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Comparison of 2 Carmustine-Containing Regimens in the Rituximab Era: Excellent Outcomes Even in Poor-Risk Patients

Paolo F. Caimi [1,2,*], Basem M. William [1,2], Carlos H. Silva Rondon [1], Pingfu Fu [2,3], Brenda W. Cooper [1,2], Erica L. Campagnaro [1,2], Stanton L. Gerson [1,2], Jane Reese-Koc [4], Robert Fox [4], Richard J. Creger [1,4], Marcos de Lima [1,2], Hillard M. Lazarus [1,2]

[1] *Division of Hematology and Oncology, Department of Medicine, Case Western Reserve University, Cleveland, Ohio*
[2] *Case Comprehensive Cancer Center, Cleveland, Ohio*
[3] *Department of Biostatistics, Case Western Reserve University, Cleveland, Ohio*
[4] *University Hospitals Seidman Cancer Center, Cleveland, Ohio*

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A B S T R A C T

High-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT) improves outcomes in relapsed lymphoma, but the relative efficacy of different preparative regimens is not well defined. We included patients undergoing autologous HCT using BEAM (carmustine, 300 mg/m^2, etoposide, cytarabine, and melphalan) or BEP (carmustine 600 mg/m^2, etoposide, and cisplatin) between January 2004 and December 2013; 65 patients received BEP and 64 patients BEAM. Both cohorts were similar for advanced-stage disease, extranodal and bulky disease, and prior therapies. Median neutrophil and platelet engraftment was 10 and 20 days for both regimens, respectively. Febrile neutropenia, serum creatinine concentration increase, and electrolyte abnormalities were more frequent with BEP. Incidence of carmustine pneumonitis was not higher with BEP, likely the result of corticosteroid prophylaxis, although 2 cases of fatal pneumonitis were observed after BEP. One-year nonrelapse mortality was 6.8% after BEP and 0% after BEAM ($P = .379$). After a median follow-up of 39.4 months (range, 1 to 128), 4-year rates of overall survival (OS) after BEP and BEAM were 80.4% and 72.3%, respectively ($P = .611$). Diffuse large B cell lymphoma patients transplanted after early relapse post-rituximab-based first-line therapy presented 3-year rates of OS and progression-free survival (PFS) of 73.8% and 65%, respectively. There were no statistically significant differences in the OS and PFS of follicular lymphoma, mantle cell lymphoma, or Hodgkin lymphoma. BEP is a valid alternative to BEAM in autologous HCT. Although associated with more renal and electrolytic toxicities, BEP results in similar disease control and long-term survival as BEAM. Prospective studies are needed to confirm whether intensification of conditioning regimens for autologous HCT can improve disease control in high-risk relapsed lymphoma patients.

INTRODUCTION

High-dose chemotherapy supported by autologous hematopoietic cell transplantation (HCT) has been shown to result in better progression-free survival (PFS) than conventional salvage chemotherapy for treatment of relapsed Hodgkin [1] and non-Hodgkin lymphoma patients [2,3]. Although the original studies validating the use of autologous HCT were done in the 1990s, more recent studies continue to demonstrate the utility of this treatment after the introduction of rituximab [4-8].

Disease status at transplant, sensitivity to salvage chemotherapy, secondary age-adjusted International Prognostic Index, and timing of recurrence have been identified as factors predicting outcome in patients with recurrent lymphoma [9]. The relative impact of conditioning regimens, however, is still uncertain [10]. Conditioning regimens include BEAM (carmustine [BCNU], etoposide, cytarabine, and melphalan); BCNU, (etoposide, cytarabine, and cyclophosphamide) [11]; CBV (cyclophosphamide, BCNU, etoposide) [12]; busulfan, etoposide, and cyclophosphamide [13]; as well as combination regimens with total body irradiation.

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* Correspondence and reprint requests: Paolo F. Caimi, Division of Hematology and Oncology, Department of Medicine, Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106.
E-mail address: paolo.caimi@case.edu (P.F. Caimi).

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We developed and investigated the combination of BCNU, etoposide, and cisplatin (BEP) in this setting [14,15]. Although BEAM and BEP preparative regimens have been well described, there have been no direct comparisons with regards to toxicity and efficacy [12,16]. We hereby present a retrospective analysis of the outcomes of 129 patients transplanted in our institution during a 10-year period (2004 to 2014) using either of these conditioning regimens.

METHODS

We searched the Stem Cell Transplant Database of the Seidman Cancer Center of University Hospitals Case Medical Center (Cleveland, OH) for all lymphoma patients who received an autologous HCT with BEP or BEAM conditioning between January 2004 and December of 2013. This retrospective study was approved by the Institutional Review Board of University Hospitals Case Medical Center. To avoid biases caused by different patient follow-up length, the start date for inclusion was the first year in which BEAM conditioning was used in our institution.

Preparative Regimens

All time calculations were based on the day of hematopoietic progenitor cell reinfusion (day 0). BEP included cisplatin 40 mg/m^2 i.v. daily from days −7 to −3 (total dose 200 mg/m^2), BCNU 200 mg/m^2 i.v. daily from days −6 to −4 (total dose 600 mg/m^2), and etoposide 800 mg/m^2 i.v. daily from days −6 to −4 (total dose 2400 mg/m^2). BEAM consisted of BCNU 300 mg/m^2 i.v. on day −6, etoposide 200 mg/m^2 i.v. daily from days −5 to −2 (total dose 800 mg/m^2), cytarabine 200 mg/m^2 i.v. twice daily from days −5 to −2 (total dose 1600 mg/m^2), and melphalan 140 mg/m^2 i.v. on day −1.

