Biol Blood Marrow Transplant 20 (2014) 536–542

Phase I/II Study of Bortezomib-BEAM and Autologous Hematopoietic Stem Cell Transplantation for Relapsed Indolent Non-Hodgkin Lymphoma, Transformed, or Mantle Cell Lymphoma

Basem M. William*,†, Mary S. Allen, Fausto R. Loberiza Jr., Robert Gregory Bociek, Philip J. Bierman, James O. Armitage, Julie M. Vose

Division of Oncology/Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska

Article history:
Received 23 September 2013
Accepted 8 January 2014

Key Words:
Stem cell transplantation
Autologous
Lymphoma
Non-Hodgkin lymphoma
Mantle cell
Bortezomib

A B S T R A C T

A phase I/II trial was designed to evaluate the safety and efficacy of adding bortezomib to standard BEAM (BCNU, etoposide, cytarabine, melphalan) and autologous hematopoietic stem cell transplantation (ASCT). Eligible patients had relapsed/refractory indolent or transformed non-Hodgkin lymphoma or mantle cell lymphoma (MCL) that was relapsed/refractory or in first partial (PR) or complete remission (CR). Patients received bortezomib on days −11, −8, −5, and −2 before ASCT. Phase I had 4 dose cohorts (.8, 1, 1.3, and 1.5 mg/m^2) and 3 patients were accrued to each. Any nonhematological ASCT-related toxicity >2 on the Bearman scale occurring between day −11 and engraftment defined the maximum tolerated dose (MTD). After the MTD has been reached, another 20 patients were enrolled at this dose to determine a preliminary overall response rate (ORR). Patients who were in CR or PR at day +100 were considered responders. The study enrolled 42 patients through August 14, 2009. The median age was 58 (range, 34 to 73) years, with 33 males and 9 females. The most common diagnoses were MCL (23 patients) and follicular lymphoma (7 patients). The median number of prior therapies was 1 (range, 0 to 6). The median follow-up was 4.88 (range, 1.07 to 6.98) years. Thirteen patients were treated in phase I and 29 patients were treated in phase II. The MTD was initially determined to be 1.5 mg/m^2 but it was later decreased to 1 mg/m^2 because of excessive gastrointestinal toxicity and peripheral neuropathy. The ORR was 95% at 100 days and 87% at 1 year. For all 38 evaluable patients at 1 year, responses were CR 84%, PR 1%, and progressive disease 13%. Progression-free survival (PFS) was 83% (95% CI, 68% to 92%) at 1 year, and 32% (15% to 51%) at 5 years. Overall survival (OS) was 91% (95% CI, 79% to 96%) at 1 year and 67% (50% to 79%) at 5 years. The most common National Cancer Institute grade 3 toxicities were neutropenic fever (59%), anorexia (21%), peripheral neuropathy (19%), orthostatic hypotension/vasovagal syncope (16%), and 1 patient failed to engraft. Compared with 26 MCL in CR1 historic controls treated with BEAM and ASCT, PFS was 85% and 43% for the BEAM group versus 87% and 57% for those who received bortezomib in addition to standard BEAM (V-BEAM) at 1 and 5 years, respectively (log-rank $P = .37$). OS was 88% and 50% for the BEAM group versus 96% and 72% for V-BEAM at 1 and 5 years, respectively (log-rank $P = .78$). In conclusion, V-BEAM and ASCT is feasible. The toxicities were manageable and we did not observe any treatment-related mortalities; however, we did observe an excess of autonomic dysfunction and ileus, which is concerning for overlapping toxicity with BEAM conditioning. Determining relative efficacy of V-BEAM compared to BEAM would require a randomized trial.

INTRODUCTION

Patients with relapsed indolent lymphomas and high-risk mantle cell lymphoma (MCL), have high complete remission (CR) rates after high-dose therapy (HDT) and autologous stem cell transplantation (ASCT), yet there are still a significant number of patients who relapse after this procedure. Follicular lymphoma (FL) accounts for approximately 25% of all newly diagnosed cases of non-Hodgkin lymphoma (NHL). The disease course of indolent lymphomas, including FL, is generally one of remissions and exacerbations followed frequently by resistance and transformation to a more aggressive NHL histology. One randomized controlled trial [1] and several retrospective analyses [2-4] demonstrated improved progression-free survival (PFS) when ASCT was used as a consolidation after salvage therapy for patients with FL in first relapse. In the European CUP (chemotherapy, unpurged marrow, purged marrow) trial, ASCT improved 2-year PFS from 26% to 58%, establishing ASCT as the standard of care of relapsed FL patients [1]. Patients who have transformed from a FL to more aggressive NHLs are felt to have a poor prognosis with standard therapies [5]. However, if patients have at least a partial response (PR) to salvage

Financial disclosure: See Acknowledgments on page 541.

* Correspondence and reprint requests: Basem M. William, MD, MRCP, Division of Hematology and Oncology, Blood and Marrow Transplant Program, Department of Medicine, University Hospitals Seidman Cancer Center, Case Western Reserve University, 11100 Euclid Avenue, LKS 5079, Cleveland, OH 44106.

