Biol Blood Marrow Transplant 21 (2015) 1479–1487

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Research: Analysis

Prospective Validation of the Predictive Power of the Hematopoietic Cell Transplantation Comorbidity Index: A Center for International Blood and Marrow Transplant Research Study

Mohamed L. Sorror [1,2,*], Brent R. Logan [3,4], Xiaochun Zhu [4], J. Douglas Rizzo [4], Kenneth R. Cooke [5], Philip L. McCarthy [6], Vincent T. Ho [7], Mary M. Horowitz [4], Marcelo C. Pasquini [4]

[1] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[2] *University of Washington, School of Medicine, Seattle, Washington*
[3] *Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[5] *Pediatric Blood and Marrow Transplantation Program, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland*
[6] *Blood and Marrow Transplant Program, Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York*
[7] *Center for Hematologic Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*

Article history:
Received 20 February 2015
Accepted 1 April 2015

Key Words:
Bone marrow transplantation
Hematopoietic cell transplantation
Autologous
Allogeneic
Hematopoietic cell transplantation–comorbidity index
Comorbidities
Validity
Inter-rater reliability

A B S T R A C T

Prospective validation of the hematopoietic cell transplantation–comorbidity index (HCT-CI) using contemporary patients treated with hematopoietic cell transplantation (HCT) across the Unites States is necessary to confirm its widespread applicability. We performed a prospective observational study including all patients (8115 recipients of allogeneic and 11,652 recipients of autologous HCT) who underwent a first HCT that was reported to the Center for International Blood and Marrow Transplant Research between 2007 and 2009. In proportional hazards models, increased HCT-CI scores were independently associated with increases in hazard ratios for nonrelapse mortality (NRM) ($P < .0001$) and overall mortality ($P < .0001$) among recipients of allogeneic HCT. HCT-CI scores of $\geq$3 were uniformly associated with higher risks for outcomes in both allogeneic and autologous HCT and in all subgroups, regardless of diagnoses, age, and conditioning intensity. Recipients of allogeneic HCT with scores of 1 and 2 who were ages $<$ 18 years or were treated with lower intensity conditioning regimens had similar outcomes compared with those with a score of 0. Higher risks for overall mortality, but not for NRM, were observed among recipients of autologous HCT with scores of 1 and 2 versus 0. Our results confirm the validity the HCT-CI in both allogeneic and autologous HCT. The index should be used as a valid standard-of-care health measure in counseling patients for HCT, in clinical trial design, and in adjusting outcome analyses.

INTRODUCTION

Organ dysfunctions (comorbidities) impact both treatment decisions and treatment outcomes in oncology and is particular salient in hematopoietic cell transplantation (HCT), where the morbidity associated with the procedure is high [1]. Until 2004, age alone had been widely used as the primary measure of a patient's ability to tolerate the conditioning regimens for allogeneic HCT [2]. Recently, the hematopoietic cell transplantation–comorbidity index (HCT-CI) was designed as a health measure suited for capturing the burden and complexity of organ dysfunctions among recipients of allogeneic HCT. The index was modeled to predict nonrelapse mortality (NRM), and initial analysis validated its ability to discriminate risks for NRM as well as overall mortality in an independent randomly selected cohort from the same institution [3]. Subsequently, comorbidity evaluation integrated in transplantation-related analyses have demonstrated the importance of risk assessment before HCT [4-7] or even conventional therapies [8-11] and its utility to better select patients for different regimen intensities [12,13]. Additional studies suggested that comorbidities may have a more important role than calendar age in determining HCT eligibility [14].

Financial disclosure: See Acknowledgments on page 1486.

* Correspondence and reprint requests: Mohamed L. Sorror, MD, Clinical Research Division (D1-100), Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, WA 98109-1024.
E-mail address: msorror@fhcrc.org (M.L. Sorror).

http://dx.doi.org/10.1016/j.bbmt.2015.04.004
1083-8791/

Although some investigators have confirmed the prognostic significance of the HCT-CI in their respective patients [15-18], others did not [19,20]. Therefore, it became important to study the prognostic significance of the HCT-CI in a prospective, well-designed, multicenter setting to confirm its utility as a prognostic health status measure of HCT outcomes. Further, there have been only a limited number of studies that assessed the performance of the HCT-CI in the autologous HCT settings [21,22]. If the utility of the HCT-CI is confirmed in adequately designed large validation studies, this index would allow for consistent integration of comorbidities into the design of randomized clinical trials in HCT, adjustment of clinical trial results across transplantation institutions, and better understanding of the biological causes of post-HCT morbidities.

We hereby summarize the results from a large multi-institutional prospective study gathering information from all United States transplantation centers that report to the Center of International Blood and Marrow Transplantation Research (CIBMTR). The study aimed to determine the discriminative capacity of the HCT-CI among recipients of allogeneic and autologous HCT and the effectiveness of the HCT-CI in stratifying outcomes among HCT patients with different diagnoses, age groups, and conditioning intensities.

PATIENT AND METHODS

Data Source

The CIBMTR is a research affiliate of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program established in 2004. It comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute data on consecutive allogeneic and autologous HCT procedures to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program Coordinating Center in Minneapolis, Minnesota. Participating centers report longitudinal data on all transplantations and compliance is monitored by on-site audits. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule.

