ASBMT
American Society for Blood and Marrow Transplantation

Bronchiolitis Obliterans Syndrome Epidemiology after Allogeneic Hematopoietic Cell Transplantation

Brandon K. C. Au,[1] Margaret A. Au,[2] Jason W. Chien[3,4]

Bronchiolitis obliterans syndrome (BOS) is a pulmonary complication of allogeneic hematopoietic cell transplantation (aHCT). Recent National Institutes of Health consensus diagnostic criteria for BOS have not been assessed in a clinical setting. Modified National Institutes of Health diagnostic consensus criteria for BOS were applied to evaluate its prevalence, risk factors, and outcomes in the modern era of aHCT. Pulmonary function tests from 1145 patients were screened to identify patients with new-onset airflow obstruction. Clinical records were reviewed to exclude pulmonary infection and other causes. The overall prevalence of BOS among all transplanted patients was 5.5%, and 14% among patients with chronic graft-versus-host disease (cGVHD). The median time from transplant to meeting spirometric criteria for BOS was 439 days (range: 274-1690). Although many previously identified risk factors were not significantly associated, lower baseline FEV_1/FVC ratio ($P = .006$), non-Caucasian race ($P = .014$), lower circulating IgG level ($P = .010$), and presence of cGVHD ($P < 0.001$) were associated with an increase in risk, with the latter associated with a 10-fold increase in risk. Multivariate analysis indicated that BOS conferred a 1.6-fold increase in risk for mortality after diagnosis. These results suggest that the National Institutes of Health diagnostic criteria can reliably identify BOS, and that it is more prevalent than previously suggested. Spirometric monitoring of high-risk patients with cGVHD may permit earlier detection and intervention for this often-fatal disease.

Biol Blood Marrow Transplant 17: 1072-1078 (2011)

KEY WORDS: Bronchiolitis obliterans syndrome, Chronic graft-versus-host disease, Allogeneic hematopoietic cell transplantation

INTRODUCTION

Bronchiolitis obliterans syndrome (BOS) is a lung complication of allogeneic hematopoietic cell transplantation (aHCT) recipients that is characterized clinically by the development of fixed new-onset airflow obstruction (AFO) and pathologically by progressive circumferential fibrosis targeting the terminal bronchioles. Because BOS is always observed in the presence of chronic graft-versus-host disease (cGVHD), and is also commonly observed after lung transplantation as host-versus-graft disease, it is likely that BOS is caused by an alloimmune response of donor hematopoietic cells against host lung antigens. Although BOS patients are typically treated with immunosuppressive agents, there is no strong evidence that any specific therapies are effective in improving long-term outcomes. Patients affected by BOS carry a poor prognosis, with an overall 2-year survival rate of 44% to 45% and a 5-year survival rate of 13% [1-3].

There is much variation in the estimated prevalence of BOS. Most studies estimate the prevalence of BOS to be 2% to 3% among aHCT recipients, or 6% among patients with cGVHD [2,4-6]. However, some suspect the prevalence of BOS may be as high as 10% to 20% [3,7,8]. This variability in prevalence estimates is largely because of a lack of consensus regarding the clinical diagnostic criteria for BOS. Indeed, there are at least 10 distinct clinical definitions for BOS after aHCT in the published literature [2,7,9-15].

In 2005, the National Institutes of Health (NIH) proposed new consensus diagnostic criteria for BOS, defining this syndrome by the presence of 4 clinical characteristics: (1) forced expiratory volume in 1 second (FEV_1) <75% predicted, (2) FEV_1/forced vital capacity (FVC) ratio <0.7, (3) evidence of air trapping, small airway thickening, or bronchiectasis on high-

From the [1]John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii; [2]Department of Epidemiology, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii; [3]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; and [4]Pulmonary and Critical Care, University of Washington, Seattle, Washington.

Financial disclosure: See Acknowledgments on page 1078.
This article has an online data supplement.

Correspondence and reprint requests: Jason W. Chien, MD, MS, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D5-280, Seattle, WA 98109-1024 (e-mail: jchien@fhcrc.org).

