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Phase I Trial of Weekly and Twice-Weekly Bortezomib with Rituximab, Cyclophosphamide, and Prednisone in Relapsed or Refractory Non–Hodgkin Lymphoma

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Abstract

Purpose: To determine the safety and efficacy of substituting weekly or twice-weekly bortezomib for vincristine in the R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) regimen in patients with relapsed/refractory indolent and mantle cell lymphoma (MCL).

Experimental Design: Of the 57 patients in this phase I trial, 55 participated in 1 of 2 dosing schedules that included rituximab (375 mg/m^2) and cyclophosphamide (750 or 1,000 mg/m^2) administered on day 1 of each 21-day cycle and prednisone (100 mg orally) days 2 to 6. In the once-weekly schedule, bortezomib was administered on days 2 and 8; on the twice-weekly schedule, bortezomib was given on days 2, 5, 9, and 12. Bortezomib and cyclophosphamide were alternately escalated. A separate cohort of 10 patients in the twice-weekly schedule received concurrent pegfilgrastim (PegG) on day 2.

Results: Both schedules of R-CBorP (rituximab, cyclophosphamide, bortezomib, and prednisone) were well tolerated. Most toxicities across all dose levels and cycles were grade 1 or 2. The overall response rates for patients on the weekly ($n = 13$) and twice-weekly ($n = 33$) schedules were 46% [23% complete response/complete response unconfirmed (CR/CRu)] and 64% (36% CR/CRu), respectively. Concurrent PegG did not increase hematologic toxicities in this regimen. A randomized phase II study is under way to further compare toxicity and efficacy of the 2 dosing schedules.

Conclusions: R-CBorP is a safe and effective regimen in patients with relapsed/refractory indolent and MCLs. Most toxicities were grade 1 or 2, and a promising response rate was seen in this phase I study. *Clin Cancer Res; 17(8); 2493–501. ©2011 AACR.*

Introduction

Indolent and mantle cell lymphomas (MCL) represent approximately 40% of newly diagnosed non–Hodgkin lymphomas (NHL) in the United States. Although these malignancies are responsive to chemotherapy, cures are rare. The relatively recent integration of immunotherapies and other new agents into treatment paradigms for these diseases may change the natural history of follicular lymphoma (FL) and MCL (1–3). The indolent lymphomas, which include FL, marginal zone lymphoma (MZL), and small lymphocytic lymphoma (SLL), typically follow a slow-growing course marked by frequent remissions to chemotherapy but inevitable relapses (4). In the age of immunochemotherapy, the course of these indolent lymphomas can span decades, during which time patients will typically undergo several courses of immunotherapy and chemotherapy. In contrast to the indolent lymphomas, the course of MCL tends to be much more aggressive and the life span of patients afflicted with this disease is shorter. Current treatments options for MCL range from conservative "watch and wait" approaches to induction chemotherapy [R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone), HyperCVAD-R (cyclophosphamide, vincristine, doxorubicin, dexamethasone, rituximab), and Maxi-CHOP-R] followed by peripheral blood stem cell transplant (5–7). Despite a diversity of treatment options, these diseases remain incurable. Well-tolerated treatment regimens that are non–cross-resistant with conventional treatment options are needed to extend and improve the quality of life in patients with these incurable lymphomas.

Bortezomib is the first proteasome inhibitor approved by the U.S. Food and Drug Administration. It was originally approved for the treatment of relapsed or refractory

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Translational Relevance

This phase I study has been built on preclinical data showing the synergies between bortezomib and rituximab, as well as between bortezomib and cyclophosphamide. To assess how these drugs can be most safely combined in the clinic, a sequential phase I trial was conducted. This trial determined the suggested phase II doses for 2 different treatment schedules of bortezomib combined with cyclophosphamide, rituximab, and prednisone. The promising toxicity profile and efficacy seen in both arms of this study have led us to bring this regimen forward into a phase II trial. A multicenter randomized phase II trial has recently been initiated to better characterize the efficacy of this regimen in a larger population of lymphoma patients and to determine which schedule of this regimen is the least toxic and most efficacious. We plan to ultimately compare this regimen directly with the R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) regimen in order to determine which is superior in this patient population. The results of this project have the potential to alter the treatment recommendations for a substantial number of patients with non–Hodgkin lymphoma.

multiple myeloma. Several phase II trials (8–10) reported marked activity in a number of NHL subtypes, including MCL, FL, and MZL. Following the promising results of 4 single-arm phase II studies reporting similar response rates in patients with relapsed or refractory MCL, the multicenter PINNACLE study established an overall response rate (ORR) of 31%, with a median duration of response of 9.2 months in 141 patients with MCL (11, 12). These findings led to approval of bortezomib for second-line treatment of MCL. Bortezomib was well tolerated in these patients, who experienced similar symptoms of neuropathy and thrombocytopenia seen in the earlier studies.