Study Design and Patients

In 2007, a new prospective multi-institutional observational study was initiated at the CIBMTR to collect comorbidities from all transplantation centers by their respective evaluators and to validate the predictive power of the HCT-CI in a large sample of patients. The HCT-CI was adapted into the Pre-Transplant Essential Data collection form number 2400. Data managers from all institutions attended an education session on comorbidity coding per the HCT-CI at the 2007 Tandem BMT Meeting in Keystone, Colorado. This session was then made public to all data managers at the CIBMTR website (www.cibmtr.org/Meetings/Materials/CRPDMC/Pages/feb2007sorror.aspx).

The study was designed to score comorbidities prospectively for all patients meeting the following criteria: (1) diagnoses of hematological malignant diseases, (2) treatment with autologous or allogeneic HCT between December 1, 2007 and December 31, 2009, (3) receiving conditioning regimens of any intensity or composition, (4) receiving grafts from HLA-matched related or unrelated donors, and (5) given marrow or granulocyte colony–stimulating factor–mobilized peripheral blood mononuclear cells grafts. No upper limit was stated for the number of patients to be enrolled into the study. Figure 1 is an organization chart depicting patient eligibility and enrollment into the study. Among 23,876 recipients (Figure 1) of first HCT in the United States between 2007 and 2009 who were reported to CIBMTR, final samples of 8115 recipients of allogeneic HCT and 11,652 recipients of autologous HCT contributed to this analysis.

Study Endpoints and Definitions

The primary outcomes studied were NRM and overall mortality. *NRM* was defined as post-transplantation death that was not preceded by disease progression or relapse. *Progression* was defined as >50% increase in the burden of primary disease compared with pretransplantation disease status and/or development of disease at new sites. *Relapse* was defined as reappearance of primary disease after achievement of post-HCT complete remission. For survival, patients were considered to have an event at time of death from any cause; survivors were censored at last contact. Conditioning regimens were classified into high-dose, reduced-intensity (RIC), or non-myeloablative (NMA) intensity based on the previously published criteria [23]. Comorbidities were evaluated by respective staff at each site, whereas total scores were assigned by the CIBMTR statistical team following previously published guidelines [3]. The HCT-CI score was derived directly from the presence of a comorbidity per the HCT-CI as collected in the Pre-Transplant Essential Data forms. Additional comorbidities that were not part of the HCT-CI but that were collected in free text fields under the "other" category were not considered for the validation of this score. We analyzed a subset of these "other comorbidity" fields to assess discrepancies between what was documented in the free text field and the HCT-CI components. We found that the content in this free text field could potentially change the overall HCT-CI score in fewer than 5% of cases. Consequently, the "other comorbidity" field was not used to modify the score reported in the HCT-CI–specific fields. To further rule out the contribution of these write-in entries, patients with an HCT-CI score of 0 but with any "other comorbidity" reported in the free text field were analyzed as a separate risk group in the statistical models.

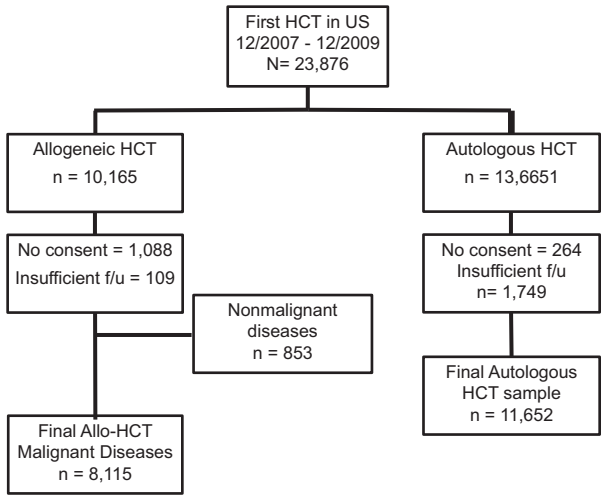

Figure 1. Organization chart of patient eligibility and enrollment into the prospective observational study. Among a total sample of 23,876 patients who received hematopoietic cell transplantation in United States between December 2007 and December 2009, 8115 recipients of allogeneic and 11,652 recipients of autologous HCT contributed to the study analyses.

Statistical Methods

Cumulative incidence and Kaplan-Meier estimates were calculated to evaluate the unadjusted associations between the HCT-CI scores and NRM and survival. Relapse or progression of the primary disease was treated as a competing risk for NRM and vice versa. Because this study investigates the impact of the HCT-CI on outcomes after the first transplantation, all outcomes were censored at the second transplantation.

Proportional hazards models were used to estimate the hazard ratio (HR) for NRM and survival associated with HCT-CI scores among the whole patient population as well as among adults versus children, high-dose versus RIC/NMA regimens, and among patients with different diagnoses. The models were adjusted for patient-related risk factors including age, Karnofsky performance status score, race, and cytomegalovirus serology results; disease-related risk factors including diagnosis category, sensitivity to last chemotherapy among patients with lymphoma, disease status among patients with acute leukemia, and interval between diagnosis and HCT; and transplantation-related risk factors, including donor type/HLA typing, stem cell source, conditioning regimen, and graft-versus-host disease (GVHD) prophylaxis regimen. Multivariate P values for a variable were based on adjustment for all other variables in the model. All P values were derived from likelihood ratio statistics and were 2 sided. In these multivariate analyses, the HCT-CI was primarily modeled as a categorical variable with group stratifications of 0, 1 and 2, and $\geq$3, similar to the initially recommended model to allow for almost uniform distribution of patient samples per risk group. A subset analysis using categorization of 0, 1, 2, 3, 4, and $\geq$5 was also performed with nested comparisons of both stratification models.