A Multicenter, Open-Label, Phase 1b Study of Carfilzomib, Cyclophosphamide, and Dexamethasone in Newly Diagnosed Multiple Myeloma Patients (CHAMPION-2)

Ralph V. Boccia,[1] Alberto Bessudo,[2] Richy Agajanian,[3] Paul Conkling,[4] Wael Harb,[5] Hui Yang,[6] Dawn Pinchasik,[6] Amy S. Kimball,[6] James R. Berenson[7]

Abstract

The CHAMPION-2 study evaluated 3 dose levels of carfilzomib when provided with fixed dose oral cyclophosphamide and dexamethasone for newly diagnosed multiple myeloma. Carfilzomib with cyclophosphamide and dexamethasone is effective and has manageable toxicity.

Introduction: This phase 1b study evaluated the safety and efficacy of 3 dose levels of carfilzomib when provided with fixed dose oral cyclophosphamide and dexamethasone (KCyd) in patients with newly diagnosed multiple myeloma (MM). **Patients and Methods:** CHAMPION-2 was a multicenter single-arm study. Patients with newly diagnosed secretory MM were enrolled and received KCyd treatment for up to 8 cycles. A 3 + 3 dose escalation scheme was used to evaluate twice-weekly carfilzomib at 36, 45, and 56 mg/m^2 dose levels, followed by a dose expansion. **Results:** No dose-limiting toxicities were observed in any of the dose evaluation cohorts. The KCyd regimen that included the maximum planned carfilzomib dose of 56 mg/m^2 twice weekly was brought forward into dose expansion. A total of 16 patients were treated at this dose level. At 56 mg/m^2 the overall response rate was 87.5% (95% confidence interval, 61.7-98.4), and the median time to response of 14 patients whose disease responded to therapy was 1 month. At this dose level, common adverse events of grade 3 or higher were anemia (25.0%), neutropenia (18.8%), acute kidney injury (12.5%), and decreased white blood cell count (12.5%). Ten of 16 patients who received carfilzomib at 56 mg/m^2 completed all 8 cycles, 5 patients discontinued study therapy before cycle 8 as a result of adverse events, and 1 patient discontinued therapy as a result of progressive disease. **Conclusion:** Carfilzomib in combination with cyclophosphamide and dexamethasone is effective and has manageable toxicity for patients with newly diagnosed MM.

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Introduction

Carfilzomib is a selective second-generation proteasome inhibitor.[1,2] In a randomized phase 3 head-to-head trial (ENDEAVOR) comparing proteasome inhibitors in combination with low-dose dexamethasone, carfilzomib at 56 mg/m^2 twice weekly resulted in significantly improved progression-free survival over bortezomib in relapsed or refractory multiple myeloma (MM) (18.7 months vs. 9.4 months; hazard ratio, 0.53; $P < .0001$).[3] Overall survival in ENDEAVOR was also significantly improved for the carfilzomib group compared to the bortezomib group (47.6 months vs. 40.0 months; hazard ratio, 0.79; $P = .0100$).[4]

[1]Center for Cancer and Blood Disorders, Bethesda, MD
[2]Cancer Care Associates for Research and Excellence, Encinitas, CA
[3]The Oncology Institute of Hope and Innovation, Downey, CA
[4]US Oncology Research, Virginia Oncology Associates, Norfolk, VA
[5]Horizon Oncology Center, Lafayette, IN
[6]Amgen Inc, Thousand Oaks, CA
[7]Institute for Myeloma & Bone Cancer Research, West Hollywood, CA

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Address for correspondence: Ralph V. Boccia, MD, 6410 Rockledge Dr, Suite 660, Bethesda, MD 20817
E-mail contact: RBoccia@ccbdmd.com