Because of the agent's impressive single-agent activity and preclinical data suggesting synergy with conventional agents (13), we sought to evaluate the safety and efficacy of substituting bortezomib for vincristine in the conventional R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) regimen. Given the lack of robust data in support of vincristine activity in this setting, we hypothesized that this substitution could improve the activity of the regimen without increasing neuropathy. Because of the differential risk of neuropathy seen in prior reports of the weekly and twice-weekly schedules of bortezomib (14, 15), we explored both schedules in this phase I study to allow for a direct comparison of toxicity. We also scheduled bortezomib after the alkylating agent on the basis of preclinical data, suggesting that this order may increase activity of the combination. Finally, because of the emergent neutropenia observed, we explored the effects of concurrent pegfilgrastim (PegG) on the hematologic toxicity profile.

Patients and Methods

Demographics

Adult patients ($\geq$18 years of age) with histologically confirmed chronic lymphocytic leukemia (CLL)/B-cell SLL, MZL, FL, Waldenström macroglobulinemia, transformed FL, and MCL were eligible (Table 1). All patients had assessable disease and must have had at least 1 prior treatment regimen, with no more than 3 prior cytotoxic chemotherapy regimens, and 1 or none prior radioimmunotherapy (RIT) regimen. Patients with prior stem cell transplantation were included (with preparative cytoreduction and high-dose therapy counted as 1 prior cytotoxic regimen). Patients could not have received any therapeutic monoclonal antibodies within 3 months of enrollment unless progression of disease (POD) was documented in the interim. A washout period of 4 weeks after prior cytotoxic chemotherapy [6 weeks for BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) or mitomycin C] and 12 weeks after last treatment with RIT was required.

All patients were required to have a Karnofsky performance status (KPS) of more than 50%, with adequate organ and marrow function as defined by absolute neutrophil count (ANC) more than 1,000/μL on day 1 of each cycle (or >500/μL if known involvement of bone marrow), platelets (Plt) more than 50,000/μL, total bilirubin less than 1.5 times the institutional upper limit of normal (ULN; or <5 mg/dL for patients with Gilbert disease), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than 2.5 times the institutional ULN (<4 times ULN for patients with hepatic involvement), and creatinine level less than 1.5 times the institutional ULN or creatinine clearance of 50% or more. Patients were not enrolled if they had brain or meningeal metastases, uncontrolled intercurrent illness, baseline neuropathy grade 2 or more, or were HIV positive by serology. All patients signed Institutional Review Board–reviewed informed consent for participation in the clinical trial. Patients were included in the safety/toxicity analysis if they received at least 1 dose of bortezomib and, in the efficacy analysis, if they received at least 2 cycles of planned therapy.

Treatment

A 3 + 3 design with cohort expansions and alternate dose escalation of bortezomib and cyclophosphamide was adopted. Two dosing schedules were explored. The first 3 patients on a weekly schedule were given 1.3 mg/m^2 bortezomib and 750 mg/m^2 of cyclophosphamide (with a constant dose of rituximab and prednisone). The last patient in each cohort was followed for 1 complete cycle (21 days) before enrollment of the next cohort. We alternately escalated bortezomib and cyclophosphamide (Table 2). Following safe dose escalation to cohort 4, the twice-weekly schedule was initiated. Cohorts 7 and 8 received prophylactic filgrastim. The maximum tolerated dose (MTD) was prospectively defined as the dose at which less than 30% of patients experienced a dose-limiting

Table 1. Patient demographics ($N = 55$)

