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Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study

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This first prospective phase 2 study of single-agent bortezomib in relapsed primary systemic AL amyloidosis evaluated the recommended (maximum planned) doses identified in phase 1 testing (1.6 mg/m^2 once weekly [days 1, 8, 15, and 22; 35-day cycles]; 1.3 mg/m^2 twice weekly [days 1, 4, 8, and 11; 21-day cycles]). Among all 70 patients enrolled in the study, 44% had ≥ 3 organs involved, including 73% and 56% with renal and cardiac involvement. In the 1.6 mg/m^2 once-weekly and 1.3 mg/m^2 twice-weekly groups, the hematologic response rate was 68.8% and 66.7% (37.5% and 24.2% complete responses, respectively); median time to first/best response was 2.1/3.2 and 0.7/1.2 months, and 78.8% and 75.5% had response durations of ≥ 1 year, respectively. One-year hematologic progression-free rates were 72.2% and 74.6%, and 1-year survival rates were 93.8% and 84.0%, respectively. Outcomes appeared similar in patients with cardiac involvement. Among all 70 patients, organ responses included 29% renal and 13% cardiac responses. Rates of grade ≥ 3 toxicities (79% vs 50%) and discontinuations/dose reductions (38%/53% vs 28%/22%) resulting from toxicities appeared higher with 1.3 mg/m^2 twice-weekly versus 1.6 mg/m^2 once-weekly dosing. Both bortezomib dose schedules represent active, well-tolerated regimens in relapsed AL amyloidosis. This study was registered at www.clinicaltrials.gov as #NCT00298766. (*Blood*. 2011;118(4):865-873)

Introduction

The amyloidoses are composed of various protein misfolding diseases that are characterized by extracellular deposition of pathologic insoluble fibrillar proteins in organs and tissues.[1] Primary systemic AL amyloidosis (AL) is the most common form and arises from the production of abnormal immunoglobulins by clonal plasma cells.[2,3] The estimated annual incidence of AL is 6 to 10 per million,[2,4-7] and the median age at diagnosis is 60 to 63 years.[2,4,7]

The aim of treatment for AL is to suppress production of the insoluble amyloidogenic immunoglobulin light-chain fragments, with the goal of restoring organ function.[4,8] The clonal plasma cell dyscrasia in AL is related to multiple myeloma (MM)[1,3,8]; thus, AL treatment is typically based on therapies that are effective in the treatment of MM.[4,8] The depth of hematologic response and, in particular, achievement of complete response (CR), has been shown to be associated with improved organ function[9] in AL patients and, as in MM, with improved overall survival (OS).[7,10,11] Intensive therapy with high-dose melphalan and stem cell transplantation is highly effective in AL, but a risk-adapted approach is required to minimize treatment-related mortality and toxicity.[9,12] Thus, because of patient age, poor performance status, and multiple organ involvement, up to 82% of patients may be ineligible for this treatment approach.[9,13,14] Oral melphalan plus dexamethasone has been the standard of care in the nontransplantation setting,[4] with other nonintensive treatment regimens, including thalidomide or lenalidomide plus cyclophosphamide and/or dexamethasone.[15-22]

The proteasome inhibitor bortezomib (VELCADE) is highly active in MM.[23-25] The pathogenic plasma cells in AL produce light chains prone to misfolding and may therefore be particularly sensitive to bortezomib-induced proteasome inhibition.[6] Indeed, case series studies suggest that bortezomib with or without dexamethasone is active in relapsed AL,[26,27] with a 72% hematologic response rate, including 25% CRs, reported in a multicenter retrospective analysis of 76 relapsed and 18 untreated AL patients.[26]

We undertook the phase 1/2 CAN2007 study, the first prospective study of single-agent bortezomib in relapsed AL, to evaluate its safety and efficacy in this patient population. In the phase 1 portion of the study, bortezomib was generally well tolerated at doses up to 1.6 mg/m^2 on a once-weekly schedule and 1.3 mg/m^2 on a twice-weekly schedule.[28] The maximum tolerated dose was not reached on either schedule.[28] Therefore, these maximum planned doses, which are consistent with those used in MM[29,30] and investigated in

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follicular lymphoma,[31] were evaluated in the phase 2 portion of the study. Here we present the final results of the phase 2 portion for patients treated at these recommended doses on each schedule.

Methods

Patients and study design

Patient eligibility and the design of the CAN2007 study (www.clinicaltrials.gov; #NCT00298766) have been reported previously.[28] Briefly, patients aged 18 years or older with a confirmed diagnosis of AL (Congo Red staining of tissue biopsy plus proof of plasma cell dyscrasia), who had previously been treated and required further treatment for AL, were eligible. As previously reported,[28] additional investigation was conducted if required to confirm the diagnosis.

Patients were required to have demonstrable M-protein and amyloid-related end-organ involvement. Multiple assessments were used at screening to determine end-organ involvement, consisting of physical examination, neurologic examination, cardiovascular examination (including electrocardiogram, echocardiogram, 24-hour Holter monitoring, and levels of cardiac biomarkers), computed tomography or magnetic resonance imaging scan, and clinical laboratory findings (including hematology, clinical chemistry, and 24-hour urinalysis). End-organ involvement was defined as previously reported[28] and included the following: renal, albuminuria $>$ 0.5 g/d in 24-hour urine analysis; cardiac, the presence of a mean left ventricular wall thickness on echocardiogram $>$ 11 mm in the absence of a history of hypertension or valvular heart disease, or unexplained low voltage ($<$ 0.5 mV) on electrocardiogram; hepatic, hepatomegaly on physical examination with an alkaline phosphatase level $>$ 200 U/L; and gastrointestinal, gastrointestinal bleeding confirmed by tissue biopsy.