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Alkylating agents have been used to treat MM since the 1960s. Since the introduction of proteasome inhibitor therapy 15 years ago, triplet combinations that include an alkylator, a proteasome inhibitor, and a steroid have moved into frontline myeloma therapy.[5] Several studies have demonstrated the activity of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) combinations in previously untreated MM, with rates of very good partial response (VGPR) or better ranging from 37% to 61%.[6-8] CyBorD is a preferred regimen recommended by the National Comprehensive Cancer Network (NCCN) MM panel for the frontline treatment of MM in both transplant-eligible and transplant-ineligible patients.[5] Despite the success of CyBorD, few trials have been performed to study the combination of the proteasome inhibitor carfilzomib with cyclophosphamide and dexamethasone (KCyd) for MM patients. In a prior study by Bringhen et al,[9] 58 transplant-ineligible, newly diagnosed MM patients were enrolled and treated with up to 9 cycles of KCyd (36 mg/m^2) followed by maintenance therapy.

The objectives of this phase 1b study were to evaluate the safety and tolerability of twice-weekly carfilzomib when used in combination with cyclophosphamide and dexamethasone for the treatment of newly diagnosed MM patients, and to estimate the overall response rate (ORR) and time to response (TTR). Whereas the population in Bringhen et al[9] was limited to transplant-ineligible patients who were $\geq$ 65 years of age, patients in this study were $\geq$ 18 years of age and were enrolled regardless of transplant eligibility.

Methods

This was a phase 1b, multicenter, open-label, dose-escalation study of twice-weekly carfilzomib provided in combination with oral cyclophosphamide and dexamethasone to patients with newly diagnosed MM (ClinicalTrials.gov identifier NCT01980589). Patients 18 years or older with newly diagnosed symptomatic MM and measurable disease were eligible. Inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; left ventricular ejection fraction $\geq$ 40%; adequate hepatic function (bilirubin $<$ 1.5 times the upper limit of normal, and aspartate aminotransferase and alanine aminotransferase $<$ 3 times the upper limit of normal); absolute neutrophil count $\geq 1.0 \times 10^9$/L; platelet count $\geq 50 \times 10^9$/L; and creatinine clearance $\geq$ 15 mL/min. Patients were excluded if they had MM of immunoglobulin M subtype, plasma-cell leukemia, Waldenstrom macroglobulinemia, grade 2 or higher neuropathy, active congestive heart failure (New York Heart Association Class III or IV), symptomatic ischemia, or myocardial infarction within 6 months before enrollment. This study permitted stem-cell collection but did not permit autologous hematopoietic stem-cell transplantation while the patient was on the study protocol. Written consent was obtained from all patients, and the study protocol received institutional review board approval by all participating institutions.

The trial was originally designed as a phase 1b/2 trial, with treatment to include 8 cycles of induction therapy with KCyd, followed by randomization to maintenance carfilzomib therapy versus observation. In 2014, as a result of slow enrollment and competing trials, the protocol was amended to include only the phase 1b component and only induction. Treatment was therefore provided with KCyd in 28-day cycles and was continued for 8 cycles, or until progression of disease, unacceptable toxicity, withdrawal of consent, or death. Oral cyclophosphamide, 300 mg/m^2, was administered on days 1, 8, and 15, and 40 mg dexamethasone was administered orally or intravenously on days 1, 8, 15, and 22. Carfilzomib was administered as a 30-minute intravenous infusion on days 1, 2, 8, 9, 15, and 16 (on days 1 and 2 of cycle 1, all patients received carfilzomib at 20 mg/m^2). Subjects were followed until withdrawal of consent or 30 days after the final treatment.

A traditional 3 + 3 design was used with carfilzomib evaluated at 36 mg/m^2, 45 mg/m^2, and 56 mg/m^2 dose levels followed by a dose-expansion cohort. The maximum tolerated dose (MTD) of KCyd was defined as the highest carfilzomib dose at which $<$ 33% of patients had a treatment-related dose-limiting toxicity during the first 28-day treatment cycle. Dose-limiting toxicities were defined as any of the following treatment-related adverse events: grade 3 or higher nonhematologic toxicity; grade 3 or higher acute kidney injury lasting $>$ 72 hours; grade 4 neutropenia lasting for $>$ 7 days; febrile neutropenia of any duration; grade 4 thrombocytopenia that persisted for $>$ 14 days despite holding treatment; or grade 3 or 4 thrombocytopenia associated with $>$ grade 1 bleeding.