The choice of conditioning regimen was influenced primarily by the presence of comorbidities (pulmonary disease, renal dysfunction, peripheral neuropathy, hearing impairment). Because of the higher doses of BCNU and etoposide, BEP was preferred for patients not in remission, whereas older patients were more commonly prescribed BEAM because of concerns of tolerance. Histologic subtype and prior therapy did not influence the choice of regimen.

Pretransplant Radiation Therapy

Involved-field radiation therapy, 2000 to 3000 cGy, administered after hematopoietic cell mobilization to sites of previous bulky disease and to persistent 18-fluorodeoxyglucose avid lesions after salvage, was prescribed under the discretion of the treating physician [17].

Supportive and Prophylactic Measures

All patients received prophylaxis against *Pneumocystis jiroveci*, fungal infections, and herpesvirus until 100 days after HCT per institutional standards. All patients received filgrastim at a dose of 480 μg s.c. starting on the day of hematopoietic cell infusion until neutrophil engraftment.

The initial studies with BEP conditioning showed high doses of BCNU were associated with an increased rate of pulmonary toxicity; this toxicity could be prevented and treated with corticosteroids. Accordingly, all patients receiving BEP were given prophylaxis with oral prednisone (2 mg/kg daily) from days +7 through +14, followed by rapid taper. In addition, forced diuresis with furosemide (20 mg i.v. 2 minutes before cisplatin) and mannitol (25 g i.v. in 100 mL dextrose 5% after each dose of cisplatin) were used to prevent nephrotoxicity.

Statistical Analysis and Definitions

The date of neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count above 500/μL, whereas platelet engraftment was defined as the first of 7 days in which a platelet count above 20,000/μL was documented, without platelet transfusions for a minimum of 7 days. Overall survival (OS) was measured from the date of transplant to the date of death or last follow-up for survivors. PFS was measured from the date of transplant to the date of relapse or death, whichever occurred first.

Cumulative neutrophil and platelet recovery rates were estimated by the Kaplan-Meier method [18]. Survival duration was compared using the log-rank test. The predictive value of covariates, including conditioning regimen and continuous variables (ie, age, comorbidity, number of prior therapies, CD34$^+$ cell count), on survival was further examined using a Cox proportional hazard regression model [19]. Cumulative incidence of nonrelapse mortality (NRM) was estimated treating relapse mortality and relapse as competing risks [20].

Continuous variables were examined using the *t*-test, whereas the association between categorical variables was examined using the chi-square test or Fisher's exact test when appropriate. The association between continuous measurements was estimated using Spearman correlation coefficient. Linear regression was used to identify factors associated with time-to-discharge, and logistic regression was used to identify the influence of covariates on the incidence of transplant-related complications. All tests were 2-sided, and $P \leq .05$ were considered statistically significant.

With the exception of pulmonary complications, toxicity analysis included all complications occurring from the day of transplant through day +100. Because pulmonary toxicity can be delayed after BCNU, patients were monitored for this complication for 1 year after transplant. Infectious complications included febrile neutropenia, positive cultures, and infections documented through imaging studies. The occurrence of transplant related toxicities was identified through review of the medical records; toxicity grading was done according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm; June 14, 2010).

RESULTS

Patient Characteristics

One hundred twenty-nine lymphoma patients underwent autologous HCT with BEP (n = 65) or BEAM (n = 64) conditioning between 2004 and 2013. Patient characteristics are summarized in Table 1. There were no statistically significant differences among patients receiving either conditioning regimen, although the median age of BEP patients was 48 versus 58 years for those treated with BEAM ($P = .078$), reflecting the preference for BEAM in older patients. Prior therapy was similar in both groups. Eighty-five patients with B cell lymphoma (BEP, n = 43; BEAM, n = 42) received rituximab at some point before autologous HCT, and only 10 did not receive this agent in first-line therapy. Sixty-nine patients had prior exposure to platinum agents (BEP, n = 30, 46.1%; BEAM, n = 39, 60.9%).

Most patients were in complete remission at HCT (BEP group, n = 46, 70%; BEAM group, n = 51, 83.6%; $P = .38$). There was no statistical difference among patients transplanted in first complete remission (CR) (BEP, n = 16; BEAM, n = 19), second CR (BEP, n = 20; BEAM, n = 25), or third CR and beyond (BEP, n = 10; BEAM, n = 7). A total of 102 patients underwent imaging with 18-fluorodeoxyglucose positron emission tomography with computed tomography (PET-CT) in the 8 weeks preceding HCT (BEP group, n = 47; BEAM group, n = 55); there was no statistical difference in the proportion of patients with negative PET-CT at the time of

Table 1
Baseline Characteristics of Patients Undergoing Autologous HCT with BEAM and BEP Conditioning

	BEAM (n = 64)	BEP (n = 65)	*P*
Male/female	36/28	40/25	.542
Age, yr, median (range)	58 (18-73)	48 (17-72)	.078
CCI, median (range)	6 (4-12)	6 (4-24)	.233
Diagnoses, n			
DLBCL	20	13	
Transformed follicular and indolent	6	10	
Very aggressive (Burkitt and lymphoblastic)	0	6	
Follicular	6	10	
Mantle cell	12	8	
T cell	4	5	
Hodgkin	16	14	
Median number of lines of prior therapy (range)	2 (1-6)	2 (1-5)	.688
Radiation therapy (involved field) before transplant, n	23	14	.119
Disease status before transplant, n			.138
CR	51	46	
Non-CR	13	18	
PET-CT status at the time of transplant, n			.678
Negative	42	39	
Positive	13	8	