E-mail address: bmw93@case.edu (B.M. William).

† Current address: Basem M. William: Division of Hematology and Oncology, Department of Medicine, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, Ohio.

1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.01.004

chemotherapy and then proceed to ASCT, they have been found to have a prognosis similar to patients receiving a similar transplantation for FL [6,7].

MCL is an aggressive form of NHL and it accounts for 5% to 6% of all new NHL diagnoses [8]. With standard therapies, the prognosis of MCL is poor, with an average PFS of 8 to 20 months [9,10]. With the introduction of rituximab and the use of upfront intensified treatment regimens, like hyper-CVAD, (cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high dose methotrexate and cytarabine) and/or ASCT in first CR, 5-year PFS of 50% to 60% has become achievable [11-15]. T cell prolymphocytic leukemia, when treated with standard therapy, has a poor prognosis. However, studies using ASCT have produced some early promising results [16].

Various HDT regimens were used before ASCT in patients with NHL, yet little is known regarding the comparative toxicity and efficacy of these regimens, as no randomized trials were performed. The BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen is one of the most popular HDT regimens employed before ASCT for lymphomas since its introduction in the 1980s [17]. Retrospective data suggested lower toxicity and improved outcomes when compared with older carmustine-based regimens [18,19]. The rate of progression after HDT and ASCT remains around 40% for relapsed or transformed indolent NHLs and high-risk MCL [1,7,12,15], and novel treatments to improve outcomes of these patients are needed. Bortezomib (Velcade, Millennium Pharmaceuticals Inc., Cambridge, MA) is a novel, small molecule proteasome inhibitor approved in the United States for treatment of multiple myeloma. The antineoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration, and angiogenesis. Nuclear factor-κB is constitutively activated in MCL [20], FL [21], and marginal zone lymphoma [22], and it is a major player in mediating resistance to chemotherapeutic agents. Inhibition of the proteasome in MCL led to rapid down-regulation of nuclear factor-κB and apoptosis of MCL cells [20]. Bortezomib has shown significant single-agent activity against relapsed/refractory indolent and mantle cell lymphomas in multiple small single-institution trials [23-25]. The landmark PINNACLE trial showed an overall response rate (ORR) for single-agent bortezomib of 33% in 144 assessable patients with relapsed/refractory MCL, with an average duration of response of 9.2 months [26].

It was hoped that the addition of bortezomib to standard BEAM conditioning would improve the outcome of patients with relapsed indolent NHL and MCL without excessive toxicity. We designed a phase I/II study to evaluate the safety and efficacy of escalating doses of bortezomib added to standard fixed dose of BEAM regimen (V-BEAM) before ASCT for relapsed indolent and high-risk MCL patients.

SUBJECTS AND METHODS

Eligibility Criteria

Inclusion criteria included age 19 years or older and persistent, relapsed, or refractory indolent NHL including FL, composite lymphomas with ≥50% of tumor showing follicular histology, transformed follicular, lymphoplasmacytic, marginal zone lymphoma, small lymphocytic lymphoma (including T cell subtypes), MCL (MCL were included only if they were in first CR), or any peripheral T cell lymphoma that was relapsed, refractory, or in first CR or PR. We included heterogeneous group of patients with NHL in whom HDT followed by ASCT is considered to be the standard of care and who have a disease that has been historically associated with a high risk of relapse after HDT and ASCT. Additional inclusion criteria were expected survival duration of 6 months or more, Karnofsky performance status of 70% or higher, liver functions <3 times upper limits of normal unless due to disease, serum creatinine <2.5 mg/dL or calculated creatinine clearance >50 mL/min, absolute neutrophil count >500 cells/mm^3, and platelet count >50 mm^3. Patients older than 60 years or with clinical signs of heart disease must have had an ejection fraction ≥ 45%. Patients with clinical signs of pulmonary insufficiency must have had diffusion capacity of carbon monoxide higher than 50% of predicted value. Patient must have been able to collect more than 1.2×10^6/kg CD34$^+$ cell for transplantation. All patients signed a written informed consent. Male and female patients of reproductive potential were required to follow accepted birth control measures.

Exclusion criteria included human immunodeficiency virus seropositivity; active infection at the time of transplantation; myocardial infarction within 6 months before enrollment; New York Hospital Association class III or IV heart failure; uncontrolled angina; severe uncontrolled ventricular arrhythmias; electrocardiographic evidence of acute ischemia or active conduction system abnormalities; a serious disease or condition that, in the opinion of the investigators, would compromise the patient's ability to participate in the study; pregnant or lactating females; or hypersensitivity to bortezomib, boron, or mannitol.