The primary end point of this study was the MTD of carfilzomib provided twice weekly in combination with cyclophosphamide and dexamethasone for patients with newly diagnosed MM, and secondary end points were ORR, TTR, and safety. Overall response was defined as a best response of stringent complete response, complete response (CR), VGPR, or partial response using the International Myeloma Working Group Uniform Response Criteria per investigator assessment. Under the amended protocol (induction KCyd therapy only), patients were followed for 30 days after last treatment, and progression-free survival was not evaluated.

Determination of adverse event severity was based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). This study was supported by Onyx Pharmaceuticals Inc, an Amgen Inc subsidiary.

Results

Twenty-two patients were enrolled onto this study, which was conducted at 9 US centers between August 29, 2013, and March 31, 2016. There were no dose-limiting toxicities at 36 mg/m^2, 45 mg/m^2, or 56 mg/m^2 of carfilzomib; thus, the MTD was not determined, and the maximum planned dose was brought forward into dose expansion. Overall, 16 patients were treated with KCyd at the maximum planned dose of 56 mg/m^2 (Table 1). Patients who received the 56 mg/m^2 dose had a median age of 65 years (50% of patients were $<$ 65 years old, 31.3% were between 65 and 74 years old, and 18.8% were $\geq$ 75 years old); 56.3% of patients were men (Table 1). Most patients had an ECOG performance status of 0 or 1 (43.8%, 50% respectively); 6.3% had an ECOG performance status of 2 (Table 1). Standard-risk cytogenetics was seen in 50% of patients, 6.3% had high-risk cytogenetics, and cytogenetics was unknown for 43.8% of patients. The baseline serum β_2 microglobulin level was $<$ 5.5 mg/L for 50% of patients, $\geq$ 5.5 mg/L for 37.5% of patients, and unknown for 12.5% of patients (median serum β_2 microglobulin, 3.9 mg/L; range, 1.7-20.1 mg/L). A history of renal disorders was present in 10 (45%) of 22 subjects.

Fourteen of 22 patients completed all 8 cycles of treatment. Ten of 16 patients in the 56 mg/m^2 cohort completed all 8 KCyd cycles;

Table 1 Patient Baseline Demographic and Disease Characteristics

Characteristic	36 mg/m^2 (N = 3)	45 mg/m^2 (N = 3)	56 mg/m^2 (N = 16)
Age, y, median (range)	56.0 (53-71)	63.0 (61-66)	65.0 (49-81)
Age group, N (%)			
<65 y	2 (66.7)	2 (66.7)	8 (50.0)
65 to <75 y	1 (33.3)	1 (33.3)	5 (31.3)
≥75 y	0	0	3 (18.8)
Sex, N (%)			
Male	3 (100.0)	1 (33.3)	9 (56.3)
Female	0	2 (66.7)	7 (43.8)
ECOG performance status, N (%)			
0	1 (33.3)	1 (33.3)	7 (43.8)
1	2 (66.7)	2 (66.7)	8 (50.0)
2	0	0	1 (6.3)
Time since initial diagnosis, months, median (range)	1.1 (1.1-37.1)	4.8 (1.4-43.0)	1.9 (0.6-46.8)
Cytogenetics by FISH, N (%)[a]			
Standard risk	0	3 (100.0)	8 (50.0)
High risk	1 (33.3)	0	1 (6.3)
Unknown	2 (66.7)	0	7 (43.8)
Baseline serum β_2 microglobulin, N (%)			
<5.5 mg/L	3 (100.0)	3 (100.0)	8 (50.0)
≥5.5 mg/L	0	0	6 (37.5)
Unknown	0	0	2 (12.5)
Medical history of renal disorders, n (%)	1 (33.3)	2 (66.7)	7 (43.8)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in-situ hybridization.
[a]High-risk group consists of genetic subtypes t(4;14), t(14;16), or deletion 17p in 60% or more of plasma cells. Standard-risk group consists of patients without t(4;14), t(14;16), and < 60% of plasma cells with deletion 17p. Unknown-risk group consists of patients with FISH result not done, failed, or insufficient quantity.