Received October 5, 2010; accepted November 17, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.11.018

resolution computed tomography (HRCT) or residual volume (RV) >120% of predicted normal and (4) absence of respiratory tract infection, or pathologic confirmation [11]. Recommendations for modifying the NIH criteria were recently made to improve the diagnostic accuracy of the consensus criteria [16]. The purpose of the current study is to use these recommendations to assess the prevalence, risk factors, and outcomes of BOS in a cohort of aHCT recipients.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board at the Fred Hutchinson Cancer Research Center (FHCRC). All patients who received their first aHCT at the FHCRC/Seattle Cancer Care Alliance (SCCA) between January 1, 2002, and June 30, 2006, were eligible for this study. The medical records of all patients who met spirometric criteria for BOS were reviewed for additional clinical, radiologic, microbiologic, and treatment data. All patients were evaluated for respiratory infection according to standard clinical protocol. When indicated, additional investigations for infection such as nasal wash, sputum culture, and bronchoscopies were performed. Assays for bacterial, viral, and fungal pathogens were routinely performed on all bronchoalveolar lavages. Details regarding the clinical data and infectious evaluation are available in the online supplement.

BOS patients were classified according to recognition status as concurrently recognized, late recognized, or never recognized. Concurrent clinical recognition was defined as clinical documentation of BOS in the medical records within 1 month of meeting NIH spirometric criteria. *Late recognized* was defined as documentation in the medical records of BOS >1 month of meeting NIH spirometric criteria. *Never recognized* was defined as the absence of documentation of BOS in the available FHCRC and non-FHCRC medical records despite meeting NIH spirometric criteria.

Pulmonary Function Testing

To avoid misclassification because of reversible changes in lung function during the first year after transplant, only pulmonary function tests (PFTs) obtained at or after 1 year posttransplant (365 ± 100 days) were evaluated for BOS. As part of clinical protocol, all patients who return for a 1-year evaluation receive a PFT. However, after the first year, PFTs are obtained at the discretion of their primary physician. For all PFTs, predicted values were calculated using published equations for children and adults [17,18]. All pulmonary function values, except for the FEV_1/FVC ratio, were expressed as a percentage of predicted values.

One-year posttransplant PFTs were defined at 365 ± 100 days. Patients surviving to at least 1 year (±100 days) were screened for BOS using modified NIH spirometry criteria: (1) FEV_1 <75% predicted, (2) FEV_1/FVC ratio <0.7, and (3) decrease of the FEV_1 by ≥10% in comparison to the pretransplant value. Patients were required to meet all 3 criteria to pass this first screen. Postbronchodilator values were used whenever available to minimize misclassification of reversible AFO. The date of the initial PFT fulfilling the above-modified NIH spirometry criteria was used as the date of BOS diagnosis, with the exception of those that were reclassified as noncases following chart review.

Pulmonary function at the time of meeting NIH spirometry criteria and after was quantified using the NIH recommended lung function score (LFS). The LFS was calculated using the FEV_1 and carbon monoxide diffusion capacity (DLCO) (≥80% = 1, 70%-79% = 2, 60%-69% = 3, 50%-59% = 4, 40%-49% = 5, and <40% = 6) [11]. Scores for FEV_1 and DLCO were then summed, categorized from 0 to 3, and defined according to NIH recommendations (LFS score 2 = category 0 [normal]; LFS score 3-5 = category 1 [mildly abnormal]; LFS score 6-9 = category 2 [moderately abnormal]; or LFS score 10-12 = category 3 [severely abnormal]).

Statistical Methods

All statistical analyses were performed using STATA 10.0 (StataCorp, College Station, TX) and R 2.6.2. Two-sided P values <.05 were considered statistically significant. t-Tests were performed to compare baseline PFT measurements in cases and noncases. Univariate analyses were performed using Pearson's chi-square test. Covariates with $P < .1$ in univariate analyses were considered in multivariate Cox regression using backward stepwise regression to assess their impact on risk for BOS. Chronic GVHD and acute GVHD (aGVHD) were treated as time-dependent covariates. Both unadjusted and adjusted (for age, disease risk, and time-dependent cGVHD and aGVHD) models were fitted to evaluate the effect of BOS on risk of nonrelapse mortality. Cumulative incidence of BOS was calculated considering death, relapse, and second transplant as competing risks. The Kaplan-Meier method was used to estimate overall nonrelapse survival in BOS cases. Stratified Kaplan-Meier curves were also calculated to investigate group survival trends in variables of interest. The log-rank test was used to evaluate survival differences across groups. Treatment for BOS was assessed using a Cox model among all BOS cases. Mean changes in LFS were compared among recognition and treatment groups using analysis of variance (ANOVA).

RESULTS

Cohort Characteristics

Between January 1, 2002, and June 30, 2006, 1145 patients received a first-time aHCT. Thirty-nine