Study Design and Preparatory Regimen

This was a single-institution phase I/II study where escalating doses of bortezomib were given with standard dose of BEAM in the inpatient setting as a conditioning regimen before ASCT. In Phase I of the study, bortezomib was administered in 4 dose cohorts: .8 mg/m^2, 1.0 mg/m^2, 1.3 mg/m^2, and 1.5 mg/m^2. Three patients were accrued in each dose cohort with enrollment starting at dose cohort 1 (.8 mg/m^2). Bortezomib was given on days −11, −8, −5, and −2. All study patients received BEAM conditioning per our standard institution protocol: carmustine (BCNU) 300 mg/m^2 on day −5, etoposide 100 mg/m^2 twice daily on days −5, −4, −3, and −2, cyatabine 100 mg/m^2 twice daily on days −5, −4, −3, and −2, and melphalan 140 mg/m^2 on day −1 before infusion of autologous stem cells. The objective of phase I was to determine the maximum tolerated dose (MTD) of bortezomib in this setting. The MTD was defined by observing any nonhematologic transplantation-related toxicity higher than grade 2 on the Bearman scale [27] occurring between day −11 (first bortezomib infusion) and engraftment. After the MTD was defined, we enrolled another 20 patients to obtain a preliminary estimate of ORR, progression-free survival, and overall survival (OS) using this regimen.

Supportive Care and Clinical Monitoring

Peripheral blood stem cells were collected per the discretion of the treating physician. Once an adequate number of CD34$^+$ cells/kg had been collected (per standard institutional protocol) the patient started the preparative regimen for transplantation. Filgrastim was started at 5 mg/kg daily at day +7 after stem cell infusion, and patients received fluconazole and acyclovir prophylaxis until count recovery (per standard intuitional protocol). Packed RBCs and platelet transfusions were administered to maintain a hemoglobin level >8 g/dL and a platelet count $>10 \times 10^9$/L. Blood cultures were drawn and patients were treated with broad-spectrum antibiotics when fever developed, per standard clinical practices. Patients were evaluated daily by physical examination and laboratory studies from day -11 until hospital discharge and then were followed on an outpatient basis, as clinically indicated. Patients were restaged at day +100, and again 1 year after ASCT with imaging studies (computed tomography, positron emission tomography–computed tomography, or magnetic resonance imaging scans as clinically indicated). Restaging bone marrow biopsies were performed only in patients who had a prior history of disease involving the bone marrow. Responses were evaluated according to those reported elsewhere by Cheson et al. [28]. All toxicities were defined by use of the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0 (2003). Patient who were in CR or PR at day +100 were considered *responders*.

Statistical Analysis

The primary objective of the study was to evaluate the toxicity and determine the MTD of bortezomib when added to a standard BEAM conditioning regimen followed by ASCT. The secondary objective of the study was to obtain a preliminary estimate of the ORR, PFS, and OS with this regimen. The phase I section of the study followed a standard 3 + 3 design: 3 patients were enrolled at the initial dose level. If 2 of the 3 patients in the initial cohort had a dose-limiting toxicity (DLT), 3 additional patients were enrolled to that dose level. If 3 of 6 patients experienced a DLT, as defined as grade >2 on the Bearman scale, no further dose escalation occurred. If 2 of 3 patients in dose cohorts 2, 3, or 4 had a DLT, 3 additional patients were enrolled to that dose cohort. If 2 of 6 patients experienced a DLT, no further dose escalation occurred. The MTD is defined to be the dose cohort below which 3

of 6 patients experience DLT, or the highest dose cohort of 1.5 mg/m^2, if 2 DLT were not observed at any dose cohort. To refine the estimate of ORR, 20 additional patients were accrued at the MTD. If 3 patients were accrued at the MTD in the phase I portion, accruing 20 additional patients reduced the maximum width of the 95% confidence interval for the response rate from .58 to .21. If 6 patients are accrued at the MTD in the phase I portion, accruing 20 additional patients reduced the maximum width of the 95% confidence interval for the response rate from .41 to .20. Patients enrolled at the MTD in the phase I portion were included in the final estimate of response rate. OS and PFS were estimated according to Kaplan-Meier method. The log-rank test was used to assess the significance of differences for each prognostic factor in the univariate analysis. The Cox proportional hazards regression model and the logistic regression models were used to assess how patients' characteristics predict PFS and OS. Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC). Two-sided tests were used in all calculations. Significance level was fixed at $P = .05$ for all the statistical analyses.

RESULTS

Patient Characteristics

In total, 42 patients were enrolled (13 patients in phase I and 29 patients in phase II) until August 14, 2009. All completed the treatment and proceeded to transplantation. Baseline characteristics are presented in Table 1. The median age of subjects was 58 years and the median number of prior therapies was 1. Fifty-five percent of these patients had MCL and 62% of the patients underwent transplantation in CR1. The median duration of follow-up was 4.88 (1.07 to 6.98) years. All patients with MCL received upfront therapy with Rituximab-HyperCVAD regimen and most subjects with other subtypes of lymphomas received cyclophosphamide, vincristine, doxorubicin, prednisone (CHOP)/cyclophosphamide, vincristine, prednisone (CVP) or R-CHOP/CVP. Cumulative exposure to vincristine was comparable across subjects. Only 2 of the subjects received bortezomib with salvage chemotherapy pretransplantation. None of the study subjects had more than grade 1 neuropathy upon enrollment.