1 patient discontinued therapy as a result of progressive disease; and 5 patients discontinued treatment as a result of adverse events (acute renal failure, n = 1; creatinine increase and dehydration, n = 1; intermittent nausea, n = 1; urinary tract infection, n = 1; and sepsis and pneumonia, n = 1). One of 3 patients dosed at 36 mg/m^2 discontinued therapy before completing the 8 cycles as a result of the development of progressive disease, and 1 of 3 patients dosed at 45 mg/m^2 died of coronary artery occlusion during cycle 3. Three of 16 patients in the 56 mg/m^2 cohort had at least 1 dose reduction of carfilzomib, 1 patient in the 45 mg/m^2 cohort had a carfilzomib dose reduction, and no patients in the 36 mg/m^2 cohort had a carfilzomib dose reduction.

Among all 22 patients, common adverse events of any grade were nausea (72.7%), anemia (40.9%), diarrhea (40.9%), vomiting (40.9%), dyspnea exertional (36.4%), edema peripheral (31.8%), neutropenia (31.8%), upper respiratory tract infection (31.8%), and dyspnea (27.3%). Common grade 3 or higher adverse events among all patients were anemia (22.7%), neutropenia (13.6%), hyperglycemia (9.1%), acute kidney injury (9.1%), and white blood cell count decreased (9.1%). Peripheral neuropathy occurred among 1 (4.5%) of 22 patients in the study. Peripheral neuropathy (grade 1) occurred in 1 patient in the 56 mg/m^2 dose cohort and did not occur in any patients in the 36 or 45 mg/m^2 dose cohorts; grade 3 or higher peripheral neuropathy did not occur among any patients in the study (Table 2). Cardiac toxicity occurred among 2 of 22 patients (9.1%) in the study. Cardiac failure occurred in 1 patient in the 56 mg/m^2 dose cohort (grade 3 or higher ejection fraction decreased), and 1 patient in the 45 mg/m^2 cohort died from coronary artery occlusion. Acute kidney injury occurred among 4 (18.2%) of 22 patients in the study. Acute kidney injury was reported among 4 patients in the 56 mg/m^2 dose cohort (2 of these had grade 3 or higher acute kidney injury) (Table 2) but was not reported among any patients in the 36 or 45 mg/m^2 dose cohorts (Table 2). Of the 2 patients with grade 3 or higher acute kidney injury, 1 case was considered to be related to carfilzomib, and the relationship to carfilzomib was uncertain for the other (a patient who was found to have progressive disease shortly after developing renal injury).

Of the 16 patients who received KCyd at the maximum planned dose of 56 mg/m^2, 14 experienced a response (ORR, 87.5%; 95% confidence interval, 61.7-98.4) (Table 3). The best overall responses in the 56 mg/m^2 cohort were CR (n = 1), VGPR (n = 7), and partial response (n = 6) (Table 3). The median TTR for the 14 patients whose disease responded to therapy in the 56 mg/m^2 dose cohort was 1 month (range, 0.9-2.8 months; Table 3). Disease of 2 patients in the 36 mg/m^2 dose cohort responded; the TTR was 1.0 month and 1.6 months, respectively. All patients in the 45 mg/m^2 dose cohort responded with a median TTR of 0.8 months (range, 0.7-1.9 months; Table 3). Patients were followed for 30 days beyond last treatment (a median follow-up of 7.2 months), and thus progression-free survival was not assessed.

