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Prognostic Value of the Hematopoietic Cell Transplantation Comorbidity Index for Patients Undergoing Reduced-Intensity Conditioning Cord Blood Transplantation

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A B S T R A C T

The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) has been validated as a tool for evaluating the risk of treatment-related mortality (TRM) in HLA-matched sibling and matched unrelated donor bone marrow and peripheral blood stem cell transplantation patients. However, the role of the HCT-CI after cord blood transplantation (CBT) has not been fully investigated. In this analysis, we sought to evaluate the predictive value of the HCT-CI in patients undergoing reduced-intensity conditioning (RIC) CBT. Between 2006 and 2013, HCT-CI scores were prospectively tabulated for patients with hematologic malignancies sequentially enrolled on multicenter RIC CBT studies coordinated by the Fred Hutchinson Cancer Research Center: 151 patients with acute myeloid leukemia/myelodysplastic syndrome (n = 101), chronic myeloid leukemia (n = 3), acute lymphocytic leukemia (n = 24), non-Hodgkin lymphoma (n = 8), Hodgkin lymphoma (n = 3), and other hematologic malignancies (n = 12) underwent RIC CBT and were included. Two patients received a single CBT and the remaining 149 received a double CBT. All patients received cyclosporine and mycophenolate mofetil for graft-versus-host disease prophylaxis. Median HCT-CI for the whole group was 3 (range, 0 to 8). Using the HCT-CI categories of low (0), intermediate (1 or 2), and high risk (>3), there was no significant difference in TRM between the 3 groups. However, when the patients were divided into 2 groups, HCT-CI ≤ 3 or > 3, the incidence of TRM at 3 years after transplantation was 26% (95% confidence interval [CI], 17 to 36) in the HCT-CI ≤ 3 group versus 50% (95% CI, 30 to 67) in the HCT-CI > 3 group ($P = .01$). Overall survival for patients with HCT-CI ≤ 3 was 40% (95% CI, 27 to 51) versus 29% in patients with HCT-CI >3 (95% CI, 12 to 48) ($P = .08$). Our study demonstrates that HCT-CI score > 3 is associated with an increased risk of TRM at 3 years after transplantation in patients undergoing RIC CBT. Because of the significant risk of TRM in patients with HCT-CI > 3 compared with risk for those with HCT-CI ≤ 3, patients with an HCT-CI score >3 should be counseled before undergoing RIC CBT.

INTRODUCTION

Three major factors influence treatment related mortality (TRM) and overall survival (OS) after hematopoietic stem cell transplantation (HCT): the patient's disease, the type of transplantation procedure and donor, and the patient's risk profile, which includes age, performance status, and comorbidities. Quantifying the risk of TRM in each individual patient is challenging, but it is essential for pretransplantation counseling. To this end, the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) was developed to capture comorbidities that are frequently seen at the time of the pretransplantation work-up [1]. The index has been shown to predict the probability of TRM and OS in allogeneic HCT recipients.

Although some authors have questioned its universal applicability, the HCT-CI has been validated with varying degrees of predictive ability in a number of independent adult and pediatric cohorts [2-8]. Several studies however, have claimed that the HCT-CI has no predictive value in their patients and others have found it necessary to divide their cohorts into binary groups to show positive predictive value of the score [9-13]. Most of the prior studies have restricted their analyses to marrow and peripheral blood stem cell transplant recipients, excluding cord blood (CB) transplantation (CBT)

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patients from their analysis to better mimic the study population included in the initial Sorror manuscript, which excluded CBT patients.

At many centers, CBT is frequently being used in patients with no sibling or suitable matched unrelated donors and in patients who need an urgent transplantation procedure. CBT is known to have inherent risks, such as preengraftment syndrome and increased infection-related mortality, as well as benefits, such as less severe chronic graft-versus-host disease, resulting in shorter duration of steroid exposure [14,15]. Herein, we sought to evaluate the usefulness of the HCT-CI as a clinical tool to determine risk of TRM and OS in patients undergoing CBT.