Safety

All 42 patients were evaluable for safety. As expected, all patients experienced at least 1 adverse event (AE), 39 (93%) experienced at least 1 grade 3 or higher AE, and 34 (81%) were related to the conditioning regimen. The most common grade 3 AEs were neutropenic fever (59%), anorexia (21%), peripheral neuropathy (19%), and orthostatic hypotension/vasovagal syncope (16%). Overall incidences of AEs are reported in Table 2. Infectious complications are reported separately in Table 3. The most common infectious complications, in addition to neutropenic fever, were bacteremias (26%) and clostridium difficile colitis (23%). The most common organisms causing bacteremias were streptococcus viridans and coagulase-negative staphylococcus.

The MTD was initially determined to be 1.5 mg/m^2 but was later decreased to 1 mg/m^2 because of excessive gastrointestinal toxicity and peripheral neuropathy (in phase II patients). Grade 3 ileus was observed in 9% of patients and 1 patient had perforation of the jejunum with necrosis; this was possibly related to the treatment. The median time to onset of neuropathy was 5 weeks (range, 2 to 24 weeks). Five of 8 (62%) patients with grade 3 neuropathy required treatment and 3 of 5 subjects were able to stop treatment of neuropathy after 1 to 6 years. None of the orthostatic hypotension/vasovagal syncope episodes observed required fludrocortisone replacement or any other specific treatment beyond administration of intravenous fluids, and all resolved before hospital discharge.

The breakdown of bortezomib dose given is shown in Table 4. No treatment-related mortality was observed in the study. All patients, except 1, had successfully engrafted with mean time to absolute neutrophil count >500 cells/mm^3 of 11 days (range, 9 to 15). Mean time to independence of RBC transfusions was 10 days (range, 1 to 38) and 7 patients did not need RBC transfusions. Mean time to independence of platelet transfusions was 16 days (range, 7 to 36). Mean number of days of granulocyte colony-stimulating factor support was 6 (range, 2 to 28).

Table 1
Patient Characteristics

Parameter	Value (N = 42)
Median age (range), yr	58 (34-73)
Male/female	33/9
Histology	23
• Mantle cell lymphoma	6
• Nodular mantle cell lymphoma	6
• Follicular lymphoma	1
• Diffuse large B cell//transformed FL-3	1
• Marginal zone lymphoma	1
• B lymphoplasmacytic lymphoma	1
• Small lymphocytic lymphoma	1
• T Prolymphocytic leukemia	1
• Anaplastic large cell lymphoma	1
Prior courses of systemic therapy, median (range)	1 (1-6)
Disease stage at transplantation (%)	
• CR1	26 (62%)
• CR3	1 (2%)
• Primary induction failure/chemosensitive disease	12 (29%)
• Relapsed	3 (7%)
Follow-up of survivors, median (range), mo	32 (12-55)

FL indicates follicular lymphoma; CR, complete remission.
Data presented are n (%) unless otherwise indicated.

Table 2
Adverse Events Reported in ≥ 20% of Patients (N = 42) Plus Incidences of Grade ≥ 3 and Treatment-Related Adverse Events

Event	Any Grade	Grade ≥ 3	Treatment Related
Neutropenic fever	29 (59%)	29 (59%)	29 (59%)
Mucositis/stomatitis	29 (59%)	0	29 (59%)
Diarrhea	23 (54%)	2 (4%)	23 (54%)
Anorexia	15 (35%)	9 (21%)	15 (35%)
Peripheral neuropathy	14 (33%)	8 (19%)	13 (30%)
Rash	12 (28%)	1 (2%)	10 (23%)
Constipation	11 (26%)	1 (2%)	10 (23%)
Vasovagal syncope/ orthostatic hypotension	10 (23%)	7 (16%)	9 (21%)
Nausea and vomiting	5 (11%)	1 (2%)	5 (11%)
Hypokalemia	5 (11%)	5 (11%)	5 (11%)
Hypoxia	5 (11%)	2 (4%)	5 (11%)
Ileus	4 (9%)	4 (9%)	4 (9%)
Renal insufficiency	4 (9%)	1 (2%)	4 (9%)

Data presented are n (%).

Table 3
Infectious Events Reported and Severity

Event	Any Grade	Grade ≥ 3
Neutropenic fever	29 (59%)	29 (59%)
Clostridium difficile colitis	10 (23%)	5 (11%)
Bacteremia	11 (26%)	10 (23%)
Cellulitis	3 (7%)	1 (2%)
Urinary tract infection	3 (7%)	2 (4%)
Herpes zoster	3 (7%)	0
Bacterial enteritis	1 (2%)	0
Upper respiratory infection	1 (2%)	0

Data presented are n (%).

