Biol Blood Marrow Transplant 22 (2016) 1197–1205

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Efficacy of Pharmacokinetics-Directed Busulfan, Cyclophosphamide, and Etoposide Conditioning and Autologous Stem Cell Transplantation for Lymphoma: Comparison of a Multicenter Phase II Study and CIBMTR Outcomes

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Financial disclosure: See Acknowledgments on page 1204.
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http://dx.doi.org/10.1016/j.bbmt.2016.03.018

Article history:
Received 23 November 2015
Accepted 15 March 2016

Key Words:
Non-Hodgkin lymphoma
Hodgkin lymphoma
Busulfan
Autologous stem cell transplantation
Stem cell transplantation
Lymphoma
Chemotherapy

A B S T R A C T

Busulfan, cyclophosphamide, and etoposide (BuCyE) is a commonly used conditioning regimen for autologous stem cell transplantation (ASCT). This multicenter, phase II study examined the safety and efficacy of BuCyE with individually adjusted busulfan based on preconditioning pharmacokinetics. The study initially enrolled Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) patients ages 18 to 80 years but was amended due to high early treatment-related mortality (TRM) in patients > 65 years. BuCyE outcomes were compared with contemporaneous recipients of carmustine, etoposide, cytarabine, and melphalan (BEAM) from the Center for International Blood and Marrow Transplant Research. Two hundred seven subjects with HL (n = 66) or NHL (n = 141) were enrolled from 32 centers in North America, and 203 underwent ASCT. Day 100 TRM for all subjects (n = 203), patients > 65 years (n = 17), and patients ≤ 65 years (n = 186) were 4.5%, 23.5%, and 2.7%, respectively. The estimated rates of 2-year progression-free survival (PFS) were 33% for HL and 58%, 77%, and 43% for diffuse large B cell lymphoma (DLBCL; n = 63), mantle cell lymphoma (MCL; n = 29), and follicular lymphoma (FL; n = 23), respectively. The estimated rates of 2-year overall survival (OS) were 76% for HL and 65%, 89%, and 89% for DLBCL, MCL, and FL, respectively. In the matched analysis rates of 2-year TRM were 3.3% for BuCyE and 3.9% for BEAM, and there were no differences in outcomes for NHL. Patients with HL had lower rates of 2-year PFS with BuCyE, 33% (95% CI, 21% to 46%), than with BEAM, 59% (95% CI, 52% to 66%), with no differences in TRM or OS. BuCyE provided adequate disease control and safety in B cell NHL patients ≤ 65 years but produced worse PFS in HL patients when compared with BEAM.

INTRODUCTION

Hodgkin (HL) and non-Hodgkin lymphoma (NHL) constitute a biologically heterogeneous group of commonly occurring hematologic malignancies with marked variability in clinical behavior, treatment approaches, and response to conventional therapy. Autologous hematopoietic stem cell transplantation (ASCT) is a useful therapeutic modality for many patients with relapsed HL and relapsed or high-risk NHL. Patients with relapsed/refractory HL who received high-dose therapy (HDT) and ASCT as compared with conventional salvage chemotherapy also experienced improved outcomes [1-4]. Prospective randomized trials and several retrospective studies have demonstrated improved outcomes when ASCT is used for consolidation after salvage chemotherapy in patients with relapsed aggressive NHL [5-10]. A randomized trial also showed that ASCT benefited patients with relapsed follicular lymphoma (FL) [11], which was further supported by registry data [12]. HDT and ASCT as initial therapy for patients with mantle cell lymphoma (MCL) and diffuse large B cell lymphoma (DLBCL) with high-risk International Prognostic Index scores remains controversial but has been commonly used [13-18]. At present, however, only limited data suggest any specific HDT regimen offers benefits over alternatives [19-24].

Busulfan (Bu), an alkylating agent, has been shown to be an effective component of the conditioning regimen for myeloablative autologous and allogeneic SCT [1,4,7,25-29]. One of the theoretical advantages of Bu-based HDT regimens over alternatives is that methods for monitoring plasma concentrations have been well established and individualized dosing is therefore possible [30]. Pharmacokinetics (PK)-directed dose adjustment for Bu was originally developed to avoid unpredictable overexposure and resultant unfavorable adverse effects such as vomiting and veno-occlusive disease of the liver (sinusoid obstruction syndrome), especially when Bu was available only in an oral formulation [25,27,30]. The introduction of i.v. Bu bypasses the problem of variable drug absorption from the gastrointestinal tract, which has reduced the incidence of adverse events (AEs). Moreover, single-institution studies showed improvement in overall survival (OS) for patients with NHL when oral Bu was replaced by i.v. Bu in HDT conditioning for ASCT [25,27,31], but multicenter data are lacking. This phase II trial was designed to examine conditioning with a PK-directed dosing regimen for i.v. Bu combined with cyclophosphamide and etoposide (BuCyE) in a multicenter setting and to compare this approach with conditioning with carmustine, etoposide, cytarabine, and melphalan (BEAM) using data collected from the Center for International Blood and Marrow Transplant Research (CIBMTR).

METHODS

Study Design

This prospective, multicenter, single-arm, phase II study investigated the safety and efficacy of an i.v. BuCyE regimen with PK-directed Bu dosing. The primary objective was to evaluate the clinical outcomes including progression-free survival (PFS; primary endpoint), OS, transplant-related mortality (TRM), and overall response rate. TRM was defined as a death after transplant due to any cause other than disease progression. Toxicity was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. The secondary objective was to compare the clinical outcomes of subjects receiving the BuCyE regimen with those receiving a conditioning regimen with BEAM from centers not participating in this clinical trial, as obtained from CIBMTR registry data [5,6,12,32]. CIBMTR data management procedures have been described previously [33]. In addition, the accuracy of PK-directed BU dose adjustment using the test-dose method was evaluated.

