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Hematopoietic Cell Transplantation–Specific Comorbidity Index Predicts Morbidity and Mortality in Autologous Stem Cell Transplantation

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A B S T R A C T

The hematopoietic cell transplantation–specific comorbidity index (HCT-CI) score is a useful tool to assess the risk for nonrelapse mortality (NRM) after allogeneic hematopoietic stem cell transplantation. Although the HCT-CI has been investigated in autologous stem cell transplantation (ASCT), its use is limited. To improve on the current use of the HCT-CI score on the morbidity and mortality after ASCT, we assessed the 100-day morbidity defined as orotracheal intubation (OTI), dialysis or shock (vasopressors need), 100-day NRM, early composite morbidity–mortality (combined endpoint that included any previous endpoints), and long-term NRM. We retrospectively reviewed a cohort of 1730 records of adult patients who received an ASCT in Argentinean center's between October 2002 and August 2016. Median follow-up was 1.15 years, and median age was 53 years. Diseases were multiple myeloma (48%), non-Hodgkin lymphoma (27%), and Hodgkin lymphoma (17%); 51% were in complete or partial remission; and 13% received ≥ 3 chemotherapy lines before transplant (heavily pretreated). Early NRM (100-day) was 2.7%, 5.4% required OTI, 4.5% required vasopressors, and 2.1% dialysis, with an early composite morbidity–mortality of 6.8%. Long-term (1 and 3 years) NRM was 4% and 5.2% and overall survival 89% and 77%, respectively. High-risk HCT-CI patients had a significant increase in 100-day NRM compared with intermediate and low risk (6.1% versus 3.4% versus 1.8%, respectively; $P = .002$), OTI (11% versus 6% versus 4%, $P = .001$), shock (8.7% versus 5.8% versus 3%, $P = .001$), early composite morbidity–mortality (13% versus 9 % versus 4.7%, $P < .001$), and long-term NRM (1 year, 7.7% versus 4% versus 3.3%; and 3 years, 10.8% versus 4% versus 4.8%, respectively; $P = .002$). After multivariate analysis these outcomes remained significant: early composite morbidity–mortality (odds ratio [95% confidence interval] compared with low risk: intermediate risk 2.1 [1.3 to 3.5] and high risk 3.3 [1.9 to 5.9]) and NRM (hazard ratio [95% confidence interval] compared with low risk: intermediate risk .97 [.8 to 2.4] and high risk 3.05 [1.3 to 4.5]). No significant impact was observed in overall survival. Other than comorbidities, significant impact

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was observed for heavily pretreated patients, age ≥ 55 years, non-Hodgkin lymphoma, and bendamustine-etoposide-citarabine-melphalan conditioning. We confirmed that the HCT-CI had a significant impact on NRM after ASCT, and these findings are mainly due to early toxicity express as 100-day NRM and the 3 main morbidity outcomes as well as the composite endpoint.

INTRODUCTION

Despite current improvement in supportive care, mortality after hematopoietic stem cell transplantation remains high [1]. Autologous stem cell transplantation (ASCT) is the standard of care for many hematologic malignancies and certain solid tumors [2]. Depending on the diagnosis, this procedure is indicated as the frontline treatment and in other cases as salvage regimens but in all cases as part of the treatment of chemosensitive diseases [3,4]. Although the morbidity and mortality of ASCT is lower than allogeneic transplant, deaths still occurs, mainly because of infectious complications [1].

The hematopoietic cell transplantation–specific comorbidity index (HCT-CI) score, described by Sorror et al. [5], is a useful tool to predict the risk for nonrelapse mortality (NRM) after allogeneic hematopoietic stem cell transplantation and is helpful in the pretransplant clinic to define the intensity of the conditioning regimen. Few studies have been published regarding the impact of this score in ASCT [6-9]. A Center for International Blood and Marrow Transplant Research analysis, including US centers, demonstrated a significant association of the score in long-term NRM after ASCT, but not much evidence has been published about the impact of the score in early post-transplant events [10]. The aim of this article is to validate in a large cohort of recent ASCTs performed in Argentina the impact of HCT-CI score on the mortality after transplant and to analyze the association of the score in early morbidity and mortality endpoints.