Other key inclusion criteria included a Karnofsky Performance Status $\geq$ 70%, creatinine clearance $\geq$ 40 mL/min within 28 days before enrollment, echocardiographic ejection fraction $\geq$ 40%, and adequate hematologic, hepatic, and renal function. Patients were excluded from the study if they had New York Heart Association classification III or IV, grade 2 or 3 atrioventricular block, symptomatic orthostatic hypotension, or grade $\geq$ 2 peripheral neuropathy (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0).

Patients were enrolled in this nonrandomized, noncomparative phase 1/2 study at 9 sites in Canada, France, Germany, Italy, Spain, and the United States between July 25, 2005, and March 9, 2009. The primary objectives were to determine the maximum tolerated dose (phase 1 component)[28] and safety (phase 2 component) for both once-weekly and twice-weekly bortezomib. The secondary objective was to determine the best hematologic response rate and duration of response (DOR) at the maximum tolerated dose, and exploratory objectives included assessing the rate of organ response and OS. Review boards at all participating institutions approved the study, which was conducted according to the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Patients were enrolled to receive bortezomib at doses up to 1.6 mg/m^2 on days 1, 8, 15, and 22 of 35-day cycles (once-weekly regimen) and then at doses up to 1.3 mg/m^2 on days 1, 4, 8, and 11 of 21-day cycles (twice-weekly regimen); details of the phase 1 dose-escalation component have been reported previously.[28] Patients received up to 8 cycles of treatment per protocol; prolonged treatment was permitted for patients showing clear evidence of clinical benefit. Dose reductions were required for specific hematologic and nonhematologic toxicities; bortezomib-related neuropathic pain and peripheral sensory neuropathy were managed according to established dose modification guidelines.[32] Patients could discontinue treatment because of unacceptable toxicity, progression of hematologic amyloid markers, or performance status and organ function deterioration, and by patient/investigator decision.

Assessments

Hematologic and organ responses were determined during the rest period of each treatment cycle by rigorous assessment according to established consensus criteria.[33] Hematologic responses were based on serum and urine M-protein electrophoresis and immunofixation, quantitative immunoglobulins, free light-chain analysis, and bone marrow aspirate and biopsy as required. Organ responses were based on the multiple procedures used at screening to determine end-organ involvement. Cardiac response required a decrease in mean interventricular septal thickness by $\geq$ 2 mm, or a 20% improvement in ejection fraction, or an improvement in New York Heart Association classification by 2 classes without an increase in diuretic use and no increase in wall thickness.[33] Renal response required a $\geq$ 50% decrease (at least 0.5 g/d) in 24-hour urine protein without a $>$ 25% reduction in creatinine clearance.[33] Hepatic response required a $\geq$ 50% decrease in an abnormal alkaline phosphatase value, or a decrease (by physical examination or radiographically) in liver size of $\geq$ 2 cm.[33] Neurologic response required improvement in clinical examination findings, or in orthostatic blood pressure, or in any symptoms or signs related to peripheral neuropathy, cranial neuropathy, or other autonomic dysfunction, or a decrease in neuropathic pain or the reported neurotoxicity score. Responses were determined by the investigators and confirmed by the study medical monitor and Independent Data Monitoring Committee, based on central laboratory measurements of efficacy parameters; a central cardiology laboratory was used for assessment of cardiac data, which was subsequently reviewed and interpreted by a single independent cardiologist.

Adverse events (AEs) were recorded throughout the study and until 30 days after the last dose of bortezomib; AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0. Safety and efficacy were reviewed regularly throughout the study by the Independent Data Monitoring Committee.

Patients completing treatment or discontinuing for reasons other than progressive disease were followed up every 6 weeks until progressive disease, and then every 3 months until study completion (until the final patient had received 8 cycles or discontinued treatment).

Statistical analysis

After completion of the phase 1 dose-escalation component of this study, in the phase 2 component the maximum planned once-weekly and twice-weekly dose cohorts were to be expanded to 18 and 33 evaluable patients, respectively. These sample sizes were determined based on an expected hematologic response rate of $\geq$ 25% to ensure that the lower limit of 2-sided 90% exact binomial proportion confidence limits exceeded the minimally meaningful hematologic response rate of 10%. More patients were treated at the recommended twice-weekly dose level as this is the approved dose for bortezomib in MM.

The safety population included all patients who received at least one dose of bortezomib; the efficacy population included all patients who received at least one cycle of treatment and were evaluable for response. Response to treatment was evaluated in the efficacy population in the recommended once-weekly and twice-weekly dose cohorts separately, and in all other dose cohorts combined; time to response and DOR were determined in responding patients. Time to hematologic disease progression and OS were evaluated in the safety population. All efficacy analyses were considered exploratory and descriptive; there were no statistical comparisons between the 2 recommended dose cohorts. For response endpoints, exact 95% confidence intervals (CIs) were provided; for time-to-event distributions based on the Kaplan-Meier method, approximate CIs were used.

