risk factors, factors that were significant at the $P < .10$ level in univariate analysis were taken into a multiple model and backward elimination was applied using Wald statistics. Analyses were done using SPSS Statistics version 22.0 (IBM Corp, Armonk, NY) software considering $P < .05$ statistically significant.

Results

A total of 50 patients who underwent alloHSCT were enrolled in the study. Of the patients, 32 (64%) were male and 18 were female (36%). The diagnosis of the patients were acute myeloid leukemia in 24 patients (48%), acute lymphoblastic leukemia in 14 patients

Table 1 Characteristics of the Patients

Variable	Results, %
Mean Age, Years	34 ± 11
Sex, Male/Female, n (%)	32 (64.0)/18 (36.0)
Infection, No/Yes, n (%)	8 (16.0)/42 (84.0)
Infection Type, n (%)	
Bacterial	14 (32.6)
Fungal	7 (16.3)
Viral	4 (9.3)
Bacterial and fungal	6 (14.0)
Bacterial and viral	6 (14.0)
Bacterial, fungal, and viral	6 (14.0)
Median Platelet Engraftment (Range), Days	12.00 (10.00-14.25)
Median Neutrophil Engraftment (Range), Days	14.00 (13.00-16.00)
Sex, Match/Mismatch, n (%)	26 (58.0)/21 (42.0)
Diagnosis, n (%)	
AML	24 (48.0)
ALL	14 (28.0)
Other	12 (24.0)
Time to Transplant, <12 months/≥12 months, n (%)	39 (78.0)/11 (22.0)
Conditioning Regimen, n (%)	
Cy/Bu	33 (66.0)
Cy/TBI	10 (20.0)
Other	7 (14.0)
Myeloablative/Nonmyeloablative, n (%)	43 (86.0)/7 (14.0)
HLA Match, Full Match/Mismatch, n (%)	46 (92.0)/4 (8.0)

Abbreviations: ALL = acute lymphoid leukemia; AML = acute myeloid leukemia; Bu = busulfan; Cy = cyclophosphamide; HLA = human leucocyte antigen; TBI = total body irradiation.