Biology of Blood and Marrow Transplantation

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Clinical Research: Supportive Care

Validation of the Hematopoietic Cell Transplantation–Specific Comorbidity Index in Nonmyeloablative Allogeneic Stem Cell Transplantation

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A B S T R A C T

The Hematopoietic Cell Transplantation (HCT)–Specific Comorbidity Index (HCT-CI) has been extensively studied in myeloablative and reduced-intensity conditioning regimens, with less data available regarding the validity of HCT-CI in nonmyeloablative (NMA) allogeneic transplantation. We conducted a retrospective analysis to evaluate the association between HCT-CI and nonrelapse mortality (NRM) and all-cause mortality (ACM) in patients receiving the total lymphoid irradiation and antithymocyte globulin (TLI/ATG) NMA transplantation preparative regimen. We abstracted demographic and clinical data from consecutive patients, who received allogeneic HCT with the TLI/ATG regimen between January 2008 and September 2014, from the Stanford blood and marrow transplantation database. We conducted univariable and multivariable Cox proportional hazards regression models to evaluate the association between HCT-CI and NRM and ACM. In all, 287 patients were included for analysis. The median age of the patients was 61 (range, 22 to 77) years. The median overall survival was 844 (range, 374 to 1484) days. Most patients had Karnofsky performance score of 90 or above (85%). Fifty-two (18%) patients relapsed within 3 months and 108 (38%) patients relapsed within 1 year, with a median time to relapse of 163 (range, 83 to 366) days. Among the comorbidities in the HCT-CI identified at the time of HCT, reduced pulmonary function was the most common (n = 89), followed by prior history of malignancy (n = 39), psychiatric condition (n = 38), and diabetes (n = 31). Patients with higher HCT-CI scores had higher mortality risks for ACM (hazard ratio [HR], 1.95; 95% confidence interval [CI], 1.22 to 3.14 for HCT-CI score 1 or 2 and HR, 1.85; 95% CI, 1.11 to 3.08 for HCT-CI score ≥ 3, compared with 0, respectively). Among individual HCT-CI variables, diabetes (HR, 2.31; 95% CI, 1.79 to 2.89; P = .003) and prior solid tumors (HR, 1.75; 95% CI, 1.02 to 3.00; P = .043) were associated with a higher risk of ACM. Higher HCT-CI scores were significantly associated with higher risk of death. HCT-CI is a valid tool for predicting ACM in NMA TLI/ATG allogeneic HCT.
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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) after nonmyeloablative (NMA) conditioning is used as a treatment for patients with hematological malignancies who are older or with comorbidities [1,2]. The median age of patients at diagnoses with hematological malignancies ranges from 65 to 70 [3], with older age associated with more comorbidities [4]. Thus, it becomes imperative to look into

the effect of pretransplantation comorbidities on transplantation outcomes after NMA transplantation. In an attempt to improve quantification of the patient's pretransplantation risk profile, Sorror et al. proposed the Hematopoietic Cell Transplantation–Specific Comorbidity Index (HCT-CI) [5-7]. The HCT-CI uses information from more pretransplantation comorbidities than the previously used Charlson comorbidity index [8] and defines 3 risk groups: (1) HCT-CI score of 0 (low risk), (2) HCT-CI scores of 1 or 2 (intermediate risk), and (3) HCT-CI score of 3 (high risk). The HCT-CI was first developed from a single-center retrospective analysis with internal validation. The majority of patients in the original cohort had received myeloablative (MA) preparative regimens, with less than one-third of the total patients receiving an NMA regimen [5]. The HCT-CI was subsequently validated in MA and

reduced-intensity conditioning (RIC) HCT via a prospective trial by Gruppo Italiano Trapianto di Midollo Osseo group [9].

The Stanford bone marrow transplant program pioneered the NMA regimen of total lymphoid irradiation (TLI)/antithymocyte globulin (ATG) [10], which has historically shown a low nonrelapse mortality (NRM) of < 10% as well as a low incidence of grades II to IV acute graft-versus-host disease (GVHD) (10%) [11]. In a prospective randomized trial where TLI/ATG was compared with fludarabine (Flu)/total body irradiation (TBI), there was a significant reduction of cumulative incidence of chronic GVHD at 2 years with the TLI/ATG regimen (Flu/TBI: 40.8 versus TLI/ATG: 17.8%) [12]. Given the HCT-CI was predictive of outcomes with the Flu/TBI NMA regimen, we sought to identify the utility of the HCT-CI in predicting survival in a large cohort of patients receiving the NMA regimen with TLI/ATG conditioning.

METHODS

We conducted analyses of retrospective data collected from consecutive patients undergoing allogeneic HCT at Stanford from January 2008 through September 2014. January 2008 is when the Center of International Blood and Marrow Transplant Registry (CIBMTR) mandated HCT-CI score reporting via the Pre-Transplant Essential Data collection; we included all patients who had TLI/ATG conditioning for allogeneic HCT using GVHD prophylaxis of mycophenolate mofetil and cyclosporine. The HCT-CI score was calculated as described by Sorror et al. [5]. Acute and chronic GVHD were graded via the revised Keystone criteria [13] and the National Institutes of Health Consensus Guidelines, respectively [14].