Results

Patient disposition and baseline characteristics

As reported previously,[28] a total of 31 patients were enrolled in 7 dose cohorts in the phase 1 component of this study. A further 39 patients were enrolled at the recommended doses of the once-weekly (N = 12) and twice-weekly (N = 27) regimens in the phase 2 component (Table 1). Thus, 18, 34, and 18 patients were

Table 1. Patient enrollment by dose level and phase of study

Schedule	dose, mg/m^2	Phase 1, n	Phase 2, n	Total, N
QW	0.7*	3*	—	9*
	1.0*	3*	—	
	1.3*	3*	—	
	1.6	6†	12	18
BIW	0.7*	3*	—	9*
	1.0*	6*	—	
	1.3	7‡	27	34
Total		31	39	70

BIW indicates twice-weekly schedule; QW, once-weekly schedule; and —, not applicable.

*Patients treated at doses lower than the recommended (maximum planned) doses on each schedule, which were evaluated in the phase 2 portion of the trial.

†One patient experienced a dose-limiting toxicity of grade 3 restrictive cardiomyopathy.

‡One patient experienced a dose-limiting toxicity of grade 3 congestive cardiac failure.

treated in the 1.6 mg/m^2 once-weekly, 1.3 mg/m^2 twice-weekly, and lower-dose groups, respectively.

Baseline demographics and disease characteristics by dose group are summarized in Table 2. Among all 70 patients, median age was 60.5 years (range, 38-80 years), 39 (56%) were male, 63 (90%) were white, and 31 (44%) had 3 or more organs involved, with 51 (73%), 39 (56%), and 20 (29%) having renal, cardiac, and gastrointestinal involvement, respectively. Overall, 67 (96%) patients had received prior melphalan, with 40 (57%) having previously undergone intensive therapy with high-dose therapy and stem cell transplantation; 57 (81%) had received prior glucocorticoids and 26 (37%) prior thalidomide or lenalidomide. Median age and the proportions of patients aged ≥ 65 years and with renal involvement were somewhat higher in the 1.3 mg/m^2 twice-weekly than the 1.6 mg/m^2 once-weekly group, whereas the proportions of patients with ≥ 3 organs involved, gastrointestinal involvement, cardiac history, neurologic history, and prior stem cell transplantation appeared somewhat higher in the 1.6 mg/m^2 once-weekly group.

At the primary study analysis, which occurred when all patients had had the opportunity to complete 8 cycles, 24 (34%) patients had completed treatment (including 8 in each of the 1.6 mg/m^2 once-weekly, 1.3 mg/m^2 twice-weekly, and lower-dose groups), 42 (60%) had discontinued (9, 25, and 8 patients, respectively), and 4 were ongoing on treatment (1, 1, and 2 patients, respectively).

Hematologic response to treatment

A total of 67 patients were evaluable for hematologic response. Three patients were excluded as they had no postbaseline hematologic assessment. Best confirmed hematologic responses to single-agent bortezomib by dose group are summarized in Table 3. The overall hematologic response rate was 68.8%, 66.7%, and 38.9% in the 1.6 mg/m^2 once-weekly, 1.3 mg/m^2 twice-weekly, and lower-dose groups, respectively, including 37.5%, 24.2%, and 11.1% rates of CR. The overall hematologic response rate was 67.3% (95% CI, 52.5%-80.1%) in the 2 recommended dose groups combined, including 28.6% who achieved CR.

The median time to first response was 2.1, 0.7, and 1.2 months, and median time to best response was 3.2, 1.2, and 1.2 months, in the 1.6 mg/m^2 once-weekly, 1.3 mg/m^2 twice-weekly, and lower-dose groups, respectively (Table 3). Median DOR and median time to hematologic disease progression were not reached in any dose group, after median follow-up of 17.5, 8.4, and 9.9 months in the

Table 2. Demographics and baseline disease characteristics for patients treated at the recommended doses on each schedule or at lower doses on either schedule

	Recommended dose groups		
	1.6 mg/m^2 QW (N = 18)	1.3 mg/m^2 BIW (N = 34)	Lower doses (N = 18)
Median age (range)	56.5 (45-74)	67.0 (42-80)	58.0 (38-77)
Age ≥ 65 y, n (%)	3 (17)	18 (53)	6 (33)
Male, n (%)	8 (44)	21 (62)	10 (56)
White, n (%)	17 (94)	30 (88)	16 (89)
Karnofsky Performance Status $< 90\%$, n (%)	7 (39)	13 (38)	7 (39)
Median time since initial diagnosis, mo (range)	27 (7-92)	28 (3-163)	32 (10-95)
No. of organs involved, n (%)			
1	2 (11)	8 (24)	4 (22)
2	6 (33)	13 (38)	6 (33)
≥ 3	10 (56)	13 (38)	8 (45)
Specific organ involvement, n (%)			
Renal	10 (56)	27 (79)	14 (78)
Cardiac	10 (56)	20 (59)	9 (50)
Hepatic	4 (22)	4 (12)	1 (6)
Gastrointestinal	9 (50)	8 (24)	3 (17)
Neurologic	2 (11)	2 (6)	3 (17)
Other*	11 (61)	14 (41)	11 (61)
Any cardiac history, n (%)	9 (50)	11 (32)	4 (22)
Any neurologic history, n (%)	12 (67)	18 (53)	11 (61)
Median baseline creatinine clearance, mL/min (range)	88 (44-153)	74 (23-146)	69 (29-149)
Prior AL treatment, n (%)	18 (100)	34 (100)	18 (100)
Melphalan	17 (94)	33 (97)	17 (94)
High-dose therapy plus stem cell transplantation	12 (67)	17 (50)	11 (61)
Glucocorticoids	16 (89)	25 (74)	16 (89)
Thalidomide/lenalidomide	7 (39)	9 (26)	10 (56)

BIW indicates twice weekly; and QW, once weekly.

