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Comorbidities, Alcohol Use Disorder, and Age Predict Outcomes after Autologous Hematopoietic Cell Transplantation for Lymphoma

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Autologous hematopoietic cell transplantation (HCT) is a treatment option for many patients diagnosed with lymphoma. The effects of patient-specific factors on outcomes after autologous HCT are not well characterized. Here, we studied a sequential cohort of 754 patients with lymphoma treated with autologous HCT between 2000 and 2010. In multivariate analysis, patient-specific factors that were statistically significantly associated with nonrelapse mortality (NRM) included HCT-specific comorbidity index (HCT-CI) scores ≥ 3 (HR, 1.94; $P = .05$), a history of alcohol use disorder (AUD) (HR, 2.17; $P = .004$), and older age stratified by decade (HR, 1.29; $P = .02$). HCT-CI ≥ 3, a history of AUD, and age > 50 were combined into a composite risk model: NRM and overall mortality rates at 5 years increased from 6% to 30% and 32% to 58%, respectively, in patients with 0 versus all 3 risk factors. The HCT-CI is a valid tool in predicting mortality risks after autologous HCT for lymphoma. AUD and older age exert independent prognostic impact on outcomes. Whether AUD indicates additional organ dysfunction or sociobehavioral abnormality warrants further investigation. The composite model may improve risk stratification before autologous HCT.

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INTRODUCTION

High-dose therapy followed by autologous hematopoietic cell transplantation (HCT) can achieve long-term remission and, in certain settings, cure patients with lymphoma. Lymphoma-specific factors such as disease status and prior treatments are known to affect nonrelapse mortality (NRM) and overall mortality (OM) after autologous HCT [1]. Whether patient-specific factors can contribute to prediction of outcomes after autologous SCT is not well characterized, and there is currently no consensus for including these variables in risk-assessment stratification.

The HCT-specific comorbidity index (HCT-CI) was designed to stratify the risk of NRM in patients undergoing allogeneic HCT for hematologic malignancies [2-4] by synthesizing an array of comorbidities weighted according to diagnosis and severity. A limited number of studies have applied the HCT-CI to relapse-free outcomes after autologous HCT [5-8], and fewer still have examined this tool in patients with lymphoma [5,7,8].

The HCT-CI incorporates measurements of patient organ function, presence of comorbid medical conditions including active infection and a history of separate malignancy, and, to a limited extent, psychiatric disease. Elements of the psychosocial domain including substance abuse are not directly captured. Here, we asked whether the HCT-CI is valid in predicting mortality risks after autologous HCT for lymphoma and whether the index could be augmented by other patient-specific risk factors to design a composite model for decision-making. To this end, we retrospectively analyzed outcomes in a large, sequential cohort of 754 patients with lymphoma treated with autologous HCT between 2000 and 2010.

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METHODS

Study Cohort

The study cohort included all patients with lymphoma who underwent autologous HCT at Fred Hutchinson Cancer Research Center and the Veterans Affairs Puget Sound Health Care System between 2000 and 2010 (N = 817). Data were collected from comprehensive medical record review and institutional databases. Patients given a planned tandem autologous–allogeneic HCT (n = 37), a planned tandem autologous–autologous HCT (n = 22), or diagnosed with Burkitt's lymphoma (n = 4) were excluded from analysis, yielding a final total sample of 754 patients. The Institutional Review Boards of both Fred Hutchinson Cancer Research Center and the Veterans Affairs Puget Sound Health Care System approved data collection and analysis for patients treated at their respective facilities.

Treatment and Definitions

The HCT conditioning regimens were determined by each individual patient's treatment team with consideration of age, comorbidities, diagnosis, remission status, and prior therapies. Conditioning regimens that consisted of only chemotherapy included busulfan, melphalan, and thiotepa or carmustine, etoposide, cytarabine, and melphalan (BEAM), with or without rituximab. Total body irradiation (TBI)-based regimens included TBI combined with cyclophosphamide with or without etoposide. High-dose radiolabeled antibody–based regimens consisted of iodine-131-labeled anti-CD20 antibodies either alone or in combination with cyclophosphamide and etoposide or combined with escalating doses of fludarabine.

HCT-CI scores were calculated by 2 investigators (J.E.V. scored 433 patients; M.L.S. scored 321 patients) according to previously published criteria [2,9]. Inter-rater reliability was evaluated using weighted kappa statistic estimates [10] with standard errors as previously described [9]. In a sample of 32 patients, there was consistent agreement between evaluators with a weighted kappa statistic estimate of .88 (standard error, 06).

Response to chemotherapy was defined as chemosensitive if complete remission or partial remission had been achieved in response to last salvage therapy given before autologous HCT according to standard criteria [11,12]. Lactate dehydrogenase values were recorded and scored as normal or elevated (above the upper limit of normal) according to the respective institutions' laboratory standards. Classification of alcohol use disorder (AUD) was performed according to standard criteria and included self-identification as a current or past alcoholic, engaging in current or prior "heavy" or "binge" drinking, convictions for alcohol-related crimes, or history of rehabilitation for alcoholism [13]. This classification was done retrospectively through comprehensive review of available medical records.