Study Eligibility

Eligible subjects were those who required a first ASCT for HL and B cell NHL. All subjects had relapsed disease after initial therapy or were initially refractory to an anthracycline-based chemotherapy and had achieved complete remission (CR) or partial remission (PR) after salvage chemotherapy according to the Cheson criteria [34]. Additionally, subjects with NHL with International Prognostic Index score of 4 to 5 [35] or MCL were eligible for study treatment as a part of primary therapy. All subjects were required to have had an Eastern Cooperative Oncology Group performance status of 0 to 2, with at least 2×10^6 $CD34^+$ cells/kg previously stored. Patients with major organ dysfunction or prior treatment with Bu or gemtuzumab ozogamicin were excluded.

The study initially enrolled subjects ages 18 to 80 years, but the protocol was amended to reduce the upper age limit to 65 years because of a high TRM rate at 100 days post-transplant for subjects aged > 65 years. All subjects provided written informed consent in accordance with the Declaration of Helsinki principles to participate in this study. The trial was registered at www.clinicaltrials.gov as NCT00948090.

The same eligibility criteria were applied to the comparator group. Selected patients were ages 18 to 65 years who had received ASCT with BEAM conditioning from 2008 to 2010 in US and Canadian transplant centers not participating in the above-mentioned clinical trial and who were registered with CIBMTR.

PK-Directed Dose Adjustment of Bu

The method of adjusting Bu dose per patient via individual PK parameters has been reported previously [36]. In brief, 6 serial blood samples were collected in sodium heparin tubes after administration of the i.v. Bu test dose (initial therapeutic drug monitoring [TDM]) and the first individualized conditioning dose on day −8 (confirmatory TDM). For the initial TDM a test dose of i.v. BU (.8 mg/kg) was administered over 2 hours between days −14 and −11. This dose was intended to achieve an area under the curve (AUC) of 1000 to 1500 μM·min. Blood samples were collected at the end of the 2-hour infusion and at 15, 30, 120, 180, and 240 minutes thereafter. For the confirmatory TDM on day −8, individual i.v. Bu doses were calculated to achieve a total AUC of 20,000 μM·min, including the AUC from the test and confirmatory doses [4,30]. Samples for confirmatory TDM were collected at the end of the 3-hour infusion and at 30, 90, 180, and 300 minutes thereafter.

The first sample for both the test dose and confirmatory TDM were drawn at the end of the infusion, and no samples were drawn during the infusion. Samples were stored on wet-ice or refrigerated immediately after collection, centrifuged at 4°C, and stored at −20°C or below until shipping. To allow same-day sample shipping and expedite availability of PK results, test dose and confirmatory TDM sampling were limited to 240 and 300 minutes after the end of infusion, respectively. Standard sampling time points were used for the test dose, based on a sampling schedule of .8 mg/kg every 6 hours [37-39]. For the confirmatory TDM sampling, Bu clearance and AUC estimates have been shown to be comparable from PK sampling over 8 (300 minutes after the end of infusion), 11, and 24 hours after the start of infusion for every 24-hour administration, and thus sampling was limited to 300 minutes after the end of infusion [40].

The PK laboratory at the Seattle Cancer Care Alliance measured plasma Bu concentrations and recommended individualized Bu dosing. Concentrations were analyzed by gas chromatography with mass selective detection as previously described [41]. The dynamic range was from 62 to 4500 ng/mL and the intraday and interday coefficient of variations were less than 5% and 8%, respectively. Bu AUC from time 0 to infinity and its estimated corresponding clearance were determined using a 1-compartment first-order elimination model via WinNonlin version 5.2 (Pharsight, Sunnyvale, CA) [38,40].

Targeted daily AUC during the conditioning regimen was calculated as targeted daily conditioning AUC (μM·min) = [20,000 (μM·min) − test dose measured AUC (μM·min)]/4. The conditioning regimen daily Bu dose was then calculated as Bu i.v. daily conditioning dose (mg) = test dose (mg) × targeted daily conditioning AUC (μM·min)/test dose measured AUC (μM·min). Accuracy of the test dose prediction was assessed by the percent error calculation: [(predicted AUC_{day-8} by the test dose − confirmed AUC_{day-8})/confirmed AUC_{day-8}] × 100. Accuracy of the dose adjustment was assessed by the percent error calculation: [(confirmed AUC_{day-8} − target AUC_{day-8})/target AUC_{day-8}] × 100.

Conditioning Regimen with BuCyE

The conditioning regimen consisted of PK-directed doses of Bu on days −8 through −5 (see previous section), etoposide 1.4 g/m^2 on day −4, and cyclophosphamide 2.5 g/m^2 on days −3 and −2, followed by stem cell infusion on day 0. Individualized doses of i.v. Bu were administered over 3 hours once daily. Intravenous Bu doses on days −6 and −5 were modified only when the second PK results on day −8 indicated further adjustment were required to achieve Bu exposure of 20,000 μM·min (±20%; cumulative Bu exposure between 16,000 and 24,000 μM·min). Although no seizure prophylaxis was instituted during the test dose of i.v. Bu administration, benzodiazepines and/or levetiracetam were used as antiseizure medications for conditioning. Peritransplant palifermin and post-transplant use of colony-stimulating factor use were not restricted.

Statistical Analysis

The endpoints of PFS and OS were depicted graphically by Kaplan-Meier curves. Median survival in months, with 95% confidence intervals (CIs), and 1- and 2-year survival rates were also estimated. Disease responses were summarized by frequency and percentage at each of the specified time points. Efficacy analyses were based on the modified intention-to-treat data set.