Characteristics	*n* (%)		
	Weekly ($n = 15$)	Twice weekly ($n = 40$)	Combined ($N = 55$)
Median age, y	66	61	64
Men	6 (40)	19 (48)	25 (45)
Histology			
FL (grade 1–3a)	5 (33)	19 (48)	24 (44)
FL (grade 3b)	1 (7)	0 (0)	1 (2)
MCL	3 (20)	8 (20)	11 (20)
MZL	2 (13)	6 (15)	8 (15)
SLL	1 (7)	3 (8)	4 (7)
Transformed FL[a]	3 (20)	4 (10)	7 (13)
Bulky disease at baseline	5 (36)[b]	21 (57)[b]	26 (50)[b]
Prior therapies			
Anthracycline combination	12 (80)	32 (80)	44 (80)
Alkylator combination	13 (87)	37 (93)	50 (91)
Auto PBSCT	3 (20)	7 (18)	10 (18)
Bortezomib	4 (27)	3 (8)	7 (13)
Platinum based	4 (27)	13 (33)	17 (31)
Purine analogue based	3 (20)	5 (13)	8 (15)
Refractory to prior therapy[c]	8 (53)	16 (40)	24 (44)
RIT	4 (27)	9 (23)	13 (24)
Rituximab	14 (93)	36 (90)	50 (91)
Median no. of treatments	4	2	2
Median PFS (months) to last prior treatment[d]	7.9	13.6	11.5

Abbreviation: PBSCT, peripheral blood stem cell transplantation.

[a]Transformation was based on clinical/radiologic characteristics in 2 patients and histologic confirmation in the other.

[b]Bulky disease was defined as any site of involvement measuring 5 cm or more in the greatest diameter. Only those patients with baseline documentation of measurable disease ($n = 14$ in the weekly group and $n = 37$ in the twice-weekly group) were included.

[c]Patients were deemed refractory to their prior therapy if they either failed to respond or progressed within 6 months of treatment.

[d]The number of patients evaluable for PFS from last prior treatment was 15 in the weekly group, 37 in the twice-weekly group, and 52 in the combined group (i.e., dates of last prior treatment and progression after that treatment were not available for 3 patients in the twice-weekly group).

toxicity (DLT). Patients who did not receive at least 1 dose of bortezomib were replaced in the cohort.

After four 21-day cycles, a restaging computed tomographic (CT) scan was evaluated using International Working Group criteria (16). Patients with stable disease (SD) or partial remission (PR) received 4 additional cycles of treatment, for a total of 8 cycles. Patients in complete remission/complete remission unconfirmed (CR/CRu) received 2 additional cycles of treatment, for a total of 6 cycles. Patients experiencing POD were removed from the protocol. A comprehensive metabolic panel and complete blood cell (CBC) count were assessed for each patient on day 1 of each cycle, and additional CBC counts were assessed on all bortezomib administration days.

Toxicities were defined according to National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0. DLT was defined as any of the following occurring during cycle 1 of treatment: (i) grade 4 neutropenia (ANC <500 cells/mm^3) for 7 or more consecutive days or febrile neutropenia (fever >38.5°C with an ANC <1,000 cells/mm^3); (ii) grade 4 thrombocytopenia (Plts <25,000), with a bleeding episode requiring transfusions or lasting for 7 consecutive days (Plts <10,000 × 1 day); (iii) neurosensory toxicity of grade 2 with pain or grade more than 2; (iv) grade 3 or more nausea and/or vomiting despite adequate/maximal medical intervention and/or prophylaxis; (v) any grade 3 or more nonhematologic toxicity (except grade 3 injection site reaction, alopecia, fatigue); and (vi) retreatment delay of more than 3 weeks.

PegG safety cohort expansion

A separate cohort of 10 patients (cohort 9) was enrolled to assess the safety of PegG administered simultaneously with bortezomib on day 2 of the twice-weekly regimen. Enrollment criteria were not changed. Patients in this cohort were treated identically to patients in cohort 7 (i.e., with a fixed dose of bortezomib 1.3 mg/m^2 and cyclophosphamide 1,000 mg/m^2), except that filgrastim

Table 2. Bortezomib and cyclophosphamide dose escalation schedule (21-day cycle)[a]

Cohort	Bortezomib, mg/m^2	Cyclophosphamide, mg/m^2	No. of patients	DLT
Weekly schedule[b]				
1	1.3	750	3	
2	1.6	750	6	Grade 3 diarrhea
3	1.6	1,000	3	
4	1.8	1,000	4	1 patient replaced[c]
Twice-weekly schedule[d]				
5	1.0	750	3	
6	1.3	750	6	2 grade 3 neutropenic fever
7[e]	1.3	1,000	12	1 patient: grade 4 Plts/grade 4 sensory neuropathy
8[e]	1.5	1,000	4	1 patient replaced[c]
9[f]	1.3[f]	1,000[f]	10	

[a]With fixed dose of rituximab (375 mg/m^2, day 1) and prednisone (100 mg daily, days 2–6).
[b]Bortezomib administered on days 2 and 8.
[c]Two patients were replaced because they did not receive at least 1 dose of bortezomib.
[d]Bortezomib administered on days 2, 5, 9, and 12.
[e]With prophylactic filgrastim on days 3, 4, 6, 7, 8, 10, and 11.
[f]With PegG on day 2.

was replaced by PegG (6 μg subcutaneously) on day 2 after bortezomib. Serial CBC counts were followed as earlier.

