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Impact of Conditioning Regimen on Outcomes for Patients with Lymphoma Undergoing High-Dose Therapy with Autologous Hematopoietic Cell Transplantation

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A B S T R A C T

There are limited data to guide the choice of high-dose therapy (HDT) regimen before autologous hematopoietic cell transplantation (AHCT) for patients with Hodgkin (HL) and non-Hodgkin lymphoma (NHL). We studied 4917 patients (NHL, n = 3905; HL, n = 1012) who underwent AHCT from 1995 to 2008 using the most common HDT platforms: carmustine (BCNU), etoposide, cytarabine, and melphalan (BEAM) (n = 1730); cyclophosphamide, BCNU, and etoposide (CBV) (n = 1853); busulfan and cyclophosphamide (BuCy) (n = 789); and total body irradiation (TBI)–containing treatment (n = 545). CBV was divided into CBV^{high} and CBV^{low} based on BCNU dose. We analyzed the impact of regimen on development of idiopathic pulmonary syndrome (IPS), transplantation-related mortality (TRM), and progression-free and overall survival. The 1-year incidence of IPS was 3% to 6% and was highest in recipients of CBV^{high} (hazard ratio [HR], 1.9) and TBI (HR, 2.0) compared with BEAM. One-year TRM was 4% to 8%, respectively, and was similar between regimens. Among patients with NHL, there was a significant interaction between histology, HDT regimen, and outcome. Compared with BEAM, CBV^{low} (HR, .63) was associated with lower mortality in follicular lymphoma ($P < .001$), and CBV^{high} (HR, 1.44) was associated with higher mortality in diffuse large B cell lymphoma ($P = .001$). For patients with HL, CBV^{high} (HR, 1.54), CBV^{low} (HR, 1.53), BuCy (HR, 1.77), and TBI (HR, 3.39) were associated with higher mortality compared with BEAM ($P < .001$). The impact of specific AHCT regimen on post-transplantation survival is different depending on histology; therefore, further studies are required to define the best regimen for specific diseases.

INTRODUCTION

High-dose therapy (HDT) with autologous hematopoietic cell transplantation (AHCT) has been a standard component of therapy for patients with Hodgkin lymphoma (HL) [1] and non-Hodgkin lymphoma (NHL) [2,3] for decades. The therapeutic rationale of HDT with AHCT relies on enhanced cytotoxicity through the delivery of myeloablative doses of chemotherapy or total body irradiation (TBI). The choice of HDT regimen has traditionally been based on institutional experience, and several regimens are considered standard and routinely used for patients with all histologies of lymphoma [4].

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Each HDT regimen is associated with its own unique toxicities, based on the individual agents or modalities used. One example is idiopathic pneumonia syndrome (IPS), which encompasses noninfectious pneumonitides caused by high-dose alkylating chemotherapy (eg, carmustine [BCNU]) or TBI and is the major pulmonary toxicity after HDT [5]. As prompt initiation of corticosteroids can often result in clinical improvement, early recognition of IPS is important, and the published risk factors for IPS after AHCT are variable [6-12].

A large study of lymphoma patients undergoing AHCT in the modern era has not been performed to define the impact of conditioning regimens on overall outcomes or to describe the incidence and risk factors for developing IPS and its impact on outcomes. To this end, we undertook a large retrospective registry study to analyze the impact of several commonly used HDT regimens on clinical outcomes.

METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) includes a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantations to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program coordinating center in Minneapolis. Participating centers are required to report all transplantations consecutively; patients are followed longitudinally and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. 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 [13].

Patient Selection

All adult patients (≥18 years) reported to the CIBMTR who received AHCT using marrow or peripheral blood stem cells for NHL or HL between 1995 and 2008 were included in this analysis. Patients were excluded for the following: no post-transplantation follow-up information (n = 138), BCNU given in a regimen other than BEAM (BCNU, etoposide, cytarabine, melphalan) [14] or CBV (cyclophosphamide, BCNU, etoposide [VP-16]) [15] (n = 145), or date of development of IPS was before the transplantation (n = 23). Among recipients of BEAM, cases were excluded if the BCNU dose per body surface area was less than 10th percentile (n = 228), greater than the 90th percentile (n = 4), or if the dose was missing (n = 166). Among recipients of CBV, patients were excluded if the BCNU dose per body surface area was less than 10th percentile (n = 137) or if the dose was missing (n = 241). Among patients who received non-BCNU regimens, only patients who received busulfan and cyclophosphamide (BuCy) [16] and TBI [17] were included to the final dataset. A total of 4917 patients were identified from 204 centers. To address the impact of BCNU dose on outcomes, the total dose administered of BCNU was divided by the calculated body surface area from height and weight data reported to the CIBMTR. According to patterns of practice, the dose distribution of BCNU varied widely among recipients of CBV, clustering approximately around 300 mg/m^2 (median, 296 mg/m^2; range, 225 to 374 mg/m^2) and at 450 mg/m^2 (median, 453 mg/m^2; range, 376 to 807 mg/m^2), which were then separated into CBV^{low} and CBV^{high}, respectively. Among recipients of BEAM, the BCNU dose distribution was approximately around 300 mg/m^2 (median, 293 mg/m^2; range, 227 to 347 mg/m^2).