*Other sites of involvement included lymph nodes, macroglossia, skin, lips, and tongue.

Table 3. Best confirmed hematologic responses to bortezomib in patients treated at the recommended doses on each schedule or at lower doses on either schedule

	Recommended dose groups		
	1.6 mg/m² QW	1.3 mg/m² BIW	Lower doses
Best confirmed hematologic response, n (%) (95% CI)	N = 16	N = 33	N = 18
Overall response rate (CR + PR)	11 (68.8) (41.3-89.0)	22 (66.7) (48.2-82.0)	7 (38.9) (17.3-64.3)
CR	6 (37.5) (15.2-64.6)	8 (24.2) (11.1-42.3)	2 (11.1) (1.4-34.7)
SD	4 (25.0) (7.3-52.4)	10 (30.3) (15.6-48.7)	11 (61.1) (35.7-82.7)
PD	1 (6.3) (0.2-30.2)	1 (3.0) (0.1-15.8)	0
Median time to hematologic response, mo (range)	N = 11	N = 22	N = 7
First response	2.1 (0.9-6.9)	0.7 (0.3-4.0)	1.2 (0.6-4.8)
Best response	3.2 (0.9-7.2)	1.2 (0.3-7.6)	1.2 (0.6-4.8)
Duration of response ≥ 1 year, % (95% CI)	78.8 (38.1-94.3)	75.5 (41.6-91.4)	83.3 (27.3-97.5)
Time to hematologic disease progression	N = 18	N = 34	N = 18
Median follow-up, mo	17.5	8.4	9.9
Patients progressing, n	4	5	4
1-year progression-free rate, % (95% CI)	72.2 (48.7-95.7)	74.6 (54.4-94.8)	88.5 (73.6-100)

QW indicates once weekly; BIW, twice weekly; CR, complete response; PR, partial response; SD, stable disease; and PD, progressive disease.

1.6 mg/m² once-weekly, 1.3 mg/m² twice-weekly, and lower-dose groups, respectively (Table 3). Overall, 77.9% (95% CI, 56.9%-89.6%) of responders had a DOR of 1 year or longer. At the time of data cutoff, 13 of 70 (19%) patients had experienced hematologic disease progression, and the overall 1-year progression-free rate was 77.4% (95% CI, 65.1%-89.7%). Time to hematologic disease progression appeared similar to the overall population in the 39 patients who had cardiac involvement, as the 1-year progression-free rate was 77.0% (95% CI, 58.8%-95.3%).

Organ responses

Organ responses among evaluable patients with the respective organ involvement in each dose group are summarized in Table 4. Overall, 14 of 49 (29%) patients had a renal response, 5 of 39 (13%) had a cardiac response based on ≥ 2 mm decreases in mean left ventricular wall thickness, and 2 of 7 (29%) had a neurologic response. A total of 22 of 51 (43%) evaluable patients had renal function improvement (≥ 50% decrease in 24-hour urine protein from baseline of 0.5 g/d, regardless of change in creatinine clearance), including 5 of 10 (50%), 13 of 27 (48%), and 4 of 14 (29%) in the 1.6 mg/m² once-weekly, 1.3 mg/m² twice-weekly, and lower-dose groups, respectively. As shown in Table 4, organ responses were usually associated with hematologic response; among evaluable patients, 12 of 38 (32%) hematologic responders compared with 3 of 24 (13%) hematologic nonresponders achieved any organ response.

Cardiac biomarker analyses

Changes in the cardiac biomarkers brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) over the course of treatment in patients with or without cardiac involvement (as defined by the study protocol) are summarized in supplemental Table 1 (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Levels of both biomarkers were substantially higher in patients with cardiac involvement compared with those without, and changes over the course of treatment appeared limited in both groups. Analyses of these changes in patients according to hematologic response and to achievement of a cardiac response in patients with cardiac involvement showed no associations (data not shown). Analyses of clinically significant

Table 4. Organ responses to bortezomib in patients treated at the recommended doses on each schedule or at lower doses on either schedule, and by hematologic response