This study had a prespecified endpoint (as described in the approved clinical protocol) comparing efficacy of BuCyE with BEAM from CIBMTR registry data. Baseline characteristics of patients enrolled in this clinical trial 65 years of age or younger were used to match with CIBMTR control subjects. All patients from the phase II study selected for efficacy analyses were matched with up to 4 patients treated with BEAM obtained from CIBMTR to provide approximately 80% power to demonstrate 11% difference in the 2-year PFS rate, assuming that the 2-year PFS rates for BuCyE and BEAM were 66% and 55%, respectively [24,42]. The 4 criteria used for matching were age ± 10 years, Karnofsky Performance Score (≥90%, <90%), disease status before transplant as defined above (CR1, CR2 or higher, PR), and histology (HL, FL, DLBCL, MCL, Burkitt, and others). All patients were followed-up for at least 1 year until May 2013, which provided an approximate median 2-year follow-up for this study. Follow-up visits were timed to match the CIBMTR registry follow-up time points for data comparability: day 100, 6 months, 1 year, and every year after 1 year.

Baseline characteristics at transplantation were tabulated and compared for the phase II BuCyE group and the matched CIBMTR cohort conditioned with BEAM. Outcomes were tabulated for patients in the phase II BuCyE trial and compared with the matched BEAM patients from the CIBMTR. Survival curves were constructed using the Kaplan-Meier method and were compared by a 2-sided log-rank test. Multivariable Cox regression analyses were conducted to compare clinical outcomes after HCT between BuCyE and BEAM. To account for the intracluster correlation resulting from covariates matching, a marginal models approach was used in all comparisons. Marginal Cox models [43] were used to evaluate prognostic factors for PFS, TRM, and OS. The proportional hazards assumption was met. An interaction test indicated a differential effect of conditioning regimen by disease type on PFS; therefore, the comparisons are presented by disease type. A level of significance (α) of .05 was defined as statistically significant. All statistics were computed using SAS version 9.3 (SAS Statistical Institute, Cary, NC, USA).

RESULTS

Patient Disposition and Demographics

Two hundred seven subjects with HL (n = 66) or NHL (n = 141) were enrolled from 32 centers in the United States and Canada between February 2010 and April 2012. Four subjects did not proceed with ASCT because of insurance or eligibility issues. One patient who experienced a syncopal episode after etoposide administration was not treated with cyclophosphamide and discontinued from the study on day −1. This patient was included in the intent-to-treat population, because stem cells were infused as planned. In addition, 4 patients were identified as ineligible but were included in the intent-to-treat analyses. These patients were deemed ineligible due to T cell lymphoma (n = 1), failure to confirm CR or PR (n = 1), history of hepatitis C (n = 1), and 1 patient with FL who did not receive prior anthracycline. The study initially enrolled subjects ages 18 to 80, but the protocol was amended to reduce the upper age limit to 65 years due to a high TRM rate at 100 days post-transplant for subjects > 65 years. We report safety for all subjects undergoing ASCT (n = 203) and efficacy from those aged ≤ 65 years (n = 186) and recipients of BuCyE who were matched to up to a maximum of 4 BEAM patients yielding a total of 729 control subjects.

At baseline, 67% of subjects were men, 87% were white and 6% were African American, and 96% had an Eastern Cooperative Oncology Group performance status of 0 to 1 (Table 1). Median time from initial diagnosis to the autologous transplant was 18.4 months (range, 71 days to 262 months). Lymphoma subtypes and disease status at transplantation are described in Table 1.

PK-Directed Dose Adjustment of Bu

Of the 203 subjects undergoing ASCT in the present study, 200 subjects used individualized Bu doses determined by initial TDM, whereas 3 subjects used 3.2 mg/kg on days −8 and −7 due to nonassessable test PK results. Confirmatory TDM samples were collected from 203 subjects on day −8 (n = 201) or day −7 (n = 2). In 1 subject confirmatory TDM was equivocal and not used. Consequently, 199 subjects had 2 sets of assessable PK parameters obtained with initial and confirmatory TDM.

Among the 199 subjects, median Bu clearance calculated from initial TDM was 2.98 mL/min/kg (range, 1.95 to 4.39). Overall, 2.9% of subjects had an AUC > 1500 μM·min and 32.8% of subjects had an AUC < 1000 μM·min (Figure 1).

Table 1
Patient Demographics (N = 203)

Characteristics	Value
Age, yr, median (range)	51 (19-72)
Male, n (%)	139 (67)
Race, n (%)	
White	177 (87)
African American	13 (6)
American Indian or Alaskan Native	2 (1)
Asian	7 (3)
Other	4 (2)
ECOG performance status, n (%)	
0	85 (42)
1	109 (54)
2	7 (3)
Missing	2 (1)
Body weight, kg, median (range)	83.4 (38.8-178.2)
Body mass index, kg/m^2, mean (SD)	29.2 (6.3)
Classifications, n (%)	
HL	66 (32)
NHL	137 (68)
DLBCL	74 (54)
FL	25 (18)
MCL	32 (23)
Other	6 (4)
Status at transplantation in ITT group, n (%)	
CR1	55 (27)
CR2	66 (32)
CR3 or higher	5 (2)
Primary induction failure/in relapse	6 (3)
PR	71 (35)
Without prior CR	46 (22)
With prior CR	20 (10)

ECOG indicates Eastern Cooperative Oncology Group; SD, standard deviation; ITT, intent-to-treat population.

In total, 35.8% of subjects would likely have been outside the AUC target range if weight-based dosing had been used without TDM. A greater proportion of obese (body mass index ≥ 30) or overweight (body mass index 25.0 to 29.9) subjects were underexposed to Bu compared with those with normal body mass indices (18.5 to 24.9) (Table 2). However, stratification by body mass index was not sufficient to identify any specific patient population that would not have required TDM. After PK-directed dose adjustments based on initial and confirmatory PK (AUC = 20,000 μM·min ± 20%, Figure 2) 95.0% of subjects fell within the target range for total AUC; 3.0% and 2.0% subjects required additional dose reductions and increases for the last 2 days, respectively. Mean absolute error for the test dose predicted $AUC_{day\text{-}8}$ (confirmatory PK) was 7.4% (95% CI, 6.5% to 8.3%). Evaluating the accuracy of test PK-based dose adjustments based on the margin of error from the desired daily target exposure, mean absolute error was 7.5% (95% CI, 6.5% to 8.4%). No significant change in clearance was observed between test PK and confirmatory PK ($P = .220$, paired t-test), indicating that intrpatient variability in clearance was minimal. Median total i.v. Bu administered was 14.5 mg/kg of actual body weight (range, 8.8 to 20.1). Bu exposure was similar to the overall population in the subgroup of patients experiencing the AEs of TRM or mucositis (Figure 3).

