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Impact of Hyperferritinemia on the Outcome of Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation for Lymphoid Malignancies

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A B S T R A C T

Hyperferritinemia has been associated with adverse outcomes after allogeneic hematopoietic cell transplantation (allo-HCT) with myeloablative conditioning. However, its characteristics and impact on the outcome in the reduced-intensity conditioning (RIC) and in the lymphoid malignancy settings are far from clear. The study includes 201 adult patients undergoing allo-HCT with RIC (allo-RIC) for lymphoid malignancies with a median follow-up for survivors of 52 months (range, 3 to 123). Median serum ferritin level at allo-RIC was 379 ng/mL (range, 4 to 10,790). In the multivariate analysis, patients with hyperferritinemia at transplantation (>399 ng/mL) showed lower 4-year overall survival (hazard ratio [HR], 1.8 [95% confidence interval {CI}, 1.2 to 2.8]; $P = .008$), higher nonrelapse mortality (NRM) (HR, 1.8 [95% CI, 1.1 to 3.2]; $P = .03$), and higher infection-related mortality (HR, 2.3 [95% CI, 1.1 to 4.8]; $P = .02$) than patients without hyperferritinemia. Neutrophil and platelet engraftment and 100-day NRM were similar between both groups. The adverse outcome associated with hyperferritinemia seemed higher in patients without major comorbidities and was not influenced by the elevation of acute phase reactants. Our results indicate that high ferritin levels at HCT are associated with an adverse outcome after allo-RIC in patients with lymphoid malignancies.

INTRODUCTION

The negative effect of hyperferritinemia on the outcome of allogeneic hematopoietic cell transplantation (allo-HCT) has been increasingly identified during the last years. Serum ferritin has been widely used as a surrogate marker of iron overload, and elevated levels have been associated with an adverse outcome of the procedure [1-4]. Nevertheless, the impact of hyperferritinemia on nonrelapse mortality (NRM) seems clearer in the myeloablative conditioning setting than in the reduced-intensity conditioning (RIC) setting, where the few studies available show contradictory results regarding its effect on NRM in these patients [5-7]. Hyperferritinemia has been demonstrated in patients with lymphoma and myeloma, and its negative impact has been suggested in the autologous HCT setting [8]. Nevertheless, the influence of hyperferritinemia has only been evaluated in myeloid malignancies or in heterogeneous populations of allo-HCT recipients but not to our knowledge, exclusively in patients with lymphoid malignancies. In an attempt to reach a better understanding of the impact of hyperferritinemia before allo-HCT on the outcome of the procedure, we conducted a study in a highly homogeneous population of allo-RIC recipients with lymphoid malignancies with a long follow-up.

METHODS

Patients

The study included all consecutive adult patients with lymphoproliferative disorders who received an allo-RIC in three transplantation centers in Spain (Hospital de la Santa Creu i Sant Pau, Barcelona; Hospital Clínic, Barcelona; and Hospital Universitario, Salamanca) between February 1998 and November 2008. Lymphoproliferative disorders included were high-grade non-Hodgkin lymphoma, low-grade non-Hodgkin lymphoma, Hodgkin lymphoma, chronic lymphocytic leukemia, and multiple myeloma. Of the 258 patients who underwent transplantation during the study period, 201 (78%) had available information on ferritin, transferrin saturation, acute-phase reactants, and albumin levels at HCT and were included in the study. The transplantation protocols were approved by national ethics committees, and patients gave written informed consent for their inclusion in each protocol.

Conditioning Regimen, Graft-versus-Host Disease Prophylaxis, and Supportive Care

All patients were treated with the same protocol, published elsewhere [9]. RIC instead of myeloablative conditioning was preferred in patients with at least one of the following: age >50 years, previous autologous HCT, or severe comorbidities. The conditioning regimen for all patients included fludarabine (150 mg/m^2) in combination with melphalan (70 to 140 mg/m^2). Graft-versus-host disease (GVHD) prophylaxis included cyclosporine A plus short-course methotrexate (days +1, +3, +6, and +11 at 10 mg/m^2, followed by folinic acid rescue) or cyclosporine A plus mycophenolate mofetil 1 g twice daily or cyclosporine A with or without steroids in a few patients receiving antithymocyte globulin. T cell depletion was used in patients receiving a transplantation from human leukocyte antigen (HLA) mismatched donors.

Acyclovir, fluconazole, and quinolones (ciprofloxacin or norfloxacin) were administered as infectious prophylaxis. Cytomegalovirus infection screening (using antigenemia pp65 before 2003 and RT-PCR after 2003) for

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Table 1
Patients Characteristics