	Recommended dose groups			Hematologic response*	
Organ	1.6 mg/m² QW	1.3 mg/m² BIW	Lower doses	CR/PR	No response
Renal, N	9	26	14	29	19
Response, n (%)	4 (44)	7 (27)	3 (21)	11 (38)	3 (16)
No change, n (%)	5 (56)	17 (65)	11 (79)	17 (59)	15 (79)
Progression, n (%)	0	2 (8)	0	1 (3)	1 (5)
Cardiac, N	10	20	9	22	14
Response,† n (%)	1 (10)	2 (10)	2 (22)	4 (18)	1 (7)
No change, n (%)	9 (90)	18 (90)	7 (78)	18 (82)	13 (93)
Hepatic, N	4	3	1	6	2
No change, n (%)	4 (100)	3 (100)	1 (100)	6 (100)	2 (100)
Neurologic, N	2	2	3	5	2
Response, n (%)	2 (100)	0	0	2 (40)	0
No change, n (%)	0	2 (100)	3 (100)	3 (60)	2 (100)
Any organ, N				38	24
Response, n (%)				12 (32)	3 (13)
No change, n (%)				25 (66)	20 (83)
Progression, n (%)				1 (3)	1 (4)

QW indicates once weekly; BIW, twice weekly; CR, complete response; and PR, partial response.
*In response-evaluable patient population.
†Based on ≥ 2-mm decreases in mean left ventricular wall thickness.

Table 5. Safety profile of bortezomib in patients treated at the recommended doses on each schedule or at lower doses on either schedule

AEs, n (%)	Recommended dose groups		
	1.6 mg/m² QW (N = 18)	1.3 mg/m² BIW (N = 34)	Lower doses (N = 18)
Any AE	18 (100)	34 (100)	18 (100)
Any treatment-related AE	17 (94)	33 (97)	17 (94)
Any grade ≥ 3 AE	9 (50)	27 (79)	7 (39)
Any grade 4 AE	2 (11)	6 (18)	0
Any serious AE	8 (44)	14 (41)	3 (17)
Patients discontinuing because of AEs	5 (28)	13 (38)	5 (28)
Patients requiring dose reductions because of AEs	4 (22)	18 (53)	1 (6)

QW indicates once weekly; and BIW, twice weekly.

(> 30%) changes in BNP and NT-proBNP among patients with adequate renal function (creatinine clearance ≥ 45 mL/min per 1.73 m²) and cardiac involvement as defined by elevated BNP (> 133 pg/mL) or NT-proBNP (> 332 pg/mL) were uninformative because of the small number of patients who had cardiac involvement according to elevated biomarker criteria (data not shown).

OS

Median OS was not reached in any dose group, after median follow-up for survival of 17.9, 10.2, and 37.7 months in the 1.6 mg/m² once-weekly, 1.3 mg/m² twice-weekly, and lower-dose groups, respectively. At the time of the study analysis, 3, 4, and 4 patients, respectively, had died, because of progressive disease in 1, 0, and 3 patients, treatment-related AEs in 0, 2, and 0 patients (as described in "Treatment exposure and safety"), and other causes in 2 (1 transformation to aggressive MM; 1 unknown), 2 (1 renal failure, graft-versus-host disease, and gastrointestinal bleeding after allogeneic transplantation; 1 sudden cardiac death), and 1 (prostate cancer) patients, respectively. The 1-year survival rates were 93.8% (95% CI, 81.9%-100%), 84.0% (95% CI, 69.0%-99.1%), and 94.1% (95% CI, 82.9%-100%) in the 1.6 mg/m² once-weekly, 1.3 mg/m² twice-weekly, and lower-dose groups, respectively. The overall 1-year survival rate for all 70 patients was 89.6% (95% CI, 81.7%-97.6%). OS appeared similar in the 39 patients who had cardiac involvement; the 1-year survival rate was 90.9% (95% CI, 80.8%-100%).

Treatment exposure and safety

The median number of bortezomib treatment cycles received in the 1.6 mg/m² once-weekly, 1.3 mg/m² twice-weekly, and lower-dose groups was 8 (range 1-13), 6 (range 1-16), and 8 (range 3-33), respectively; in total, 10 (56%), 11 (32%), and 11 (61%) patients were treated for at least 8 cycles, respectively. During cycles 1 to 8, the dose intensity was 6.0, 4.1, and 3.8 mg/m² per cycle, the cumulative total dose was 43.10, 22.15, and 22.40 mg/m², and the percentage of the maximum possible bortezomib dose actually received was 94%, 79%, and 100% in the 1.6 mg/m² once-weekly, 1.3 mg/m² twice-weekly, and lower-dose groups, respectively.

The safety profile of bortezomib in each of the dose groups is summarized in Table 5. At the recommended doses, the twice-weekly regimen appeared to result in higher rates of grade ≥ 3 AEs (79% vs 50%), grade 4 AEs (18% vs 11%), and discontinuations (38% vs 28%) and dose reductions (53% vs 22%) because of AEs than the once-weekly regimen. The safety profile appeared milder in the lower-dose group. Two patients in the 1.3 mg/m² twice-weekly group died within 30 days of their last dose of bortezomib because of AEs considered by the investigators to be possibly related to treatment, specifically interstitial lung disease and acute cardiac failure. The first patient had a medical history inclusive of pleural effusion and cardiac disease, and clinically significant abnormalities on baseline chest x-ray. The serious AE of interstitial lung disease occurred during cycle 2; the patient died 6 days after their final dose. The second patient had a medical history inclusive of cardiac disease and coronary artery disease, with heart failure evident at baseline. The serious AE of acute cardiac failure occurred in cycle 2; the patient died 2 days after receiving bortezomib.