Discussion

Cyclophosphamide and dexamethasone have been combined with bortezomib (CyBorD, VCD, and VCD-mod) for the treatment of newly diagnosed MM in several prior studies,[6-8,10] and current NCCN guidelines list CyBorD as a preferred regimen for both newly diagnosed and relapsed MM treatment.[5] Though different groups used somewhat different dosing schedules to evaluate CyBorD, all showed encouraging response rates with responses of VGPR or greater ranging from 37% to 61%.[6-8,10] Response rates to cyclophosphamide, bortezomib, and dexamethasone triplet regimens are thus similar to the 50% VGPR or better seen here and the 71% rate of VGPR or better seen for KCyd with 36 mg/m^2 twice-weekly carfilzomib dosing by Bringhen et al.[9] Other studies of carfilzomib in newly diagnosed MM have reported rates of VGPR or better of 72% for carfilzomib, lenalidomide, and low-dose dexamethasone (carfilzomib at 36 mg/m^2, n = 36 patients) and of 58% for carfilzomib, melphalan, and prednisone (carfilzomib at 36 mg/m^2, n = 50 patients).[11,12]

The rate of peripheral neuropathy observed in trials of CyBorD is higher than that reported among patients treated with KCyd. For example, Reeder et al[8] reported that any-grade peripheral neuropathy occurred in 66% of patients who received CyBorD (with twice-weekly bortezomib), whereas we found that any-grade

Table 2 Frequency of Adverse Events

Adverse Event	Any Grade				Grade 3 or Higher			
	36 mg/m^2 (N = 3)	45 mg/m^2 (N = 3)	56 mg/m^2 (N = 16)	All Patients (N = 22)	36 mg/m^2 (N = 3)	45 mg/m^2 (N = 3)	56 mg/m^2 (N = 16)	All Patients (N = 22)
Acute kidney injury	0	0	4 (25.0)	4 (18.2)	0	0	2 (12.5)	2 (9.1)
Anemia	1 (33.3)	0	8 (50.0)	9 (40.9)	1 (33.3)	0	4 (25.0)	5 (22.7)
Cardiac failure (group term)[a]	0	0	1 (6.3)	1 (4.5)	0	0	1 (6.3)	1 (4.5)
Diarrhea	0	0	9 (56.3)	9 (40.9)	0	0	0	0
Dyspnea	3 (100.0)	1 (33.3)	2 (12.5)	6 (27.3)	0	1 (33.3)	0	1 (4.5)
Dyspnea exertional	2 (66.7)	2 (66.7)	4 (25.0)	8 (36.4)	1 (33.3)	0	0	1 (4.5)
Edema peripheral	1 (33.3)	1 (33.3)	5 (31.3)	7 (31.8)	1 (33.3)	0	0	1 (4.5)
Hyperglycemia	1 (33.3)	1 (33.3)	0	2 (9.1)	1 (33.3)	1 (33.3)	0	2 (9.1)
Nausea	2 (66.7)	3 (100.0)	11 (68.8)	16 (72.7)	0	0	0	0
Neutropenia	1 (33.3)	0	6 (37.5)	7 (31.8)	0	0	3 (18.8)	3 (13.6)
Peripheral neuropathy	0	0	1 (6.3)	1 (4.5)	0	0	0	0
Upper respiratory tract infection	1 (33.3)	0	6 (37.5)	7 (31.8)	0	0	0	0
Vomiting	1 (33.3)	2 (66.7)	6 (37.5)	9 (40.9)	0	0	0	0
White blood cell count decreased	0	0	3 (18.8)	3 (13.6)	0	0	2 (12.5)	2 (9.1)

Data are presented as n (%).
[a]Standardized Medical Dictionary for Regulatory Activities Queries Narrow Search.

peripheral neuropathy occurred among only 6.3% of patients treated at the 56 mg/m^2 dose. This is consistent with findings from the ENDEAVOR study, in which the rate of grade 2 or higher peripheral neuropathy was significantly lower for patients receiving carfilzomib at the same dose and schedule with dexamethasone compared to bortezomib and dexamethasone.[3] These observations suggest that KCyd may have advantages over CyBorD in patients who have peripheral neuropathy before starting treatment.