Table 4
Breakdown of Bortezomib Dose Given during Phase I and Phase II

Bortezomib Dose	No. of Patients
Phase I	
• .8 mg	3
• 1.0 mg	4
• 1.3 mg	3
• 1.5 mg	3
Phase II	
• 1.0 mg	6
• 1.3 mg	12
• 1.5 mg	11

Outcomes

All patients enrolled in the study progressed on at least 1 line of therapy, except for MCL patients who underwent transplantation in CR1. The median duration of follow-up was 4.88 (1.07 to 6.98) years. At day +100 after ASCT, 40 patients were evaluable for response; 36 (86%) were in CR and 2 (5%) were in PR with ORR of 95%. One patient had stable disease (5%) and another patient had disease progression (PD) (5%). At 1 year after ASCT, 38 patients were evaluable for response; 32 (84%) were in CR and 1 (3%) was in PR with ORR of 87%. Five patients (13%) had PD. The PFS was 83% (95% confidence intervals [CI], 68% to 92%) at 1 year and 32% (95% CI, 15% to 51%) at 5 years. The OS was 91% (95% CI, 79% to 96%) at 1 year and 67% (95% CI, 50% to 79%) at 5 years (Figure 1). Phase II patients (n = 29) were analyzed separately and at day 100 after ASCT, 28 patients were evaluable for response; 26 (90%) were in CR, 1 (3%) was in PR, and 1 (3%) had stable disease with ORR of 96%. At 1 year after ASCT, 27 phase II patients were evaluable for response: 22 (81%) were in CR and 1 (4%) was in PR with ORR of 89%. Four patients (15%) had PD. The PFS was 83% (63% to 92%) at 1 year and 42% (15% to 67%) at 5 years. The OS was 96% (78% to 96%) at 1 year and 74% (52% to 86%) at 5 years (Figure 2). In an exploratory analysis, PFS and OS were not different between patients based on histology: PFS and OS at 3 years were 72% and 82% for MCL versus 75% and 100% for FL versus 67% and 100% for other histologies (log-rank $P = .95$ and $P = .58$, respectively). There was a trend towards better PFS at 3 years for patients who underwent transplantation in CR1 (85%) versus others (50%), yet that was not statistically significant (log-rank $P = .15$). OS at 3 years based on disease status at transplantation was not different, though; 90% for patients who underwent transplantation in CR1 versus 86% for others (log-rank $P = .94$).

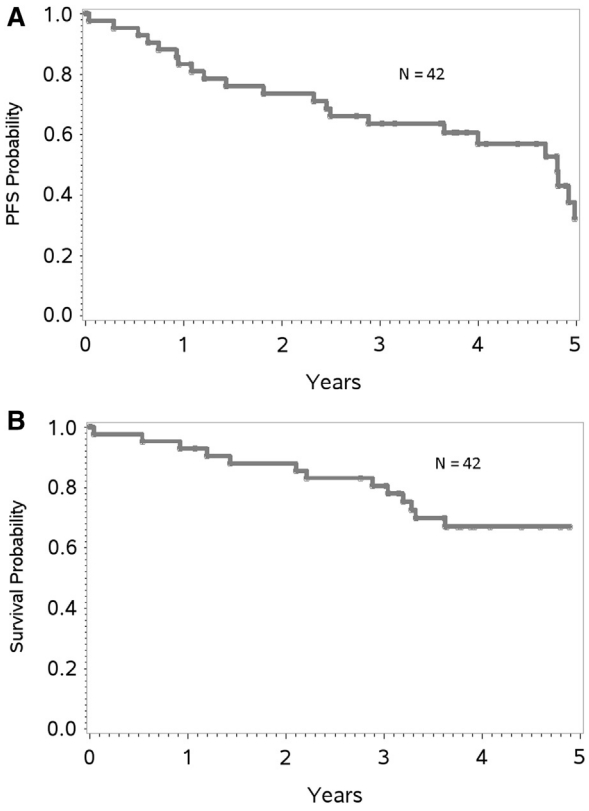

Figure 1. Kaplan-Meier curves for all study patients (N = 42). (A) Shows progression-free survival and (B) shows overall survival.

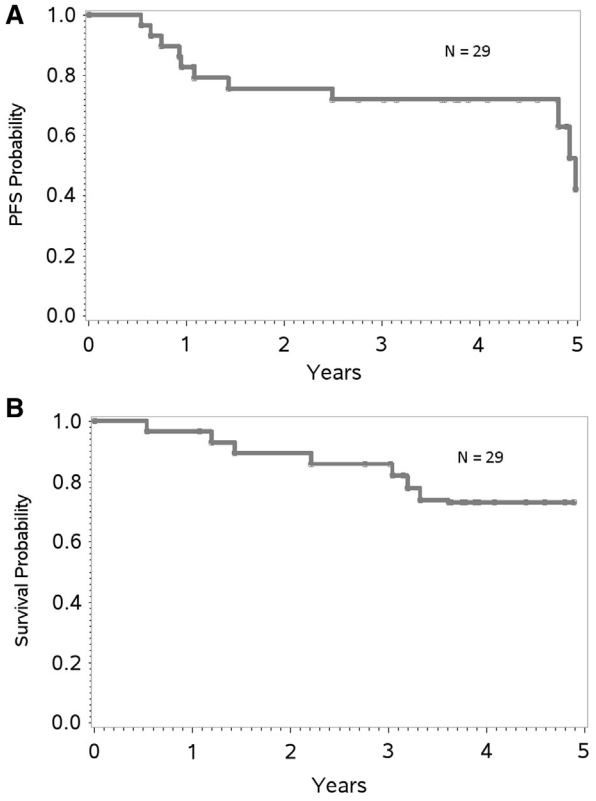

Figure 2. Kaplan-Meier curves for phase II patients (n = 29). (A) Shows progression-free survival and (B) shows overall survival.