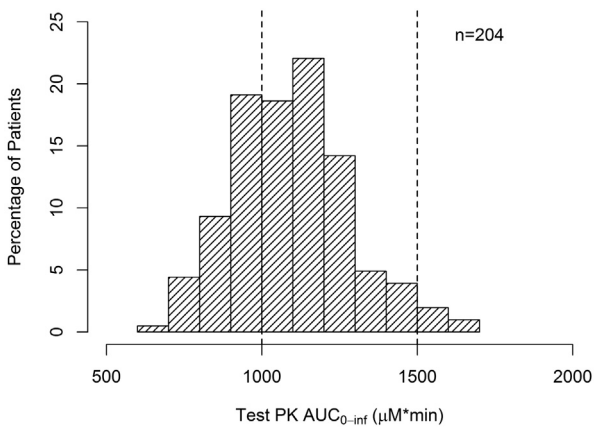

Figure 1. Measured AUC from .8 mg/kg of i.v. Bu as a preconditioning test PK on of the days, day −14 to day −11 (n = 204). Dotted line represents ± 20% range of the target AUC (1000-1500 μM·min).

Adverse Events

An early subset analysis by age in June 2011 revealed that 4 of 17 subjects age > 65 years suffered TRM by day 100, which met a protocol-specified stopping rule for this population. The TRM rates by day 100 for all patients (n = 203), patients > 65 years (n = 17), and patients ≤ 65 years (n = 186) were 4.5% (95% CI, 2.1% to 8.3%), 23.5% (95% CI, 6.8% to 49.9%), and 2.7% (95% CI, 0.9% to 6.2%), respectively. The most common AEs leading to death were respiratory failure (4 subjects, 1.9%), sepsis (3 subjects, 1.4%), multiorgan failure (2 subjects, 1.0%), and acute respiratory distress syndrome (2 subjects, 1.0%). Serious AEs with an incidence of 2% or greater were recorded for 90 subjects (43.5%). The most common grades 3 to 4 AEs observed in subjects ≤ 65 years were febrile neutropenia (grade 3, 54%; grade 4, 3%), stomatitis (grade 3, 41%; grade 4, 0%), nausea (grade 3, 10%; grade 4, 0%), and pneumonia (grade 3, 7%; grade 4, 0%). There were no instances of seizure or hepatic veno-occlusive disease based on the Baltimore criteria [44]. Other grade ≥3 AEs are listed in Table 3.

Efficacy of BuCyE

Efficacy was analyzed for 186 subjects ≤65 years old with HL (n = 65) or NHL (n = 121), including DLBCL (n = 63), MCL (n = 29), and FL (n = 23). Of the 186 patients, 156 (84%) underwent transplant in PR or CR2 or higher. The remainder (n = 30) underwent ASCT in CR1/CRu1 (complete remission 1 with a persistent radiographic abnormality of unknown significance), including 19 patients with MCL. With a median follow-up of 20 months, the estimated rates of 2-year PFS were 33% for HL and 58%, 77%, and 43% for DLBCL, MCL, and FL, respectively. The estimated rates of 2-year OS were 76% for HL and 65%, 89%, and 89% for DLBCL, MCL, and FL, respectively. The OS and PFS curves for the phase II study of PK-directed BuCyE are shown in Figures 4 and 5, respectively.

Comparisons of BuCyE with Matched CIBMTR Patients

Of the 186 patients, 183 recipients of BuCyE with lymphoma in complete or partial response were matched at a maximum ratio of 4:1 with 729 CIBMTR control subjects based on age, performance status, disease status before transplant, and lymphoma histology. No matches were found for 3 patients. In total, 177 patients had 4 matched control subjects, and 97% of BuCyE-treated subjects had an age difference from control subjects of ≤ 5 years. A comparison of patients from the phase II trial of BuCyE and the matched cohort of patients conditioned with BEAM from the CIBMTR is shown in Table 4. Patients were well-matched for age, performance status, histologic subtype, and response before transplant, and the median follow-up was 22 months in both cohorts.

Two-year cumulative incidences of TRM were 3.3% (95% CI, 1.4% to 6.6%) and 3.9% (95% CI, 2.4% to 5.7%) for BuCyE and

Table 2
AUC Exposure from Test Dose (.8 mg/kg i.v. Bu) by Body Mass Index Category

BMI Category (kg/m^2)	BMI (kg/m^2) (mean ± SD)	Clearance (mL/min/kg) Median (range)	AUC (n)			Total (n)
			<1000 μM·min	<1000 to 1500 μM·min	>1000 μM·min	
Underweight (<18.5)	17.9 ± .51	2.76 (2.50-2.30)	0	4 (100%)	0	4
Normal (18.5-24.5)	22.9 ± 1.63	2.85 (1.95-4.39)	10 (18.5%)	40 (74.0%)	4 (7.4%)	54
Overweight (25.0-29.9)	27.6 ± 1.48	2.92 (2.15-4.11)	23 (33.8%)	42 (62.7%)	2 (3.0)	67
Obese (30.0)	35.4 ± 5.10	3.16 (2.43-4.20)	34 (43.0)	45 (56.9%)	0	79

BMI indicates body mass index.