Table 6 presents the system organ classes and individual preferred terms for which there was a difference of at least 10% in the AE rate between the 1.6 mg/m² once-weekly and 1.3 mg/m² twice-weekly dose groups. All grade ≥ 3 AEs reported in more than 2 patients are also shown in Table 6. The rate of peripheral neuropathy of any grade was 22%, 35%, and 6% in the 1.6 mg/m² once-weekly, 1.3 mg/m² twice-weekly, and lower-dose groups, respectively. No grade 3 peripheral neuropathy was reported in any group; low rates of discontinuations or dose reductions for peripheral neuropathy were also reported. Discontinuations for peripheral neuropathy were required in 0, 3 (9%), and 0 patients in the 3 dose groups, respectively, and dose reductions for peripheral neuropathy were required in 1 (6%), 2 (6%), and 0 patients, respectively. Cardiac disorders appeared more frequent in the 1.3 mg/m² twice-weekly than the 1.6 mg/m² once-weekly group.

Discussion

The findings from this first prospective phase 1/2 evaluation of single-agent bortezomib in AL suggest that bortezomib is an active agent in relapsed AL and is generally well tolerated with a manageable safety profile at the doses investigated. As discussed in our report of the phase 1 component of this study,[28] it should be noted that patients with the poorest prognosis and cardiac status were excluded to ensure a comprehensive characterization of the safety profile of bortezomib in AL. The selected nature of our patient population is highlighted by the relatively low median age and high proportion of patients who had prior stem cell transplantation compared with the general AL patient population, and the long median time from diagnosis in these patients with relapsed disease, all factors suggestive of a more robust patient population. Nevertheless, our findings show that bortezomib 1.6 mg/m² once weekly and 1.3 mg/m² twice weekly produced high hematologic response rates, of 68.8% and 66.7%, respectively, and high CR rates of 37.5% and 24.2%, which is important given the reported association between CR and prolonged survival.[9,10,19,34] Notably, these responses were durable, with 78.8% and 75.5% of responders, respectively, remaining in remission for at least 1 year. Furthermore, the overall 1-year hematologic progression-free and OS rates in this study were 77.4% and 89.6%, respectively, which appear

Table 6. AEs of all grades (by SOC and MedDRA preferred term) with a ≥ 10% difference in rate between the QW and BIW recommended dose cohorts, plus all grade ≥ 3 AEs reported in > 2 patients

	Recommended dose groups		
SOC/MedDRA preferred term	1.6 mg/m² QW (N = 18)	1.3 mg/m² BIW (N = 34)	Lower doses (N = 18)
Blood and lymphatic system disorders	3 (17)	15 (44)	4 (22)
Anemia	2 (11)	7 (21)	2 (11)
Thrombocytopenia	1 (6)	8 (24)	1 (6)
Cardiac disorders	1 (6)	10 (29)	3 (17)
Gastrointestinal disorders	17 (94)	31 (91)	13 (72)
Constipation	8 (44)	20 (59)	5 (28)
Diarrhea	14 (78)	23 (68)	9 (50)
Nausea	15 (83)	18 (53)	9 (50)
Vomiting	13 (72)	13 (38)	4 (22)
General disorders and administration site conditions	15 (83)	30 (88)	15 (83)
Chills	4 (22)	3 (9)	0
Infections and infestations	14 (78)	18 (53)	13 (72)
Upper respiratory tract infection	5 (28)	3 (9)	2 (11)
Nervous system disorders	15 (83)	22 (65)	13 (72)
Dizziness	7 (39)	9 (26)	5 (28)
Peripheral neuropathy*	4 (22)	12 (35)	1 (6)
Respiratory, thoracic, and mediastinal disorders	8 (44)	22 (65)	8 (44)
Cough	3 (17)	12 (35)	4 (22)
Skin and subcutaneous tissue disorders	8 (44)	19 (56)	11 (61)
Pruritus	4 (22)	2 (6)	3 (17)
Vascular disorders	5 (28)	16 (47)	5 (28)
Orthostatic hypotension	1 (6)	7 (21)	1 (6)
Grade ≥ 3 AEs reported in > 2 patients overall			
Fatigue	2 (11)	6 (18)	3 (17)
Thrombocytopenia	0	6 (18)	0
Vomiting	0	4 (12)	0
Diarrhea	1 (6)	2 (6)	0
Pneumonia	1 (6)	2 (6)	0
Syncope	0	2 (6)	1 (6)

SOC indicates system organ class; MedDRA, Medical Dictionary for Regulatory Activities; QW, once weekly; and BIW, twice weekly.
*High-level term, including "neuropathy peripheral," "peripheral motor neuropathy," and "peripheral sensory neuropathy" preferred terms.

promising for patients with relapsed AL, albeit in our selected patient population. Of particular interest, these outcomes appeared similar in patients with cardiac involvement, which is typically associated with poor prognosis in AL.[7,35] Organ responses were also reported in both the once-weekly and twice-weekly groups; reflecting the findings of studies of other regimens in AL,[9,36] these responses were typically associated with hematologic response. Notably, 29% of patients with renal involvement had a renal response, and 43% had an improvement in renal function. Furthermore, 13% of patients with cardiac involvement had a cardiac response based on ≥ 2-mm decreases in mean left ventricular wall thickness, and no cardiac disease progression was seen; cardiac AL is typically rapidly progressive, and so bortezomib treatment may be of benefit in this subpopulation.