Comparison with Historic MCL Patients

In an exploratory analysis, we compared 23 patients with MCL accrued to this study (V-BEAM group) to 26 historic MCL patients (BEAM group) who received standard BEAM followed by ASCT at our institution between the years of 2006 and 2009 to determine if the addition of bortezomib had a dramatic influence on outcomes in patients with MCL. There was no significant difference in baseline characteristics between study and historic patients, as summarized in Table 5. PFS (Figure 3A) was 85% and 43% for the BEAM group versus 87% and 57% for V-BEAM at 1 and 5 years, respectively (log-rank $P = .37$). OS at 1 and 5 years (Figure 3B) was 88% and 50% for the BEAM group versus 96% and 72% for V-BEAM, respectively (log-rank $P = .74$).

DISCUSSION

Recent data demonstrated improved survival of patients with MCL over the last 2 years because of adoption of HDT

Table 5
Comparison between Patient Characteristics of Study Patients and Historic Patients with Mantle Cell Lymphoma

Variable	BEAM	V-BEAM	*P* Value
Number	26	23	
Age, median (range), yr	57 (36-74)	58 (36-71)	.87
Male sex	23 (88)	17 (74)	.19
Ann Arbor staging at diagnosis			.90
I	1 (4)	2 (9)	
II	1 (4)	1 (4)	
III	3 (12)	3 (13)	
IV	21 (80)	17 (74)	
Presence of B symptoms	5 (19)	7 (30)	.46
Elevated serum LDH	9 (35)	5 (22)	.37
Time from diagnosis to treatment, median (range), mo	6 (4-62)	6 (4-9)	.42
Interval from diagnosis to treatment			.17
≤ 1 year	24 (92)	23 (100)	
>1 year	2 (8)	—	
No. of prior treatments			.55
1	21 (81)	20 (87)	
2	5 (19)	3 (13)	
Follow-up time of survivors, median (range), yr	1.97 (.99-4.89)	2.79 (1.07-4.56)	.06

LDH indicates lactate dehydrogenase.

regimens. The introduction of rituximab in the early 90s improved CR rates; however; it did not improve PFS or OS in patients when added to standard CHOP chemotherapy [9]. Earlier retrospective single-institution data have shown improved outcomes with HDT followed by ASCT [29]. The European Mantle Cell Lymphoma Network designed a prospective randomized trial comparing consolidation with myeloablative radiochemotherapy followed by ASCT versus interferon maintenance in patients with MCL who attained a CR after CHOP induction. Of the 122 evaluable patients, the median PFS was better for the transplantation arm (39 months versus 17 months) and an OS benefit was confirmed for ASCT on an updated analysis [26,30]. The Nordic Lymphoma Group published the largest prospective multicenter trial of 160 patients with MCL who received induction with a "maxi-CHOP" plus rituximab alternating with high-dose cytarabine and rituximab for a total of 6 courses. Responders received HDT with BEAM or high-dose carmustine, etoposide, cytarabine, and cyclophosphamide plus rituximab followed by ASCT. The 6-year PFS and OS were 66% and 70%, respectively, with no relapses occurring after 5 years [13]. These results were further supported by the CALGB 59909, in which 77 patients received augmented R-CHOP and methotrexate induction followed by HDT, with etoposide-cytarabine-rituximab, and ASCT resulting in comparable 5-year PFS and OS of 56% and 64%, respectively [14]. These data demonstrates that, in the modern era of rituximab-based induction and intensified chemotherapy/ASCT, about 60% of patients with MCL can be cured, yet the sobering fact remains that 30% to 40% of patients still eventually relapse after ASCT, and new consolidation therapies are required to improve the outcomes of these patients.