METHODS

We retrospectively reviewed a cohort of 1730 medical records of patients (age ≥ 15 years) who received an ASCT in 10 Argentinean centers between October 2002 and August 2016. Median follow-up was 1.15 years, with all patients followed to at least day 100. Variables collected were age, gender, disease, lines of treatment before transplant (heavily pretreated defined as 3 or more), pretransplant status (complete remission, partial remission, or progressive/stable disease), conditioning, and low stem cell cellularity (defined as less than $CD34^+$ 3×10^6/kg). Comorbidities were assessed by HCT-CI score as low risk (score 0), intermediate risk (score 1 to 2), or high risk (score ≥ 3). Study endpoints were 100-day morbidity that included orotracheal intubation (OTI), dialysis or shock (defined as need for vasopressors), 100-day NRM, early composite morbidity–mortality (combined endpoint that included any of the previous endpoints), and long-term NRM (at 1 and 3 years). Secondary endpoint was overall survival (OS) (at 1 and 3 years).

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL) and R version 3.2 (https://r-project.org). In univariate analysis the OS probability was compared using the log-rank statistic and calculated with the Kaplan-Meier method. For relapse and NRM we used Gray's test and analyzed these outcomes using the cumulative incidence method. The competing event for NRM was relapse and for relapse was death without relapse. For OTI, shock, dialysis, and combined early morbidity–mortality we used the chi-square test. For multivariate analysis we use the Cox regression model for OS, Fine-Gray regression for competing event endpoints (NRM, relapse), and the logistic regression for dichotomous variables. We included all factors in the univariate analysis with a $P < .2$. Outcomes were considered to be significant with $P < .05$, whereas a trend was considered with $P = .05$ to 0.1.

RESULTS

Cohort characteristics are listed in Table 1. Median age was 53 years (range, 15 to 74 years), and 58% were male. Prevalent diseases were multiple myeloma (48%), non-Hodgkin lymphoma (27%), and Hodgkin lymphoma (17%); 51% were in complete remission, 46% in partial remission, and 3% in stable/progressive disease; and 46% received 1 chemotherapy line before transplant, 41% received 2 lines, and 13% received 3 or more (heavily pretreated). Regarding conditionings, melphalan was used in 48% of the cases, carmustine, cyclophosphamide, etoposide in 24%, carmustine, etoposide, cytarabine, melphalan in 8%, and bendamustine-etoposide-citarabine-melphalan (BendaEAM) in 7.5%. Twenty-six percent received an infusion of stem cells $CD34^+ < 3 \times 10^6$/kg. In respect to comorbidities, 60% had low-risk HCT.CI, 29% intermediate risk, and 13% high risk.

Table 1
Cohort Characteristics (N = 1730)

Characteristic		No. of Patients (%)
Age, mean 53 years (range, 15-74)	<55 yr	944 (55)
	≥ 55 yr	786 (45)
Gender	Male	1008 (58)
	Female	722 (42)
Diseases	Multiple myeloma	837 (48)
	Non-Hodgkin lymphoma	475 (27)
	Hodgkin lymphoma	299 (17)
	Acute myeloid leukemia	58 (3.4)
	Others*	61 (3.5)
Pretransplant treatment (chemotherapy lines)	1 line	718 (46)
	2 lines	629 (41)
	≥3 lines	201 (13)
	Missing	182
Pretransplant status	Complete remission	876 (51)
	Partial remission	777 (46)
	Stable-progressive	47 (3)
	Missing	30
Conditioning	Melphalan	833 (48)
	Carmustine, cyclophosphamide, etoposide	407 (24)
	Carmustine, etoposide, cytarabine, melphalan	141 (8)
	BendaEAM	131 (7.5)
	Busulfan-cyclophosphamide	56 (3)
	Others	161 (9.5)
HCT-CI score	Low risk (0)	1032 (60)
	Intermediate risk (1-2)	502 (29)
	High risk (≥3)	196 (11)

* Other diseases includes germinal cell tumors, neuroblastoma, meduloblastoma, Ewing sarcoma, and osteosarcoma.

Early NRM (100-day) was 2.8%. By day 100 5.4% required OTI, 4.5% required vasopressors, and 2.1% dialysis, with an early composite morbidity–mortality of 6.8%. Regarding time-dependent variables, NRM at 1 year was 4% and at 3 years 5%, and OS was at 1 year was 85% and at 3 years 75%.

High-risk HCT-CI patients had a significant increase in 100-day NRM compared with intermediate risk and low risk (6.1 versus 3.2% versus 1.8%, respectively; $P = .002$). Similarly, the score increased the need for OTI (11% versus 6% versus 4%, $P = .001$) and vasopressors (8.7% versus 5.8% versus 3%, $P = .001$) and significantly increased the early composite morbidity–mortality endpoint (13% versus 9% versus 4.7%, $P < .001$), whereas it showed a trend with higher dialysis need