METHODS

Transplantation Procedures

This study includes 151 consecutive CBT patients who were enrolled on 1 single-center and 2 multicenter reduced-intensity conditioning (RIC) CBT protocols coordinated by the Fred Hutchinson Cancer Research Center between 2006 and 2013. Patients received a double CBT if a suitable single CB graft could not be found, as determined by protocol criteria. Selected CB units were required to be matched to the recipient at 4 of the 6 HLA loci on the basis of intermediate-resolution typing at HLA-A and -B and allele-level typing for HLA-DRB1. RIC conditioning consisted of either fludarabine (Flu) 40 mg/m^2 i.v. daily for 5 days, a single dose of cyclophosphamide (Cy) 50 mg/kg i.v., and a single fraction of total body irradiation (TBI) 200 cGy or Flu 30 mg/m^2 i.v. daily for 5 days, treosulfan (Treo) 14 g/m^2 i.v. daily for 3 days, and a single fraction of TBI 200 cGy. Patients receiving the Flu/Cy/TBI conditioning regimen who received either no previous chemotherapy or no chemotherapy in the 3 months preceding CBT were given equine antithymocyte globulin (ATGAM, Pfizer, New York, NY) at a dose of 30 mg/kg recipient body weight i.v. once daily on days –6, –5, and –4, for a total dose of 90 mg/kg (n = 8; stopped in 2006) or a greater dose of TBI at 300 cGy (n = 21; starting in 2006). Decisions regarding the RIC treatment protocol were determined by protocol inclusion criteria and the clinical judgment of the treating clinician. All patients received prophylactic immunosuppressive therapy for the prevention of graft-versus-host disease consisting of cyclosporine A and mycophenolate mofetil. The patient's underlying disease was categorized as standard or high risk on the basis of previously described criteria [16].

Patients and Comorbidity Scoring System

Pretransplantation HCT-CI scores were tabulated according to the original HCT-CI for all patients on the above-mentioned studies [1,17]. Patients were excluded if they were younger than 16 years of age. Patients had HCT-CI scores collected prospectively at the time of enrollment as part of the eligibility criteria for their respective clinical trial; no scores were modified for the purpose of this analysis. Patients >50 years of age with HCT-CI scores ≥ 5 were purposely excluded from the Treo/Flu/TBI trial based on protocol exclusion criteria and were placed on the Flu/Cy/TBI trial. Written informed consent was obtained from all patients before registration. The study was approved by the institutional review board of each participating center and was conducted in accordance with the Declaration of Helsinki.

Statistical Methods

The primary endpoints were TRM and OS at 3 years after CBT. Probability of OS was calculated using the method of Kaplan and Meier. Probability of TRM was summarized using cumulative incidence estimates. The cause-specific hazards ratios of failure for each endpoint was compared between the original HCT-CI using 3 groups: low (score = 0), intermediate (1 and 2), and high (≥3) using Cox regression as previously reported [1]. We then pursed an additional HCT-CI risk stratification by dividing the larger group into 2 groups at the median of 3. Based on this, scores of 0 to 3 were restratified as low risk and scores 4 and above as high-risk, and data were reanalyzed. These models were adjusted for patient age, disease risk, Karnofsky performance status, year of transplantation, conditioning regimen, and cytomegalovirus (CMV) serostatus. All statistical analyses were performed using STATA 13.0 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. The median age at transplantation for 79 males and 72 females was 54 years (range, 16 to 73). Eighty-two patients (54%) received Flu/Cy/TBI and 69 (46%) received Treo/Flu/TBI pretransplantation conditioning. All patients received a double CB graft, except for 2 patients (3%) who received a single CB graft. The most common diagnoses were acute myeloid leukemia (n = 79), myelodysplastic syndrome (n = 22), acute lymphocytic leukemia (n = 24), non-Hodgkin lymphoma (n = 8), and Hodgkin lymphoma (n = 3).

Table 1
Patient Characteristics

Patient Characteristics	Total (n = 151)	HCT-CI ≤ 3 (n = 109)	HCT-CI > 3 (n = 42)	*P* Value
Female	72 (48)	54 (50)	18 (43)	.47
Male	79 (52)	55 (50)	24 (57)	
Age, median (range), yr	54 (16-73)	53 (16-73)	55 (21-70)	.25
Race				.35
Caucasian	94 (62)	65 (60)	29 (69)	
Non-Caucasian	57 (38)	44 (40)	13 (31)	
CMV serostatus				.08
Positive	100 (66)	77 (71)	23 (55)	
Negative	51 (34)	32 (29)	19 (45)	
Disease type				.63
AML	79 (52)	54 (49)	25 (60)	
MDS	22 (15)	18 (17)	4 (9)	
CML	3 (1.9)	3 (3)	0 (0)	
ALL	24 (16)	16 (15)	8 (19)	
NHL	8 (5)	6 (5)	2 (5)	
Hodgkin disease	3 (2)	3 (3)	0 (0)	
Other	12 (8)	9(8)	3 (7)	
Disease risk				
High	68 (45)	47 (43)	21 (50.0)	.47
Low	83 (55)	62 (57)	21 (50.0)	
Conditioning regimen				.02
Flu/Cy/TBI (200-300cGy)	82 (54)	53 (49)	29 (69)	
Treo/Flu/TBI	69 (46)	56 (51)	13 (31)	
HCT-CI median, range	3 (0-8)	2 (0-3)	5 (4-8)	-

Data presented are n (%) unless otherwise indicated.
AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin lymphoma.