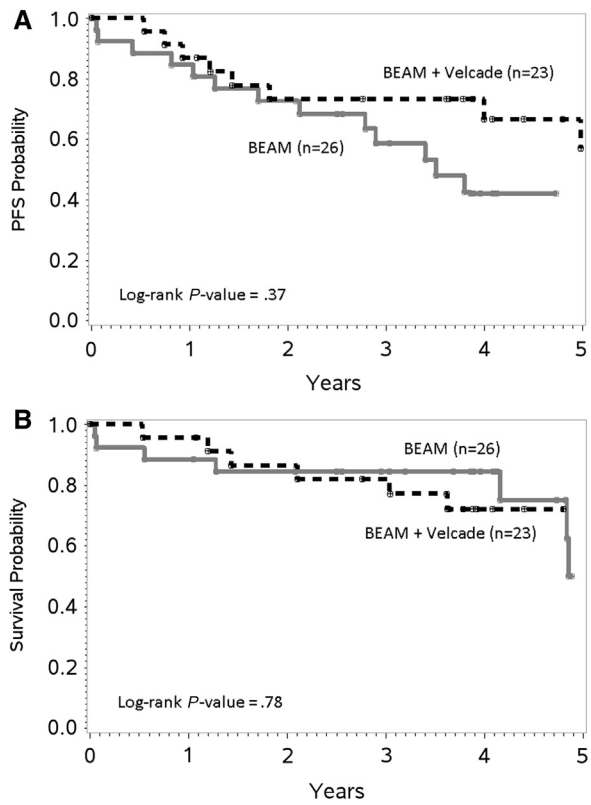

Figure 3. Comparison between study MCL patients (V-BEAM) versus historic MCL patients (BEAM). (A) Shows progression-free survival and (B) shows overall survival.

The CUP trial was conducted in the prerituximab era and randomized patients with FL in first relapse after salvage chemotherapy to either standard chemotherapy, HDT followed by ASCT, and HDT followed by ASCT with ex vivo purging of the graft. The trial closed early secondary to poor accrual and only 70 patients were evaluable. HDT followed by ASCT significantly improved PFS at 2 years compared with standard chemotherapy (26% versus 58%) and graft purging did not improve outcomes [1]. A recent single-institution retrospective analysis has proven that the benefit of HDT and ASCT in first relapse of FL is sustained in patients who received rituximab with induction therapy [31]. Despite the long duration of remission after ASCT for FL and other indolent lymphomas, disease progression is inevitable, and novel therapies are also required to improve the depth of remission in these patients.

Bortezomib has demonstrated single-agent activity in relapsed/refractory indolent NHL and MCL [23-25], including an ORR of 33% in the PINNACLE landmark trial [26]. In our MCL subjects, we observed a median PFS of 57% and OS of 72% at 5 years, which is comparable to what was observed in the Nordic Lymphoma Group and CALGB 59909 trials, suggesting that incorporation of bortezomib to standard BEAM conditioning did not result in a dramatic improvement in outcomes. Also, we performed an exploratory analysis comparing our MCL study cohort to an historic cohort of patients with MCL treated at our institution with standard BEAM conditioning, and outcomes were essentially identical. Demonstrating a benefit for adding bortezomib to standard BEAM regimen would require a randomized controlled trial. It is possible that bortezomib would be more efficacious as a maintenance regimen after ASCT, and the CALGB 50403 is in progress to answer this question (NCT00310037). It is also possible that bortezomib would have a role in induction chemotherapy, in addition to R-CHOP (ECOG- E1405), R-EPOCH, or R-HyperCVAD. Studies are in progress to answer these questions (NCT00433537, NCT00114738 and NCT00477412, respectively).

The safety profile of bortezomib was predictable, manageable, and similar to that in relapsed/refractory multiple myeloma [32]. The incidences of peripheral neuropathy, of all grades and of grades $\geq$ 3, were higher than what were observed in the landmark myeloma APEX trial [32], but they were comparable to what was observed in the PINNACLE trial of relapsed/refractory MCL patients [26]. The higher incidence of peripheral neuropathy in our patients, compared with myeloma patients treated in the APEX trial, is readily explainable by greater exposure to neurotoxic chemotherapeutic agents in induction. Grade 3 ileus was observed in 9% of treated patients with 1 case of perforated jejunum, which is higher than what was reported in the PINNACLE and APEX trials. We also observed a higher rate of autonomic dysfunction, manifesting as vasovagal syncope and orthostatic hypotension. We postulate that the higher risk of autonomic dysfunction, which also likely contributed to ileus, is related to the confounding effect of mucositis induced by the standard BEAM conditioning regimen, resulting in fluid loss through the gastrointestinal tract and making the study patients more vulnerable to bortezomib-induced autonomic neuropathy.

In conclusion, the addition of bortezomib to standard BEAM conditioning is feasible. The toxicities were manageable and we did not observe any treatment-related mortalities. However, we did observe an excess of autonomic dysfunction and ileus, which is concerning for overlapping toxicity with BEAM conditioning. Out study was not designed to demonstrate an additional benefit of adding bortezomib to BEAM conditioning; however, we did not observe a dramatic benefit of such combination over historical controls from our institution or from the published literature. The demonstration of a benefit for adding bortezomib to standard BEAM regimen would require a randomized controlled trial. However, the lack of a hint of a benefit and higher than usual toxicities observed in our study would generate less enthusiasm for developing a phase III clinical trial to answer that question, especially with many effective targeted agents in the pipeline.

ACKNOWLEDGMENTS

Conflict of interest statement: J.A.O. is a consultant for Ziopharm, Seattle Genetics, GlaxoSmith Kline, Genetech, Roche, and Spectrum. J.M.V receives research grant support from Spectrum, Bristol-Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Incyte, Janssen Biotech, Millennium, Onyx Pharmaceuticals, Pharmacyclics, Sanofi-Aventis US, and US Biotest. The remaining authors have nothing to disclose.