Statistical Methods

Patient characteristics and causes of death were compared using a Fisher's exact test where applicable. Cumulative incidence of NRM was estimated by standard methods [14], with relapse of lymphoma treated as a competing risk. Overall survival (OS) was calculated from the date of autologous HCT using Kaplan-Meier estimates.

Patient-, lymphoma-, and treatment-specific factors were assessed for associations with NRM in univariate analysis. Age was stratified by decade. All factors with a $P < .1$ were entered into a Cox proportional hazard regression model stratified by the institution at which the autologous HCT was performed. Two-sided $P \leq .05$ were considered statistically significant. Patient-specific factors that affected NRM after multivariate analysis were added to generate a composite risk factor score. The multivariate analysis considered age stratified by decade; to fit age into the composite risk factor model the variable was dichotomized and a cutoff > 50 was selected based on optimal separation of outcomes comparing different age cutoff values. The discriminative capacity of age (stratified by decade), AUD, HCT-CI, and the composite model for NRM was evaluated using *c*-statistic estimates [15].

RESULTS

Patient Characteristics

Seven-hundred fifty-four patients met the above criteria and were evaluated in this study, with a median follow-up period of 3.0 years (range, .1 to 13). Patient-specific characteristics are shown in Table 1; characteristics specific to lymphoma and treatment are shown in Supplementary Table 1. The median age at autologous HCT was 53 years (range, 18 to 78). Most patients were white (86%), married (69%), never-smokers (55%), and, at the time of evaluation for autologous HCT, active consumers of alcohol at least occasionally (56%). Eighty-one patients (11%) had a history of AUD. The median HCT-CI was 1 (range, 0 to 9), with 44% of patients having a, HCT-CI ≥ 3.

Table 1
Demographic and Clinical Characteristics of Study Cohort (N = 754)

Patient-Specific Factors	N (%)
Median age, yr (range)	53 (18-78)
Sex	
Male	516 (68)
Female	238 (32)
Race	
White	583 (86)
Other	93 (14)
Unknown	78
Marital status	
Married	512 (69)
Other	230 (31)
Unknown	12
Tobacco use	
Never smoker	418 (55)
Former smoker	229 (30)
Current smoker*	105 (14)
Unknown	2
Tobacco quantity (smokers only)	334 (100)
<15 pack-years	80 (32)
15-30 pack-years	74 (31)
≥30 pack-years	95 (40)
Unknown	85
Alcohol use	
No current use	332 (44)
Current use*	422 (56)
No AUD	673 (89)
AUD	81 (11)
HCT-CI	
Median (range)	1 (0-9)
0	151 (20)
1-2	274 (36)
≥3	328 (44)
LDH	
Normal	495 (67)
Elevated	247 (33)
Unknown	12

LDH indicates lactate dehydrogenase.
* At time of HCT intake.

NRM and Its Predictive Factors

Direct unadjusted comparison of NRM among subgroups identified 3 patient-specific factors associated with worse outcomes (Table 2): HCT-CI ≥ 3 (hazard ratio [HR], 2.38; 95% confidence interval [CI], 1.3 to 4.5; $P = .007$), AUD (HR, 2.85; 95% CI, 1.7 to 4.7; $P < .0001$), and age (HR, 1.27; 95% CI, 1.0 to 1.5; $P = .01$). Race, marital status, use of alcohol concurrent with autologous HCT, and smoking status had no statistically significant correlation with NRM. A history of heavy smoking, quantified as more than 30 total pack-years, showed some suggestion of association with NRM (HR, 1.57; 95% CI, .9 to 2.8; $P = .12$) but did not meet significance statistically.

Multivariate analysis was performed for NRM adjusting for all examined variables significant at the $P < .10$ (overall) level in univariate analysis, including disease status at the time of autologous HCT, conditioning regimen, HCT-CI, age, and history of AUD (Table 2). The patient-specific factors HCT-CI ≥ 3 (HR, 1.94; 95% CI, 1.0 to 3.7; $P = .05$), a history of AUD (HR, 2.17; 95% CI, 1.3 to 3.7; $P = .004$), and age (HR, 1.29; 95% CI, 1.0 to 1.6; $P = .02$) each retained association with NRM (Table 3 and Supplementary Table 1).

The effect of these patient-specific factors on NRM and OS is shown in Figure 1A-C and Figure 2A-C, respectively. Combining HCT-CI with AUD and age into a patient-specific composite risk factor score stratified patients into 3 groups: those with zero risk factors (n = 158, 21%), 1 risk factor (n = 359, 48%), 2 risk factors (n = 206, 27%), and 3 risk factors