BEAM, respectively. Corresponding 2-year probabilities of OS were 76% (95% CI, 68% to 82%) and 78% (95% CI, 74% to 82%). Tables 5 and 6 compare outcomes for NHL and HL separately. Multivariate analysis demonstrated a significant interaction between disease and conditioning regimen in evaluation of disease progression and treatment failure. Analyses by histology demonstrated that among patients with NHL, there were no differences in outcomes between groups. Among patients with HL treated with BuCyE or BEAM, respectively, the 2-year cumulative incidences of progression were 66% (95% CI, 53% to 77%) and 38% (95% CI, 31% to 45%) and 2-year PFS rates were 33% (95% CI, 21% to 46%) and 59% (95% CI, 52% to 66%), with no difference in TRM or OS. The 2-year cumulative incidences of TRM were 3.3% (95% CI, 1.4% to 6.6%) and 3.9% (95% CI, 2.4% to 5.7%) for BuCyE and BEAM, respectively. Survival curves comparing BuCyE and BEAM conditioning from this matched analysis for NHL and HL are shown in Figures 6 and 7.

DISCUSSION

This was the first large-scale, multicenter, prospective study in North America in which the i.v. weight-based Bu dose was further adjusted based on PK results from a preconditioning test dose. We found that simple preconditioning TDM accurately estimated Bu clearance, allowing for adequate conditioning dosing. Accuracy of the test dose prediction and accuracy of test dose–based dose adjustments were high, comparable with previous studies in which clearance remained consistent across a preconditioning test PK and a conditioning regimen for oral and i.v. Bu [45-47]. Although infusion rates differed between the test dose and the first therapeutic dose by approximately 2- to 4-fold, infusion rate–dependent nonlinear behavior was not noted. This may be due to determination of Bu AUC and its estimated corresponding clearance using a 1-compartment model versus noncompartmental analysis. Bu AUC estimates appear to more variable using noncompartmental analysis [40]. In addition, a population PK analysis demonstrated that Bu PK can be adequately described by a linear PK model without interoccasional variability [48]. In this study more than one-third of patients would have had suboptimal exposure to i.v. Bu if weight-based dosing alone had been used for conditioning, whereas 95% of subjects achieved the target range of Bu exposure after the introduction of individualized TDM. A preconditioning test dose may be more convenient for transplant centers relying on external PK laboratories and can offer another opportunity for TDM on the first day of conditioning if the initial PK results are not assessable.

Results from the present study further showed that such PK-directed Bu doses in combination with cyclophosphamide and etoposide constituted a tolerable regimen for lymphoma patients < 65 years of age and was associated with expected transplant conditioning toxicities and a TRM < 5%. BuCyE was not well tolerated in patients ≥ 65 years, resulting in unacceptable early TRM for older patients with lymphoma. For patients with NHL, PK-directed i.v. BuCyE produced similar PFS and OS to contemporary patients treated with BEAM; however, a statistically significant difference in PFS was observed between BuCyE and BEAM in subjects with HL, indicating superior outcomes for BEAM in terms of relapse and PFS. Although this trial and the additional matched cohort study design were not originally powered to test the difference between the BuCyE and BEAM

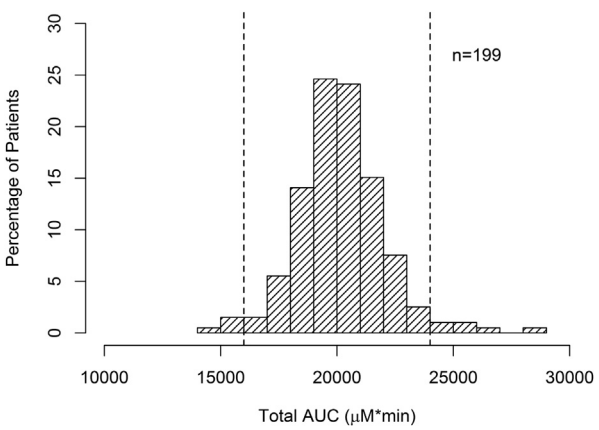

Figure 2. Histograms of estimated total AUC from test PK and confirmatory PK results (n = 199). Dotted line represents the ± 20% range of the target AUC (16,000-24,000 μM·min).

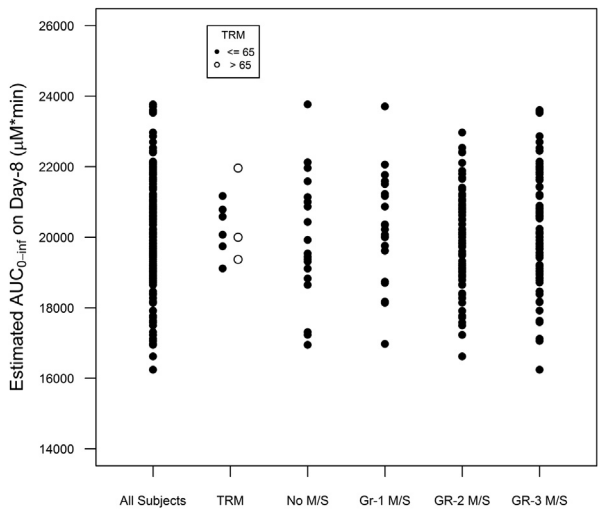

Figure 3. Scatter plot of total estimated Bu AUC for all patients and of actual Bu AUC for patients with AEs of TRM and mucositis/stomatitis (M/S). Scatter plots represent subjects with no M/S and grades (GR) 1, 2, and 3 M/S. There were no cases of GR 4 M/S.

Table 3
Grades 3 to 4 AEs after PK-Directed BuCyE Conditioning (N = 203)

Adverse event	Grade 3	Grade 4	Total of Grade ≥ 3
Febrile neutropenia	110 (54)	7 (3)	117 (57)
Stomatitis	84 (41)	0	84 (41)
Nausea	21 (10)	0	21 (10)
Hypophosphatemia	14 (7)	2 (1)	16 (8)
Pharyngeal inflammation (esophagitis)	10 (5)	0	10 (5)
Pneumonia	15 (7)	0	15 (7)
Hypokalemia	12 (6)	1 (0.5)	13 (6)
Diarrhea	12 (6)	0	12 (6)
Decreased appetite	13 (6)	0	13 (6)
Hypoxia	11 (5.3)	1 (0.5)	12 (6)
Hepatic veno-occlusive disease (Baltimore criteria)	0	0	0

Values are total number of cases with percents in parentheses.

arms for subjects with HL, the sample size for the phase II cohort subset and the 4:1 matching approach were reasonably large for examining this comparison and strength of the association warrants notice.