Supportive care and follow-up

Filgrastim was allowed for patients on the weekly schedule according to American Society of Clinical Oncology (ASCO) guidelines. Erythropoietin was allowed for anemia. Antiemetic treatment and precautions for rituximab and cyclophosphamide followed institutional guidelines. Additional intravenous normal saline during each injection of bortezomib was allowed. All patients received prophylactic acyclovir (17) and sulfamethoxazole/trimethoprim (or other suitable pneumocystis pneumonia prophylaxis in patients with allergies to sulfa drugs) during and for 3 months following treatment.

All patients had a restaging CT scan 3 to 4 weeks after the end of treatment. Repeat CT scans were required at least every 4 months thereafter for 2 years. Both pretreatment bone marrow biopsy and aspirate were required; this was repeated only as required to document CR.

Statistical analysis

A competing risks analysis was used to analyze progression-free survival (PFS), where progression is the event of interest and death caused by other reasons is regarded as the competing risk. R (http://cran.r-project.org/) package "cmprsk" was used for the competing risks analysis.

To assess the safety of PegG support administered concurrently with the first dose of bortezomib in the twice-weekly schedule, hematologic toxicities and absolute values for total white blood cell count, hemoglobin, ANC, and Plts were compared between cohorts 7 and 9, using data from the first 4 treatment cycles. The Wilcoxon rank-sum test was used to compare the highest grades of all hematologic toxicities. Ordinary least-squares regression was used for each patient and each type of measurement to compute the slope of the fitted line for each laboratory trend. The slopes of plotted values for hemoglobin, ANC, and Plts were then compared between groups, using the Wilcoxon rank-sum test.

Results

Fifty-seven patients were enrolled in this phase I trial, 16 on the weekly schedule (cohorts 1–4) and 41 on the twice-weekly schedule (cohorts 5–9). The median number of prior treatments (including cytotoxic and noncytotoxic therapies) was 4 for the weekly group and 2 for the twice-weekly group, with 90% or more of each group having had prior exposure to rituximab and more than three-fourths of each group having been treated with prior anthracycline-containing regimens (Table 1). Only 2 patients (1 in each treatment group) had received rituximab as their sole treatment prior to enrollment.

Toxicity

One patient (cohort 4) who developed pancytopenia immediately after his first dose of cyclophosphamide and rituximab before receiving a dose of bortezomib was replaced, and 1 patient in cohort 8 who experienced a

Table 3. Hematologic toxicities[a]

Toxicity	Weekly				Twice weekly			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	8 (53)	6 (40)			23 (58)	6 (15)	3 (8)	
Leukopenia	6 (40)	2 (13)	7 (47)	1 (7)	10 (25)	7 (18)	8 (20)	3 (8)
Lymphopenia			8 (53)	3 (20)	4 (10)		24 (60)	5 (13)
Neutropenia		4 (27)	5 (33)	3 (20)	1 (3)	3 (8)	4 (10)	11 (28)
Thrombocytopenia	6 (40)		3 (20)	2 (13)	20 (50)	8 (20)	4 (10)	3 (8)

[a]All toxicities are corrected for baseline. Values given are number (percentage).

grade 3 reaction to rituximab was removed from study before other drugs were given. Hence, 55 patients received at least 1 dose of bortezomib and are included in the safety analysis.

Both treatment schedules were well tolerated. Nine patients on the weekly schedule (60%) did not complete the full course of planned therapy (i.e., 6–8 cycles): 5 because of doctor or patient choice for lack of desired response, 1 after patient choice once CR was achieved, 1 because of clinical POD, and 2 because of adverse events deemed to be unrelated to the treatment (1 patient had a nonresolving lung nodule later found to represent a primary lung malignancy, and another patient withdrew to undergo elective surgical repair of a preexisting prolapsed rectum). Fourteen patients on the twice-weekly schedule (35%) failed to complete planned therapy: 1 chose to withdraw for lack of response, 9 had adverse events (1 had pneumonia during a treatment delay, which required hospitalization and so the patient decided to withdraw from the trial and seek home hospice care, 7 had sensory neuropathy, one had 2-week delay due to grade 3 thrombocytopenia), and 4 chose to withdraw for clinical POD. Toxicities are presented and corrected for baseline. The most common toxicities in both treatment schedules were grades 1 and 2 (Tables 3 and 4).