Our primary outcome measure was NRM 3 months after transplantation. *NRM* was defined as death without relapse of malignancy from date of transplantation; patients were right censored at 3 months. In addition, we examined the following secondary outcomes: (1) NRM over 1 year (patients were right censored at 1 year), (2) *all-cause mortality* (ACM), defined

as death due to any cause, from date of transplantation until date of last follow-up or death, and (3) time to relapse from date of transplantation to date of relapse (patients were right censored at date of last follow-up).

We examined the HCT-CI score as both a continuous variable as well as by 3 categorical groups: 0, 1 to 2, and ≥ 3, based on prior validation studies of the HCT-CI score [5].

Cox proportional hazards regression models were used to determine outcomes. We created a univariable regression model for NRM over 3 months and univariable and multivariable models for NRM over 1 year, ACM, and time to relapse. For 3-month NRM and 1-year NRM, we used a competing-risk model with NRM as the outcome of interest and relapse as a competing risk [15]. For time to relapse, we used a competing risk model with relapse as the outcome of interest and death as a competing risk. A noncompeting risk model was created for ACM. We assessed the proportional hazards assumption and stratified the models by the variables not meeting the proportional hazards assumptions (disease status, diagnosis status, gender, and donor type). The following covariates were included in the multivariable models: age, and transplantation number. Additionally, as exploratory analyses, we conducted multivariable survival models separately for each individual HCT-CI comorbid condition to assess its association with ACM. A 2-sided *P* value less than .05 was considered significant for all tests. Analyses were conducted using R software [16].

RESULTS

Two hundred ninety-nine patients received TLI/ATG conditioning from 2008 to 2014. We excluded 12 patients with missing HCT-CI scores, resulting in 287 patients being included in our analytic cohort (Table 1). The median follow-up time was 2.3 years (range, 1 to 4.1 years). Patients were a median age of 61 (range, 54 to 65) years at transplantation. The Karnofsky performance score was 90% or higher in 85% of the patients. The majority of the patients had acute myeloid leukemia, myelodysplastic syndrome or non-Hodgkin's lymphoma, and two-thirds of the patients were

Table 1
Patient Demographic and Clinical Characteristics

Characteristic	All patients (N = 287)	HCT-CI Score (0) (n = 92)	HCT-CI Score (1-2) (n = 115)	HCT-CI Score (3-7) (n = 80)
Age, median (range), yr	61 (22.0-77.0)	60.5 (22-74)	62 (23-77)	61 (22-76)
Karnofsky performance score, median (range)	90 (70.0-100.0)	90 (70-100)	90 (70-100)	90 (70-100)
Gender				
Female	117 (40.8%)	35 (38%)	42 (36.5%)	40 (50%)
Male	170 (59.2%)	57 (62%)	73 (63.5%)	40 (50%)
Donor				
HLA-matched identical sibling	123 (42.9%)	47 (51.1%)	46 (40%)	30 (37.5%)
URD: identical	110 (38.3%)	30 (32.6%)	44 (38.3%)	36 (45%)
URD: mismatched	53 (18.5%)	15 (16.3%)	25 (21.7%)	13 (16.2%)
HLA-matched other relative	1 (.3%)	0 (0%)	0 (0%)	1 (1.3%)
Disease status				
Noncomplete remission	113 (39.4%)	39 (42.4%)	39 (33.9%)	35 (43.8%)
Complete remission	174 (60.6%)	53 (57.6%)	76 (66.1%)	45 (56.2%)
Diagnosis				
AML	102 (35.5%)	36 (39.1%)	46 (40%)	20 (25%)
MDS	53 (18.5%)	14 (15.2%)	18 (15.7%)	21 (26.2%)
NHL	59 (20.6%)	18 (19.6%)	22 (19.1%)	19 (23.8%)
Other*	73 (25.4%)	24 (26.1%)	29 (25.2%)	20 (25%)
Acute GVHD group				
None	206 (71.8%)	67 (72.8%)	85 (73.9%)	54 (67.5%)
I-II	69 (24.0%)	21 (22.8%)	25 (21.8%)	13 (28.7%)
III-IV	12 (4.2%)	4 (4.3%)	5 (5.3%)	3 (3.7%)
Chronic GVHD				
No	189 (65.9%)	57 (62%)	76 (66.1%)	56 (70%)
Yes	96 (33.4%)	35 (38%)	38 (33%)	23 (28.7%)
Missing	2 (.7%)	0 (0%)	1 (.9%)	1 (1.3%)
Transplantation number				
1	246 (85.7%)	80 (87%)	100 (87%)	66 (82.5%)
2	41 (14.3%)	12 (13%)	15 (13%)	14 (17.5%)
Time to relapse, median (range), d	163 (3-2026)	160 (3-2026)	167 (5-1173)	144 (14-1139)
Survival time, median (range), mo	28.1 (.6-93)	40.1 (1.3-93)	24.4 (.6-85.9)	26.1 (.9-80.9)

Data presented are n (%) unless otherwise indicated.
URD indicates unrelated donor; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma.
* Other diagnosis status includes Hodgkin lymphoma and all leukemia excluding AML.