Study Endpoints

The primary endpoint of this analysis was overall survival (OS) among the different conditioning regimens. Secondary endpoints included IPS, transplantation-related mortality (TRM), relapse or progression, and progression-free survival (PFS). *TRM* was defined as any death without recurrent lymphoma. *Relapse* and *progression* were defined as evidence of disease recurrence censored at the date of last contact and using death in remission as the competing hazard. *PFS* was defined as survival without death or relapse censored at the date of last contact.

Statistical Analysis

Patient-, disease-, and transplantation-related characteristics were described according to each conditioning regimen and compared using chi-square tests or Kruskal-Wallis tests, as appropriate. The cumulative incidence function was used for calculating IPS, TRM, relapse, or progression outcomes accounting for competing risks. OS and PFS were analyzed by the Kaplan-Meier method. Multivariable analysis for each outcome was performed using a Cox proportional hazards model. The effect of development of IPS on subsequent TRM, treatment failure (relapse progression or death), and overall mortality was performed by fitting a Cox model with a time-dependent effect for prior development of IPS. Preparative regimens were included in all models as the main effect. The proportional hazards assumption was checked using graphical approaches or time-dependent covariates. Stepwise model building was used to identify additional predictors besides preparative regimen, from among the following candidate variables included: age (18 to 39, 40 to 49, 50 to 59, ≥ 60), gender, body mass index (<18.5, 18.5 to 25, 25 to 30, > 30, unknown), Karnofsky performance status (KPS) (<90, 90 to 100, unknown), disease status at AHCT, number of prior chemotherapy regimens received, year of AHCT (1995 to 1999, 2000 to 2004, 2005 to 2008), history of smoking, time from diagnosis to AHCT, prior use of rituximab in NHL patients, and graft type (bone marrow versus peripheral blood stem cells). Interactions between preparative regimen and other baseline characteristics were checked. Disease was tested in 2 ways: first, separating HL and NHL and second, separating NHL according to histologies. Both ways demonstrated a significant interaction between disease and conditioning on several outcomes. Details of the final model are shown for the 4 largest disease groupings: HL, follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). Considering multiple comparisons across conditioning regimens, only P values ≤.01 were considered significant.

RESULTS

Clinical Characteristics

Patient characteristics for each regimen are summarized in Table 1. The cohorts differed in age, distribution of disease, year of AHCT, KPS, prior chemotherapy, time from diagnosis to AHCT, and prior use of rituximab in NHL patients. Recipients of AHCT with BEAM were older: age ≥ 54 years, BEAM, 53%; CBV^{low}, 38%; CBV^{high}, 34%; BuCy, 50%; and TBI, 40%; $P < .001$. A lower proportion of BEAM and TBI patients had HL: BEAM, 18%; CBV^{low}, 23%; CBV^{high}, 37%; BuCy, 21%; and TBI, 4%; $P < .001$. BEAM was used more frequently in later years of the study period: year of AHCT 2002 or later; BEAM, 70%; CBV^{low}, 18%; CBV^{high}, 26%; BuCy, 49%. and TBI, 19%; $P < .001$. For patients with NHL, prior rituximab use was different: BEAM, 67%; CBV^{low}, 18%; CBV^{high}, 29%; BuCy, 43%; and TBI, 21%; $P < .001$. Among patients with available age-adjusted IPI, the proportion of patients with low and low-intermediate IPI was in the range of 82% to 88% across the conditioning groups. The cohorts were similar in terms of gender and median follow-up for survivors.

Idiopathic Pneumonia Syndrome

The incidence of IPS by 1 year after AHCT was as follows: BEAM, 3% (95% confidence interval [CI], 2% to 4%); CBV^{low}, 3% (95% CI, 2% to 4%); CBV^{high}, 6% (95% CI, 4% to 8%); BuCy, 4% (95% CI, 2% to 5%); and TBI, 5% (95% CI, 3% to 7%). Multivariate analysis showed that in comparison to BEAM, the risk of IPS for each regimen was as follows: CBV^{low}, hazard ratio (HR), 1.07 (95% CI, .72 to 1.60); $P = .742$; CBV^{high}, HR, 1.88 (95% CI, 1.24 to 2.83); $P = .003$; BuCy, HR, 1.25 (95% CI, .82 to 1.92); $P = .30$; and TBI, HR, 2.03 (95% CI, 1.30 to 3.19); $P = .002$ (Table 2). Additional risk factors associated with the development of IPS include the following: (1) diagnosis of HL (HR, 2.33; 95% CI, 1.68 to 3.24; $P < .001$), (2) female gender (HR, 1.39; 95% CI, 1.05 to 1.82; $P = .019$), (3) chemotherapy-resistant disease at time of AHCT (HR, 1.9; 95% CI, 1.29 to 2.79; $P = .001$), and (4) age ≥ 55 (HR, 1.54; 95% CI, 1.13 to 2.09; $P = .006$). In the entire cohort, patients who developed IPS had a significantly higher rate of TRM (HR, 4.02; 95% CI, 3.09 to 5.24; $P < .001$),