One episode of grade 3 diarrhea was observed in cohort 2 (weekly bortezomib, 1.6 mg/m^2 + cyclophosphamide 750 mg/m^2), and this cohort was expanded to 6 patients. Because no further DLTs were seen, enrollment continued to the preplanned maximum administered dose levels for the weekly schedule. In cohort 6 (twice-weekly bortezomib, 1.3 mg/m^2 + cyclophosphamide 750 mg/m^2), a neutropenic fever caused the initial cohort to be expanded to 6 patients. A second neutropenic fever was observed, and the protocol was modified to include prophylactic filgrastim administration at 380 mg on days 3, 4, 6, 7, 8, 10, and 11 in all subsequent patients (Table 2). For safety, 6 patients were enrolled in the first cohort of filgrastim-supported twice-weekly dosing (cohort 7). This cohort was expanded to 12 patients when 1 person experienced both grade 4 thrombocytopenia lasting 7 consecutive days and grade 4 peripheral neuropathy. No additional DLTs were seen in this cohort, and dose escalation continued to the eighth cohort without additional DLTs. An MTD was therefore not reached in either dosing schedule.

Grades 3 and 4 clinical toxicities are shown in Table 4. Although the overall rate of neuropathy was similar between the treatment schedules, 2 instances of severe neuropathy (1 grade 3; 1 grade 4) were seen in the twice-weekly group. Patients were followed until resolution or stabilization of neuropathic symptoms. Of the patients who developed neuropathy, 83% in the weekly group experienced resolution after a median of 0.7 months and 58% in the twice-weekly group after a median of 4 months. Patients reported a variable level of relief with clinical interventions (18). Peripheral neuropathy leading to hospitalization occurred in 2 patients in the twice-weekly group (both at the 1.3 mg/m^2 bortezomib dose level). One patient developed grade 3 neuropathy after 4 cycles of treatment and recovered to a grade 1 neuropathy after 3.3 months; the other patient developed grade 4 neuropathy after 1 cycle of treatment and remained at grade 4 until her death from progression 26 months after completion of treatment.

Hematologic toxicities for patients in the PegG-supported group (cohort 9) were similar to those of patients treated with nonoverlapping filgrastim (cohort 7). The Wilcoxon rank-sum test failed to show a significant difference in rate of the highest overall hematologic toxicity between the 2 groups ($P = 0.64$), with similar results obtained for each subtype of toxicity (anemia, $P = 1$; neutropenia, $P = 0.45$; and thrombocytopenia $P = 0.71$). The trend of each hematologic value, as characterized by the best-fit slope across 4 cycles, was also not significantly different between the 2 groups (ANC, $P = 0.47$; hemoglobin, $P = 0.08$), with the exception of a significant but mild decline in Plts ($P = 0.007$) in the PegG group (cohort 9).

Efficacy

Patients were considered evaluable for response if they received at least 2 cycles of the intended treatment. The ORR in the combined 46 evaluable patients for the entire study was 59% [47% by intention to treat (ITT)], with an ORR of 46% (38% ITT) and 64% (51% ITT) in the weekly and twice-weekly schedules, respectively. Thirteen of the 15 patients in the weekly group were evaluable for response

Table 4. Nonhematologic toxicities[a] above baseline (grade 1 and 2 toxicities occurring in ≥10% and all grade 3 and 4 toxicities are shown)