Previous clinical data using Bu and cyclophosphamide with or without etoposide have yielded clinical results that are comparable with the other preparative regimens for ASCT in both NHL and HL [4,7,24,26,27,29,30]. Bu exposure (as assessed by AUC) has been associated with differences in survival and AEs. Kebriaei et al. [49] showed that an optimally dosed group had a significantly better survival rate than those with lower or higher exposures. Fixed-dose i.v. Bu administration resulted in two-thirds of all subjects achieving AUC values within the optimal window, but PK-directed dosing increased the frequency of patients

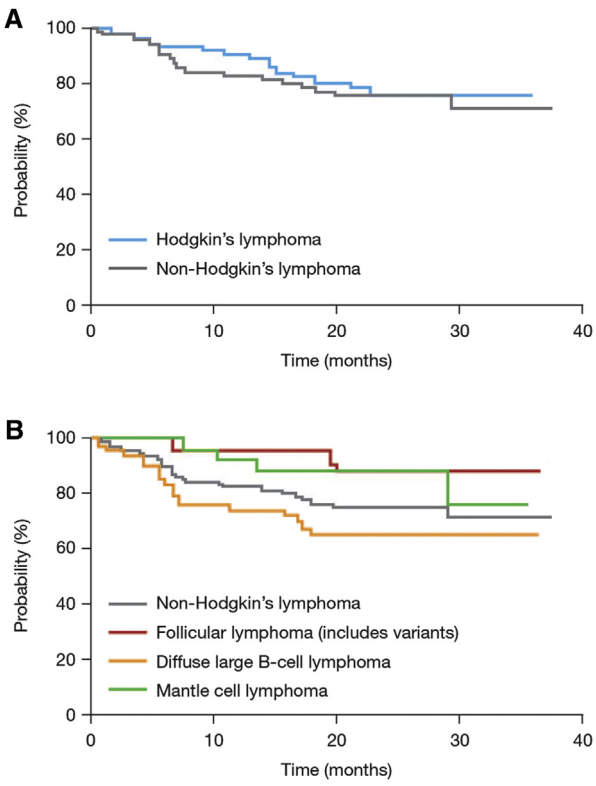

Figure 4. OS for the phase II study of PK-directed BuCyE conditioning and ASCT for lymphoma. (A) HL/NHL. (B) NHL subtypes.

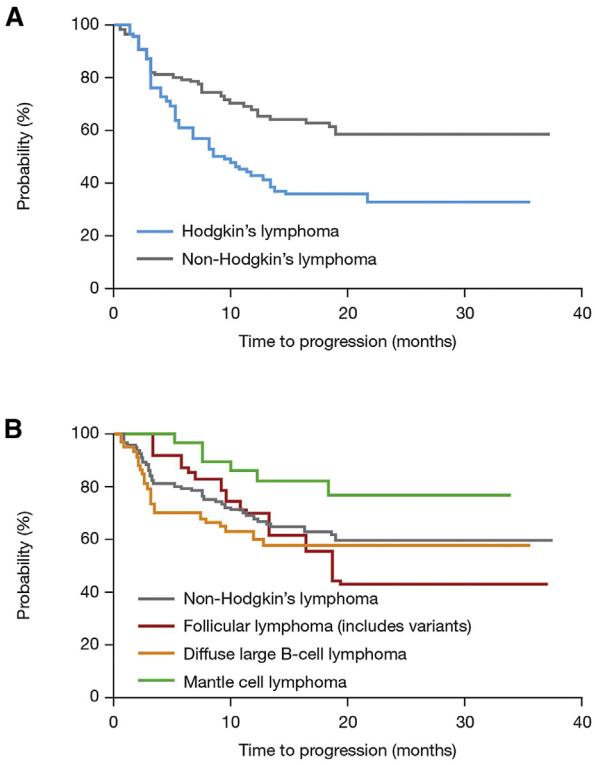

Figure 5. PFS for the phase II study of PK-directed BuCyE conditioning and ASCT for lymphoma. (A) HL/NHL. (B) NHL subtypes.

within the targeted range of AUC exposure up to 95%. The 2-year OS and PFS rates were 85% and 57%, respectively, for patients with HL and 67% and 64%, respectively, for patients

Table 4
Characteristics of Patients Aged ≤ 65 Years in the Matched Analysis of Phase II BuCyE and Contemporary Lymphoma Patients Treated with BEAM from CIBMTR

	BuCyE (n = 183)	BEAM (n = 729)
Age at transplant, yr, median (range)	52 (19-65)	50 (19-65)
Age group at transplant, n (%)		
18-20 yr	1 (<1)	10 (1)
20-30 yr	23 (11)	102 (13)
30-40 yr	29 (16)	99 (14)
40-50 yr	38 (21)	153 (21)
50-60 yr	59 (32)	229 (32)
60-65 yr	33 (18)	132 (18)
Karnofsky score, n (%)		
<90%	42 (23)	167 (23)
≥90%	139 (76)	552 (76)
Missing	2 (1)	6 (1)
Histology, n (%)		
NHL		
FL	23 (13)	90 (12)
DLBCL	62 (34)	246 (34)
MCL	29 (16)	112 (15)
Other	5 (2)	21 (3)
HL		
Lymphocyte predominant	2 (1)	1 (<1)
Nodular sclerosis	46 (24)	212 (29)
Mixed cellularity	7 (4)	13 (2)
Lymphocyte depleted	0	2 (<1)
Nodular lymphocyte predominant	2 (1)	11 (1)
Unclassified not further specified	7 (4)	17 (2)

Table 5
Comparison of Outcomes for NHL Patients in the Matched Analysis of Phase II BuCyE and Contemporary Lymphoma Patients Treated with BEAM from CIBMTR