These findings from one of the largest prospective studies of single-agent therapy for AL are supported by the activity reported in retrospective analyses and case series of bortezomib with or without dexamethasone in first-line and relapsed AL.[26,27,37,38] For example, an overall hematologic response rate of 72%, including 25% CRs, plus a 30% organ response rate, was reported by Kastritis et al in a multicenter retrospective analysis of 94 AL patients,[26] 18 of whom were previously untreated and 84 of whom received concomitant dexamethasone. In contrast to the present study, the population included a substantial proportion of patients with advanced cardiac disease (63% New York Heart Association class ≥ 2). Outcomes appeared slightly less favorable compared with those reported in our prospective study, with a median time to hematologic progression of 25.5 months and a 1-year OS rate of 76%.[26] Promising results have also been reported from an ongoing trial of the addition of bortezomib to melphalan-dexamethasone, the nonintensive standard of care in first-line AL[39]; among 35 patients with AL, light-chain deposition disease, or smoldering myeloma, 54% of whom had ≥ 3 organs involved and 54% of whom had relapsed disease, the overall hematologic response rate was 88%, including 39% CRs.[39] As noted, these studies have shown the activity of bortezomib-based therapy in patients with poorer prognostic factors than the present population. Thus, although the findings of our study may not necessarily be applicable to the general population because of the more robust nature of our patients, these results from other studies suggest that bortezomib may be a useful therapeutic agent alone and in combination in the broader, less stringently selected, AL patient population.

Encouraging findings have also been reported from studies in AL using combination regimens of other novel agents, such as the immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide, plus dexamethasone, with or without cyclophosphamide or melphalan. Hematologic response rates of 40%-75%,[15-22,40] including CR rates of up to 29%,[22] plus organ response rates of up to 50%,[20] have been reported with these combinations. Comparisons of activity between studies are not feasible because of the use of single-agent and combination therapy approaches, the small population sizes, and other confounding factors, such as the heterogeneous nature of the AL patient population. Nevertheless, the findings from the present study of single-agent bortezomib appear

notable in the context of these data from studies of combination regimens, and, in general, the use of novel agents, such as bortezomib and the immunomodulatory drugs in regimens for the treatment of AL appears to offer high hematologic response rates and promising organ responses.

It is important to highlight the rapid time to hematologic response seen in the present study, particularly with the twice-weekly schedule, as well as in other studies of novel agents. The median times to first and best hematologic response in the present study were 2.1 and 3.2 months in the 1.6 mg/m^2 once-weekly group and 0.7 and 1.2 months in the 1.3 mg/m^2 twice-weekly group; responses thus appeared to be more rapid with the more dose-intensive twice-weekly regimen, although it should be noted that response assessments were more frequent using this schedule. It may be speculated that a subset of patients who achieve deep responses rapidly may not require the full protocol-specified course of bortezomib; however, further studies are required to elucidate the long-term benefit of continued treatment beyond best response. Median times to response were similarly short in the retrospective analysis of bortezomib with or without dexamethasone (1.7 months)[26] and in the ongoing study of bortezomib plus melphalan-dexamethasone (two 4-week cycles to achieve best response),[39] as well as in studies of thalidomide or lenalidomide plus cyclophosphamide and dexamethasone (1.4-2.9 months).[16,18,21,41,42] These rapid responses represent an important improvement on the median time to response of 3.1 to 6.4 months reported with other nonintensive regimens, including melphalan-dexamethasone in previously untreated patients.[15,17,34,36,41-44] Rapid hematologic responses are important as organ responses lag behind hematologic responses, and patients may not survive long enough to experience the benefit of treatments that are overly slow-acting.[8]

Our analyses of changes in the cardiac biomarkers BNP and NT-proBNP were limited in scope. It should be noted that the start of the CAN2007 study predated the routine use of these biomarkers, which has evolved during the course of the study and was not an endpoint of the trial. Nevertheless, it is clear that the levels of both biomarkers differentiate patients with and without cardiac involvement, with the former having substantially elevated BNP and NT-proBNP, as would be expected. Further, the results indicate that biomarker levels appeared stable over the course of treatment, with limited or no deterioration or improvement in either group of patients. In other analyses not presented here, the numbers of patients with adequate renal function and cardiac involvement based on elevated biomarker values were too small to draw any meaningful conclusions; these very limited patient numbers may in part reflect study enrollment criteria, which excluded patients with more severe cardiac disease, who would be more likely to demonstrate elevated BNP and/or NT-proBNP levels. In addition, analyses regarding biomarker changes and association with hematologic and cardiac response did not appear informative; this may suggest limited utility and sensitivity of cardiac biomarkers for patients with more limited cardiac amyloid involvement, such as in the present selected patient population. By contrast, the multicenter retrospective analysis by Kastritis et al in 94 AL patients,[26] which included a substantial proportion of patients with advanced cardiac disease, showed that hematologic responses were associated with cardiac response and reduction in NT-proBNP and that NT-proBNP was independently associated with survival.