Financial disclosure: The authors have nothing to disclose.

REFERENCES

1. Schouten HC, Qian W, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol*. 2003;21:3918-3927.
2. Sebban C, Brice P, Delarue R, et al. Impact of rituximab and/or high-dose therapy with autotransplant at time of relapse in patients with follicular lymphoma: a GELA study. *J Clin Oncol*. 2008;26:3614-3620.
3. Rohatiner AZ, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. *J Clin Oncol*. 2007;25:2554-2559.
4. Brice P, Simon D, Bouabdallah R, et al. High-dose therapy with autologous stem-cell transplantation (ASCT) after first progression prolonged survival of follicular lymphoma patients included in the prospective GELF 86 protocol. *Ann Oncol*. 2000;11:1585-1590.
5. Lerner RE, Burns LJ. Transformed lymphoma: an Achilles' heel of non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 2003;31:531-537.
6. Cao TM, Horning S, Negrin RS, et al. High-dose therapy and autologous hematopoietic-cell transplantation for follicular lymphoma beyond first remission: the Stanford University experience. *Biol Blood Marrow Transplant*. 2001;7:294-301.
7. Williams CD, Harrison CN, Lister TA, et al. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. *J Clin Oncol*. 2001;19:727-735.
8. Williams ME, Densmore JJ. Biology and therapy of mantle cell lymphoma. *Curr Opin Oncol*. 2005;17:425-431.
9. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol*. 2005;23:1984-1992.
10. Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. *J Clin Oncol*. 2002;20:1288-1294.
11. Vandenberghe E, Ruiz de Elvira C, Loberiza FR, et al. Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. *Br J Haematol*. 2003;120:793-800.
12. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. *Blood*. 2005;105:2677-2684.
13. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008;112:2687-2693.
14. Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. *J Clin Oncol*. 2009;27:6101-6108.
15. Lacasce AS, Vandergrift JL, Rodriguez MA, et al. Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL Database. *Blood*. 2012;119:2093-2099.
16. Absi A, Hsi E, Kalaycio M. Prolymphocytic leukemia. *Curr Treat Options Oncol*. 2005;6:197-208.
17. Mills W, Chopra R, McMillan A, et al. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol*. 1995;13:588-595.
18. Puig N, de la Rubia J, Remigia MJ, et al. Morbidity and transplant-related mortality of CBV and BEAM preparative regimens for patients with lymphoid malignancies undergoing autologous stem-cell transplantation. *Leuk Lymphoma*. 2006;47:1488-1494.
19. William BM, Loberiza FR, Whalen V, et al. Impact of conditioning regimen on outcome of 2-year disease-free survivors of autologous stem cell transplantation (ASCT) for Hodgkin lymphoma (HL). ASCO Meeting Abstracts 2011. *J Clin Oncol*. 2011;29(15 suppl):8043.
20. Pham LV, Tamayo AT, Yoshimura LC, et al. Inhibition of constitutive NF-kappa B activation in mantle cell lymphoma B cells leads to induction of cell cycle arrest and apoptosis. *J Immunol*. 2003;171:88-95.
21. Suzuki Y, Yoshida T, Horie R, et al. Constitutive activity of nuclear transcription factor kappaB is observed in follicular lymphoma. *J Clin Exp Hematop*. 2010;50:45-50.
22. Novak U, Rinaldi A, Kwee I, et al. The NF-{kappa}B negative regulator TNFAIP3 (A20) is inactivated by somatic mutations and genomic deletions in marginal zone lymphomas. *Blood*. 2009;113:4918-4921.
23. Goy A, Younes A, McLaughlin P, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2005;23:667-675.
24. O'Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol*. 2005;23:676-684.
25. Strauss SJ, Maharaj L, Hoare S, et al. Bortezomib therapy in patients with relapsed or refractory lymphoma: potential correlation of in vitro sensitivity and tumor necrosis factor alpha response with clinical activity. *J Clin Oncol*. 2006;24:2105-2112.

26. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol*. 2006;24:4867-4874.
27. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol*. 1988;6:1562-1568.
28. Cheson BD. The International Harmonization Project for response criteria in lymphoma clinical trials. *Hematol Oncol Clin North Am*. 2007; 21:841-854.
29. Vose JM, Bierman PJ, Weisenburger DD, et al. Autologous hematopoietic stem cell transplantation for mantle cell lymphoma. *Biol Blood Marrow Transplant*. 2000;6:640-645.
30. Hoster E, Metzner B, Forstpointner R, et al. Autologous stem cell transplantation and addition of rituximab independently prolong response duration in advanced stage mantle cell lymphoma. ASH Annual Meeting Abstracts. 2009 J Clin Oncol 2009;114:880.
31. Kothari J, Ljubic A, Peggs KS, et al. Autologous Stem Cell Transplantation Using BEAM conditioning is highly effective in patients with follicular lymphoma regardless of prior rituximab exposure. ASH Annual Meeting Abstracts. 2011 J Clin Oncol 2011; 118:2025.
32. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352:2487-2498.