	BuCyE (Estimate n [95% CI])	BEAM (Estimate n [95% CI])	*P*
TRM			
No. of subjects	119	466	
At 1 yr	4 (1-9)	3 (2-5)	.626
At 2 yr	4 (1-9)	4 (2-7)	.924
Relapse/progression			
No. of subjects	119	466	
At 1 yr	26 (19-35)	27 (23-32)	.847
At 2 yr	36 (27-46)	41 (35-46)	.410
PFS			
No. of subjects	119	466	
At 1 yr	69 (61-77)	70 (65-74)	.984
At 2 yr	60 (50-69)	55 (49-60)	.398
OS			
No. of subjects	119	468	
At 1 yr	83 (76-89)	84 (80-87)	.839
At 2 yr	76 (67-84)	75 (70-79)	.816

with NHL. Although the outcomes associated with BuCyE for NHL appear to be similar to BEAM in the present matched analysis, this is not the case for HL.

One common concern of Bu-based conditioning for patients with HL has been the possibility of overlapping toxicity with prior HL therapies such as bleomycin, alkylating agents, and radiation. However, our findings do not suggest poor outcomes from BuCyE due to excess toxicity or TRM. Indeed, day −28 and day −100 TRM rates were 0% and 1.6%, respectively, for HL patients who received BuCyE conditioning. The primary differences observed between BuCyE and BEAM in this analysis of HL patients was an increase in early relapses, suggesting that BuCyE may be an inferior regimen for disease control among patients with relapsed HL. Why this regimen would produce worse PFS in HL but not in NHL or any NHL subtype remains unclear. A prior single-institution study of 72 patients with HL or NHL conditioned with either cyclophosphamide, etoposide, and carmustine or BEAM found a higher prevalence of diarrhea in the BEAM group (81% versus 51%, $P = .0026$) but a higher OS with BEAM than with cyclophosphamide, etoposide, and carmustine (84% versus 60%); however, outcomes were not stratified by lymphoma subtype [50]. Chen et al. [51] compared outcomes after ASCT across different conditioning regimens and among patients with HL and found that Bu-based regimens were also associated with inferior outcomes.

Table 6
Comparison of Outcomes for HL Patients in the Matched Analysis of Phase II BuCyE and Contemporary Lymphoma Patients Treated with BEAM from CIBMTR

	BuCyE (Estimate n [95% CI])	BEAM (Estimate n [95% CI])	*P*
TRM			
No. of subjects	64	253	
At 1 yr	2 (0-6)	2 (1-4)	.805
At 2 yr	2 (0-6)	3 (1-6)	.514
Relapse/progression			
No. of subjects	64	253	
At 1 yr	55 (43-67)	30 (24-36)	<.001
At 2 yr	66 (53-77)	38 (31-45)	<.001
PFS			
No. of subjects	64	253	
At 1 yr	43 (31-55)	68 (62-74)	<.001
At 2 yr	33 (21-46)	59 (52-66)	<.001
OS			
No. of subjects	64	255	
At 1 yr	90 (82-96)	95 (92-98)	.241
At 2 yr	76 (64-87)	85 (79-91)	.168

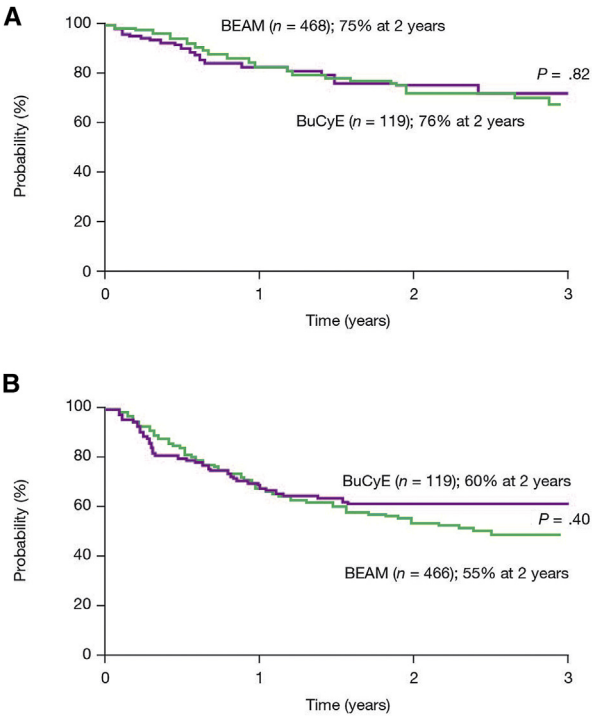

Figure 6. Comparison of survival for NHL patients in the matched analysis of phase II BuCyE and contemporary lymphoma patients treated with BEAM from CIBMTR. (A) OS. (B) PFS.

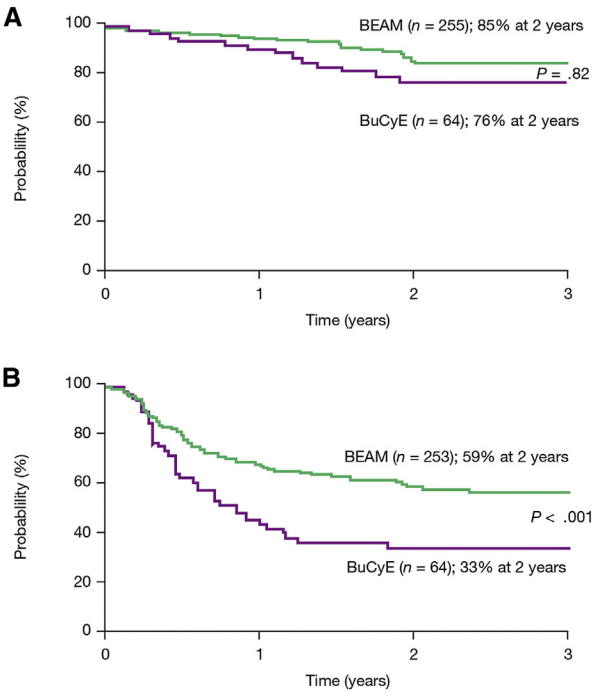

Figure 7. Comparison of survival for HL patients in the matched analysis of phase II BuCyE and contemporary lymphoma patients treated with BEAM from CIBMTR. (A) OS. (B) PFS.