Toxicity	Weekly				Twice weekly			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Albumin, low	6 (40)	2 (13)			12 (30)			
Alkaline phosphatase	5 (33)				19 (48)			
Allergic rhinitis	3 (20)				2 (5)	1 (3)		
ALT	8 (53)	2 (13)			15 (38)	1 (3)		
Anxiety	2 (13)				0 (0)			
AST	9 (60)				15 (38)			
Bilirubin	1 (7)	2 (13)			3 (8)	2 (5)	1 (3)	
Bruising	2 (13)				4 (10)			
Calcium, low	5 (33)	3 (20)			0 (0)			
Constipation	6 (40)	4 (27)			11 (28)	15 (38)		
Cough	13 (87)				10 (25)			
Creatinine	5 (33)				11 (28)	1 (3)		
Dehydration			1 (7)					
Diarrhea	6 (40)	3 (20)	1 (7)		14 (35)	5 (13)		
Dizziness	2 (13)				0 (0)			
Dry mouth					4 (10)			
Dyspnea	8 (53)				12 (30)	5 (13)		
Edema	7 (47)				4 (10)			
Fatigue	7 (47)	6 (40)			19 (48)	8 (20)	3 (8)	
Febrile neutropenia			1 (7)		0 (0)		2 (5)	
Fever	9 (60)	2 (13)			6 (15)	2 (5)	1 (3)	
Glucose, high	9 (60)	4 (27)			18 (45)	2 (5)		
Glucose, low	4 (27)	1 (7)	1 (7)		7 (18)	1 (3)		
Hypoxia							1 (3)	
Incontinence, anal			1 (7)					
Infection			2 (13)				1 (3)	
Insomnia	2 (13)				6 (15)			
Magnesium, low	2 (13)	1 (7)			3 (8)	1 (3)		
Nausea	8 (53)	2 (13)			10 (25)	6 (15)		
Neuropathy: sensory	4 (26)	2 (13)			15 (38)	9 (23)	1 (3)	1 (3)
Phosphate, low		4 (27)	3 (20)		0 (0)	6 (15)	1 (3)	
Potassium, high					7 (18)	3 (8)		
Potassium, low	2 (13)		2 (13)		4 (10)		1 (3)	
Pruritus	2 (13)	1 (7)			4 (10)			
Rash	2 (13)	1 (7)			3 (8)	3 (8)		
Rigors/chills	5 (33)				4 (10)			
Sodium, high	7 (47)				14 (35)			
Sodium, low	5 (33)				9 (23)			
Sweating	2 (13)				1 (3)			
Urinary frequency	2 (13)				3 (8)			
Vomiting	3 (20)	1 (7)			4 (10)	2 (5)		

[a]All toxicities are corrected for baseline. Values given are number (percentage).

(Table 5). Responses were seen in 6 patients (46%), with 3 CR/CRu (23%) and 3 PR (23%). Thirty-three of the 40 patients in the twice-weekly group were evaluable for response, and responses were seen in 21 patients (64%) with 12 CR/CRu (36%) and 9 PR (27%). Fifty patients were evaluable for the competing risk survival analysis, among which 34 patients progressed, 7 patients died, and 9 patients were censored. There was no statistically significant difference between the twice-weekly and weekly treatment groups for the cumulative incidence functions ($P = 0.83$). The median time to progression for all patients treated was 13 months. The median time to progression

Table 5. Overall response in evaluable patients ($N = 46$)

Response evaluation	*n* (%)					
	POD	SD	PR	CR/CRu	ORR	ITT ORR
Weekly ($n = 13$)	1 (8)	6 (46)	3 (23)	3 (23)	6 (46)	6 (38)
Twice weekly ($n = 33$)	3 (9)	9 (27)	9 (27)	12 (36)	21 (64)	21 (51)
By histology						
FL grade 1–3a ($n = 23$)	1 (4)	8 (35)	7 (30)	7 (30)	14 (61)	14 (58)
FL grade 3b ($n = 1$)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)
MCL ($n = 10$)	1 (10)	3 (30)	1 (10)	5 (50)	6 (60)	6 (50)
MZL ($n = 6$)	0 (0)	1 (17)	3 (50)	2 (33)	5 (83)	5 (56)
SLL ($n = 2$)	1 (50)	0 (0)	0 (0)	1 (50)	1 (50)	1 (25)
Transformed ($n = 4$)	2 (50)	2 (50)	0 (0)	0 (0)	0 (0)	0 (0)
By response to last prior therapy						
Refractory[a] ($n = 21$)	1 (5)	7 (33)	10 (48)	3 (14)	13 (62)	13 (52)
Responsive ($n = 22$)	3 (14)	7 (32)	2 (9)	10 (45)	12 (55)	12 (48)

Abbreviation: ITT ORR, intention-to-treat ORR including all patients enrolled ($n = 16$ weekly, 41 twice weekly).
[a]Patients were deemed refractory to their prior therapy if they either failed to respond or progressed within 6 months of treatment.