We noted in our initial report of the phase 1 component[28] that the safety profile of bortezomib in AL in the present study appeared similar to that reported in studies in MM.[24,29,30] This has been borne out by the results from the phase 2 component and from other studies of bortezomib-based regimens in AL.[26,38,39] It should be noted that before study initiation there was a theoretical concern that bortezomib may result in an increase in end-organ fibril deposition because of inhibition of the degradation of misfolded proteins, thereby worsening the clinical manifestations of AL; however, this potential risk does not appear to have materialized, as reflected by the safety profile derived in the present study and in other reports of bortezomib in AL.

The commonly reported AEs in the present study generally mirrored those seen with bortezomib in relapsed MM[29]; in particular, the overall safety profile in the 1.3 mg/m^2 twice-weekly group appeared very similar to that reported in the Assessment of Proteasome Inhibition for Extending Remissions phase 3 study in relapsed MM in terms of rates of grade ≥ 3 AEs, serious AEs, and discontinuations because of AEs.[29] However, in contrast, we recorded no grade ≥ 3 peripheral neuropathy, including in the 1.3 mg/m^2 twice-weekly group; this dose and schedule resulted in 9% grade 3/4 peripheral neuropathy in the Assessment of Proteasome Inhibition for Extending Remissions study.[29] Thus, this apparent difference may not be the result of a limited exposure to treatment in our patients, as suggested in our phase 1 report, but perhaps more the result of the differences in the underlying disease-related neuropathy between AL and MM.[45] In addition, because 10% of our patients had baseline neurologic involvement and more than half had some neurologic history, these factors do not appear to be contraindications to treatment with bortezomib.

Overall, our results showed that the safety profile appeared generally milder with the 1.6 mg/m^2 once-weekly regimen compared with the 1.3 mg/m^2 twice-weekly regimen, with treatment duration being longer and consequently the cumulative dose being higher. As would be expected, toxicity also appeared reduced in the lower-dose group; response to treatment appeared similarly affected, however, suggesting that the use of the recommended doses is warranted for optimal efficacy. Nevertheless, treatment initiation at lower doses, with subsequent escalation if tolerated, may be an approach for less healthy patients. There were a number of apparent differences in the incidences of AEs between the 2 recommended dose groups, including the rates of some gastrointestinal events, infections, chills, and dizziness appearing higher in the 1.6 mg/m^2 once-weekly group, and the rates of blood and lymphatic system disorders, peripheral neuropathy, and orthostatic hypotension appearing higher in the 1.3 mg/m^2 twice-weekly group. These differences may arise because some acute toxicities, such as some gastrointestinal events, may be more dependent on maximum plasma concentration, whereas other toxicities, such as peripheral neuropathy and hematologic events, may be more affected by dosing frequency or dose density of the regimen.

The apparent difference between the groups in the frequency of all-grade cardiac AEs, with a higher incidence in the twice-weekly group, is difficult to interpret because of the similar frequency of amyloid cardiac involvement in both groups, as well as the cardiac responses seen. However, in general, cardiac involvement does not appear to be a contraindication to bortezomib treatment. This is supported by findings from other studies and case reports in AL.[37,46,47] Notably, Brunvand and Bitter[37] reported the case of an AL patient with cardiac involvement who had relapsed after stem cell transplantation. The patient achieved a hematologic CR and full resolution of cardiac involvement and thus became eligible for a second transplantation after bortezomib plus dexamethasone therapy.[37] Similarly, Charaf et al reported a significant hematologic response with single-agent bortezomib in an AL patient with

cardiac involvement, which was accompanied by significant regression of cardiac amyloid infiltration, improved left ventricular ejection fraction, and decreased interventricular septum and posterior wall thicknesses.[46]

In conclusion, these results suggest that single-agent bortezomib has notable activity in this selected population of patients with relapsed AL. Both bortezomib 1.6 mg/m^2 once weekly and 1.3 mg/m^2 twice weekly represent active regimens for these patients, offering high hematologic response rates and rapid and durable responses, together with organ responses. The 1.3 mg/m^2 twice-weekly regimen appeared to result in more rapid responses, but toxicity appeared generally lower with 1.6 mg/m^2 once weekly. Based on the currently available data from this and other studies, bortezomib with or without dexamethasone is currently included as a primary treatment option for AL in the United States National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[48] Ongoing studies of bortezomib in combination with melphalan-dexamethasone in previously untreated AL,[39] including a phase 3 study of melphalan-dexamethasone with or without bortezomib (#NCT01078454), and of the use of bortezomib within a stem cell transplantation approach,[49,50] will help further define the activity and optimal use of this agent for the treatment of AL within the broad patient population, including in patients with cardiac involvement.

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Authorship

Contribution: D.E.R., D.-L.E., H.v.d.V., and A.C. designed the research; D.E.R., U.H., V.S., G.M., G.P., J.B., J.-P.F., H.H., L.H., R.A.V., and R.L.C. performed the research; D.E.R., U.H., V.S., G.M., G.P., J.B., J.-P.F., H.H., L.H., R.A.V., K.L., C.E., H.v.d.V., A.C., and R.L.C. collected data; D.E.R., U.H., V.S., G.M., G.P., J.B., J.-P.F., H.H., L.H., R.A.V., K.L., C.E., D.-L.E., H.v.d.V., A.C., and R.L.C. analyzed and interpreted data; K.L., C.E., and A.C. performed statistical analysis; D.E.R., A.C., and R.L.C. wrote the manuscript; and all authors reviewed and approved the manuscript.

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