Characteristics	All Patients (n = 201)	Ferritin >399 ng/mL (n = 94)	Ferritin ≤399 ng/mL (n = 107)	*P* Value
Median age, y (range)	51 (19-67)	50 (20-67)	51 (19-65)	.6
Gender male, n (%)	120 (60)	65 (69)	55 (51)	.07
Female donor to male recipient	54 (27)	27 (29)	27 (25)	.6
Underlying disease, n (%)				
Hodgkin lymphoma	45 (22)	25 (27)	20 (19)	.2
NHL	68 (34)	35 (37)	33 (31)	—
CLL	33 (16)	18 (19)	15 (14)	—
Multiple myeloma	55 (27)	16 (17)	39 (36)	—
Disease status				
CR	59 (29)	23 (24)	36 (34)	.1
PR	105 (52)	47 (50)	58 (54)	—
NR/progressive	37 (18)	24 (25)	13 (12)	—
Advanced disease*	166 (83)	81 (86)	86 (80)	.3
Previous SCT	102 (51)	49 (52)	53 (50)	.5
Time from diagnosis to HCT (>12months)	174 (87)	87 (89)	87 (81)	.2
Recipient/donor CMV serology, n (%)				
Recipient and donor negative	21 (10)	10 (9)	11 (10)	.8
Recipient and/or donor positive	180 (90)	84 (89)	96 (90)	-
Donor type, n (%)				
HLA identical sibling	164 (82)	74 (79)	90 (84)	1.0
Alternative (VUD or MM related)	37 (18)	21 (21)	16 (16)	—
T cell depletion,† n (%)	30 (15)	15 (16)	15 (15)	.7
Peripheral blood stem cells, n (%)	191 (95)	87 (93)	104 (97)	.7
GVHD prophylaxis, n (%)				
CsA-MTX	143 (71)	67 (71)	76 (71)	1.0
CsA-MMF	47 (23)	20 (21)	27 (25)	.6
Other	11 (5)	7 (7)	4 (4)	.7

NHL indicates non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; CsA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil; CMV, cytomegalovirus; VUD, volunteer unrelated donor; MM, HLA mismatch; CR, complete remission; PR, partial remission; NR, nonresponse.

* Advanced disease was considered following the European Group for Blood and Marrow Transplantation criteria [14].

† T cell depletion includes patients receiving antithymocyte globulin (n = 22) or alemtuzumab (n = 8) as part of the conditioning.

guiding preemptive therapy was performed as described elsewhere in detail [10]. Galactomannan Platelia® assay (Bio-Rad Laboratories, Hercules, CA) in blood samples was routinely performed since 2003 [11]. Patients included in the study did not receive phlebotomies or chelation therapy before transplantation.

Iron Parameters Determination and Laboratory Analysis

All laboratory tests performed within the 30 days before transplantation were included in the analysis. Ferritin, transferrin saturation, and albumin determinations were performed using standard procedures in each center's laboratory. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were the acute-phase reactants considered for the analysis. High ESR and CRP were considered above 10 mm/h for men and 15 mm/h for women and 10 mg/L, respectively. When both markers were available, CRP was preferred because it appears to be a more accurate inflammation marker than ESR [12]. Hepatic or cardiac magnetic resonance imaging or liver biopsy to determine iron liver content were not routinely performed in any of the centers in allo-HCT recipients.

Study Definitions, Endpoints, and Statistical Analysis

Hyperferritinemia was defined as ferritin levels above the value with higher sensitivity and specificity for overall survival (OS) determined by the analysis of the receiver-operating characteristic curves. NRM was defined as the time from day 0 of the transplantation to death from any cause but relapse. Infection-related mortality (IRM) was defined as patients whose main cause of death was considered to be a clinical and/or microbiological documented infection. To exclude the influence of inflammation in a single ferritin determination, we also included CRP/ESR and albumin determinations in the same time point as positive and negative inflammation markers, respectively.

Patients were classified into four risk groups for 4-year NRM according to the ferritin and CRP/ESR levels: group 1, ferritin ≤399 ng/mL and low CRP/ESR; group 2, ferritin ≤399 ng/mL and high CRP/ESR; group 3, ferritin >399 ng/mL and low CRP/ESR; and group 4, ferritin >399 ng/mL and high CRP/ESR. The HCT comorbidity index was calculated as originally defined [13], and advanced risk was defined following the European Group for Blood and Marrow Transplantation criteria [14].

The primary endpoint of the study was to determine the impact of high ferritin levels before transplantation on OS and NRM after allo-RIC. The secondary endpoint was to describe the characteristics of patients with high ferritin levels at HCT.

The probability of OS was estimated from the time of transplantation using Kaplan-Meier curves [15] and compared using log-rank tests. Cumulative incidence of NRM and IRM was estimated by using competitive risk method with the Gray test. Comparison of characteristics between patients with high and low ferritin levels was performed using 2 × 2 tables made by means of chi-square or Fisher exact t-tests for dichotomic variables and by means of t-test for continuous variables. Univariate Cox regression analysis was used to estimate risk factors of NRM, OS, and relapse. Variables tested in the univariate Cox regression analysis for transplantation outcomes appear in Table 2. Multivariate analysis was performed taking into account the competing risk structure [16,17], including those variables with a significance level of $P \leq .1$ in the univariate Cox regression analysis.

All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL). The exception was the cumulative incidence analyses, which were carried out with NCSS 2004 (Number Cruncher Statistical System, Kaysville, UT).

RESULTS

Patient Characteristics

Pretransplantation characteristics and outcome (4-year NRM and 4-year OS) were similar between the 201 patients included in the study and the 57 patients in the cohort not included due to missing data on iron parameters (Supplementary Table 1). Pretransplantation characteristics of the patients in the study are summarized in Table 1. One hundred two patients had received a previous autologous HCT. Among patients ≤50 years (n = 101), RIC was chosen because of pervious autologous HCT (n = 73) and severe comorbidities (n = 28). Median follow-up for survivors was 52 months (range, 3 to 123).

Ferritin Levels at HCT

The median ferritin level at transplantation was 379 ng/mL (range, 4 to 10,790). Quartile distribution of ferritin levels was as follows: quartile 1, 4 to 129; quartile 2, 130 to 379; quartile 3, 380 to 851; and quartile 4, 852 to 10,790. Forty-four patients (22%) had ferritin levels >1,000 ng/mL at