for the weekly and twice-weekly treated patients was 9 and 14 months, respectively. By diagnosis, responses were seen in 14 of 23 patients (61%) with FL, 6 of 10 patients (60%) with MCL, 5 of 6 patients (83%) with MZL, 1 of 2 patients (50%) with SLL, and none of 4 (0%) patients with transformed indolent lymphoma (2 of these were classified as transformed on the basis of clinical/radiographic characteristics but not histologically proven to represent transformed histology). The one patient with grade 3b FL achieved a PR that lasted 5.3 months. Responses were seen in 12 of 22 patients (59%) who responded to their prior treatment, and 13 of 21 patients (62%) deemed to be refractory to their last prior treatment. Of the 41 patients who had received prior treatment with an anthracycline-based regimen, responses were seen in 22 (53.6%). Of the 41 evaluable patients who had received either R-CVP or R-CHOP at some point prior to enrollment, responses were seen in 20 (48.8%). Many of these patients had received R-CVP or R-CHOP early in the course of their disease, and the median time between the end of R-CVP or R-CHOP and R-CBorP (rituximab, cyclophosphamide, bortezomib, and prednisone) was 28 months (range, 1–172). Four patients in the weekly R-CBorP treatment group (2 with MCL and 2 with FL) had received prior bortezomib at a dose of 1.5 mg/m^2 twice weekly. One patient (with MCL) had an initial PR to bortezomib but SD with a second course upon relapse. The other 3 patients did not respond to single-agent bortezomib (2 SD and 1 POD). With R-CBorP, 2 of these patients responded (1 CR in the MCL patient with an initial response to single-agent bortezomib and 1 PR) and 2 had SD. Three patients in the twice-weekly R-CBorP group (all with FL) had prior bortezomib at a dose of 1.8 mg/m^2 weekly. All 3 patients were refractory to the single agent (2 SD and 1 POD). With R-CBorP, 2 of these patients achieved PR and 1 had SD.

Discussion

We set out to exploit the preclinical synergy and nonoverlapping activity of bortezomib by incorporating it into the popular and effective R-CVP regimen. Two similar combination regimens in which bortezomib was added to R-CVP (19) or R-CHOP (20) have recently been reported in abstract form. In these reports, neuropathy was not significantly more severe than expected with either *Vinca* alkaloids or bortezomib alone. However, both trials enrolled untreated patients who had not been previously exposed to potentially neurotoxic chemotherapeutic agents. Because the single-agent activity of vincristine is not well established in this setting, we chose to replace vincristine with bortezomib, instead of simply adding bortezomib to the regimen. To best characterize the toxicity profile of this regimen, a conservative 3 + 3 design and alternate dose escalation were adopted. Given recent reports suggesting similar efficacy and greater tolerability of bortezomib given on a weekly schedule with rituximab (15), we compared 2 dosing schedules in the combination regimen. Although this design required greater patient resources, it allowed for a thorough analysis of potential adverse events, and the larger patient numbers provided substantial estimates of efficacy.

The R-CBorP regimen was well tolerated, with relatively few grade 3 or 4 toxicities. Only 1 DLT requiring cohort expansion (a grade 3 diarrhea in cohort 2) was seen in patients treated with weekly bortezomib. Dose escalation proceeded without further cohort expansion to the highest predetermined doses of bortezomib and cyclophosphamide. The most concerning hematologic toxicity in the twice-weekly group was neutropenia. Because 2 of 6 patients experienced this toxicity in the

sixth cohort, the effective MTD of this regimen without growth factor support is 1.3 mg/m^2 bortezomib and 750 mg/m^2 cyclophosphamide. Given the fact that neutropenia was the only DLT to emerge up to that point on the twice-weekly schedule, it was thought that growth factor support might allow for maximization of therapeutic potential without putting patients at significant risk. Such support is routinely used to allow for chemotherapy intensification in lymphomas, and the investigators believed that it would be safe and would not compromise the study to add growth factor support to this regimen. Although the use of filgrastim and PegG did not significantly change the overall incidence of neutropenia measured during treatment, there were no further neutropenia-related DLTs noted after growth factor support was instituted and its use allowed for dose escalation to all preplanned dose levels. Of note, thrombocytopenia was not severe, even in this population including several heavily pretreated patients who were allowed to enroll with liberal pretreatment (>50,000) and predosing (>25,000 on bortezomib days) Plt requirements. Of the nonhematologic toxicities, the most clinically concerning was neuropathy. The incidence of mild neuropathy (grades 1 and 2) was 40% and 60% in the weekly and twice-weekly bortezomib groups, respectively. Two instances of severe (grades 3 and 4) neuropathy were seen in the twice-weekly group, whereas none were seen in the weekly group. Interestingly, neuropathy resolved in a greater proportion of patients over a shorter period of time in the weekly group than in the twice-weekly group. These findings are similar to those reported in a recent phase II study using 2 schedules of bortezomib with rituximab (15) and support prior observations of resolution after discontinuing bortezomib (21).