Interpretation of our findings should also consider the limitations of a nonrandomized comparison between the patients and control subjects. Despite constructing a matched cohort of CIBMTR patients for comparison, unmeasured but important factors could be unbalanced between the 2 groups, which could bias the interventions. Nevertheless, the matching strategy effectively identified a large, contemporary cohort of patients who were similar in age, performance status, and lymphoma subtype, which were previously identified as important determinants of outcome. Additionally, the control cohort patients were from centers not participating in the clinical trial, which minimized selection bias.

At present, identifying the preferred therapy for relapsed HL remains complex, and the most effective form of HDT may differ by patient characteristics. Nevertheless, given the dearth of randomized controlled trials to inform the management of patients with relapsed HL undergoing ASCT, careful consideration of these findings should be undertaken and BEAM conditioning should be preferred for patients with HL undergoing ASCT when all other factors are equivalent.

ACKNOWLEDGMENTS

The authors thank the patients, their caregivers, and the staff at participating centers. The authors also thank Louie Yu and Shiva Patil for pharmacokinetic support, Jeanne Burkart for registry support, Agnes Elekes for medical review, Cathy Zhao and Peter Loonan for statistical analysis, and David Norris, PhD, for editorial assistance provided during the preparation of this report. This assistance was paid for through funding supplied by OPDC to Ecosse Medical Communications, LLC (Falmouth, MA).

Participating centers were as follows: Cedars Sinai Medical Center (Drs. Michael Lill and Stephen Lim), Medical University of South Carolina (Drs. Luciano Costa and Robert Stuart), Emory University (Drs. Christopher Flowers and Edmund Waller), Medical College of Weill Cornell University (Drs. Tsiporah Shore and Koen van Besien), University of Alabama at Birmingham (Drs. Donna Salzman and William Vaughan), West Virginia University (Dr. Michael Craig), South Texas Veterans Health Care System and The University of Texas Health Science Center at San Antonio (Dr. Cesar Freytes), University of North Carolina Chapel Hill (Dr. Thomas Shea), Loyola University Chicago (Dr. Tulio Rodriguez), Sarah Cannon Research Institute (Dr. Ian Flinn), New Brunswick Stem Cell Transplant Program (Dr. Terrance Comeau), The University of Arizona Cancer Center (Dr. Andrew Yeager), University of Utah (Dr. Michael Pulsipher), The University of Ottawa (Dr. Isabelle Bence-Bruckler), McGill University Health Center (Dr. Pierre Laneuville), University of Nebraska Medical Center (Dr. Philip Bierman), Oregon Health & Science University (Dr. Andy Chen), University of Michigan (Drs. Shin Mineishi and Daniel Couriel), University of Illinois Cancer Center (Dr. Damiano Rondelli), Duke University Medical Center (Dr. Mitchell Horwitz), Baylor University Medical Center (Dr. Joseph Fay), Scripps Clinic (Dr. James Mason), Florida Hospital Cancer Institute (Drs. Vijay Reddy and Melhem Sohl), Montefiore Medical Center (Dr. Ira Braunschweig), The University of California, San Francisco Medical Center (Dr. Weiyun Ai), Texas Transplant Institute (Dr. Paul Shaughnessy), Saskatoon Cancer Center (Dr. Waleed Sabry), The University California Davis Medical Center (Dr. Mehrdad Abedi), Sutter Cancer Center (Dr. Michael Carroll), Louisiana State University in Shreveport (Drs. Francesco Turturro, Gerhard Hildebrandt, and Nebu Koshy), Virginia Commonwealth University (Dr. John McCarty), Queen Elizabeth II Health Sciences Center (Dr. Stephen Couban), University of Oklahoma (Dr. George Selby), Rocky Mountain Blood and Marrow Transplant Program (Drs. Peter McSweeney and Michael Maris), University of Kansas Medical Center (Dr. Joseph McGuirk), Alta Bates Summit Medical Center (Dr. Oleg Krijanovski), University California, San Diego Medical Center (Dr. Edward Ball), University of Chicago (Dr. Sonali Smith), Indiana University (Dr. Sherif Farag), University of Maryland (Drs. Gorgun Akpek and Saul Yanovich), Western Pennsylvania Hospital (Dr. Entezam Sahovic), and Fred Hutchinson Cancer Research Center (Dr. Leona Holmberg).

Financial disclosure: Otsuka Pharmaceutical Development & Commercialization, Inc. sponsored this study and provided the i.v. Bu for the analyses.

Conflict of interest statement: C.R.F., L.J.C., M.C.P., J.L.-R., M.L., T.B.S., W.V., M.C., T.C.S., M.E.H., J.W.F., I.B., W.A., R.F.Y., T.E.R., I.F., A.M.Y., M.A.P., I.B.-B., P.L., P.B., and A.I.C. declare no financial conflicts of interest for this study. C.O.F. has received grant/research support from Otsuka and Merck, is a consultant to Otsuka and Clinipace, and serves on the speaker's bureau for Sanofi and advisory boards for Spectrum Pharmaceutical. S.M. has received research support from Otsuka for an unrelated subject. D.R. has received honoraria for advisory boards and speaker's bureaus from Sanofi and a research grant from Otsuka. J.M. serves as a consultant to Pfizer and Genoptix. T.C. serves on advisory boards for Celgene, Johnson & Johnson, and Lundbek. K.K., Y.W., C.X., and A.J.S. have been or are currently employees of Otsuka Pharmaceutical Development & Commercialization, Inc. E.K.W. has served as a consultant to Otsuka.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbmt.2016.03.018.

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