Shortly after we added filgrastim support to the twice-weekly regimen, it was shown that patients with multiple myeloma treated with overlapping doses of filgrastim and bortezomib did not seem to exhibit any detrimental effects on stem cells (22). We therefore sought to show the safety of administering PegG support simultaneously with bortezomib. Serial CBC counts failed to show significantly greater hematologic toxicities in this group when compared with a prior cohort of patients treated with nonoverlapping short-acting filgrastim, and none of the 10 patients in the overlapping PegG cohort experienced a DLT. To augment the safety analysis, the trend of each hematologic data point over 4 cycles was compared between these 2 groups and the only significant finding was a slightly greater decline in Plts over time in the PegG group. PegG is therefore safe and effective in patients treated with overlapping doses of bortezomib.

The ORR in evaluable patients of 46% (weekly) and 64% (twice weekly) with an overall time to progression of 13 months is encouraging. A greater number of patients received the twice-weekly schedule of treatment because of toxicities leading to more cohort expansions for this schedule. Given the difference in patient numbers, the greater number of patients treated at the highest dosing levels in the twice-weekly group and higher number of prior treatments (including greater prior use of bortezomib) seen by chance in patients in the weekly group (Table 1), response rates and survival cannot be directly compared in this phase I study. Of patients whose disease was refractory to their last prior treatment, 62% achieved a response with responses seen even in patients treated previously with components of the current regimen (some of whom were refractory to those treatments). These results support the idea that a combination of these agents can overcome resistance to common treatment regimens--even if these regimens contained similar agents. Data are beginning to emerge that show safe and effective combinations of bortezomib with other active agents in these diseases as well (23, 24).

Conclusions

R-CBorP seems to be safe and effective in treating indolent and MCLs and exhibits activity in heavily pretreated patients with prior exposure to similar agents. Overlapping growth factor support to prevent neutropenia is safe and effective with this regimen. Although our prior experience with single-agent bortezomib suggests that a weekly schedule of administration is inferior to a twice-weekly schedule (14), the current combination regimen is designed to exploit preclinical synergies seen between the agents, and it may not be possible to extrapolate single-agent activity to multiagent regimens in which such synergies may exist. In a recent study comparing weekly with twice-weekly bortezomib in combination with rituximab, both schedules yield similar clinical outcomes (25). As discussed earlier, we cannot make definitive comparisons between the efficacy of the 2 treatment schedules studied in this phase I trial and there may be significant differences in toxicity profile. We have therefore proceeded to a randomized phase II study to compare toxicity and efficacy between the 2 regimens described in this report.

Disclosure of Potential Conflicts of Interest

J. Gerecitano (unpaid), O.A. O'Connor, and A.D. Zelenetz have served as advisors to Millennium Pharmaceuticals, Inc. the Takeda Oncology Group; A.D. Zelenetz has served as an advisor to Genentech and Roche Pharmaceuticals; J. Gerecitano and P. Hamlin have served on a speaker's bureau for Genentech and Biogen-Idec; and C. Portlock, C.H. Moskowitz, A. Noy, D. Straus, P. Schulman, O. Dumitrescu, D. Sarasohn, J. Pappanicholaou, A. Iasonos, Z. Zhang, Q. Mo, E. Horanlli, and C.N. Rojas declare no competing financial interests.

Author Contributions

J. Gerecitano helped to design the clinical trial, treated patients on trial, documented toxicities, analyzed data, and wrote the manuscript. C. Portlock helped to design the clinical trial, treated patients on trial, and edited the manuscript. P. Hamlin contributed to ongoing revisions of the trial, treated patients on trial, and edited the manuscript. C.H. Moskowitz contributed to ongoing revisions of the trial, treated patients on trial, and edited the manuscript. A. Noy contributed to ongoing revisions of the trial, treated patients on trial, and edited the manuscript. D. Straus contributed to ongoing revisions of the trial, treated patients on trial, and edited the manuscript. P. Schulman treated patients on trial, documented toxicities,

and edited the manuscript. O. Dumitrescu assessed patient responses and helped to analyze patient data. D. Sarasohn assessed patient responses and helped to analyze patient data. A. Iasonos helped to design the trial and analyze data. Z. Zhang helped to analyze data. Q. Mo helped to analyze data. E. Horanlli entered and helped evaluate data. A.D. Zelenetz contributed to ongoing revisions of the trial, treated patients on trial, and edited the manuscript. O.A. O'Connor helped to design the clinical trial, treated patients on trial, documented toxicities, analyzed data, and edited the manuscript.

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