The safety and efficacy of the KCyd regimen for the treatment of newly diagnosed MM reported here are similar to those from a larger experience reported by Bringhen et al[9] using the KCyd combination with 36 mg/m^2 carfilzomib dosing. In that study, a lower carfilzomib dose than 56 mg/m^2 was evaluated, and a lower rate of renal toxicity (5% all grades, 4% grade 3 or higher) was observed than the 25% rate of any-grade renal toxicity observed here. The ORR noted by Bringhen et al was 95%, and after 9 cycles, 23% of patients experienced a stringent CR. The higher rate of CR seen in the study of Bringhen et al compared to this study may arise from a higher tolerance of therapy at the 36 mg/m^2 carfilzomib dose. In Bringhen et al, 43 (74%) of 58 patients completed all 9 cycles of treatment, compared to 10 (63%) of 16 patients who completed all 8 cycles of treatment here. Thus, KCyd with 36 mg/m^2 carfilzomib was safe and effective in a population of patients 65 years or older with newly diagnosed MM,[9] and given the higher rates of response observed by Bringhen et al, KCyd with 36 mg/m^2 carfilzomib may be preferable to KCyd with 56 mg/m^2 carfilzomib in younger transplant-eligible patients.

Table 3 Best Overall Response and Time to Response

Response	36 mg/m^2 (N = 3)	45 mg/m^2 (N = 3)	56 mg/m^2 (N = 16)
Best overall response, N (%)			
Complete response	0	0	1 (6.3)
Very good partial response	1 (33.3)	2 (66.7)	7 (43.8)
Partial response	1 (33.3)	1 (33.3)	6 (37.5)
Stable disease	0	0	2 (12.5)
Progressive disease	1 (33.3)	0	0
Overall response rate, % (95% confidence interval)[a]	66.7 (9.4-99.2)	100 (29.2-100.0)	87.5 (61.7-98.4)
Time to response, months, median (range)[b]	1.3 (1.0-1.6)	0.8 (0.7-1.9)	1.0 (0.9-2.8)

[a]Overall response rate includes stringent complete response, complete response, very good partial response, and partial response.
[b]Time to response is defined as months from treatment start to first documentation of response of partial response or better. Time to response includes patients with confirmed response of partial response or better.

Conclusion

Combination regimens for carfilzomib continue to be explored to optimize efficacy and safety. The findings reported here for the phase 1b CHAMPION-2 study demonstrate that carfilzomib administered twice weekly can be used at 56 mg/m^2 in combination with cyclophosphamide and dexamethasone for newly diagnosed MM. The results reported here are consistent with another phase 2 study of KCyd in transplant-ineligible, newly diagnosed MM that included 36 mg/m^2 carfilzomib.[9] KCyd represents a novel option for newly diagnosed MM that is effective and has manageable toxicity.

Clinical Practice Points

- Carfilzomib is a selective, irreversible proteasome inhibitor currently approved for the treatment of relapsed and refractory MM.
- The CHAMPION-2 study evaluated 3 dose levels of carfilzomib when provided as a component of KCyd combination therapy in patients with newly diagnosed MM.

- We found that 56 mg/m^2 carfilzomib (provided on days 1, 2, 8, 9, 15, and 16) combined with weekly cyclophosphamide and dexamethasone on a 28-day cycle was effective and had manageable toxicity.
- Ten of 16 patients who received 56 mg/m^2 carfilzomib completed all 8 cycles, and the ORR was 87.5%.
- The CHAMPION-2 study demonstrated a favorable risk–benefit profile for KCyd, and supports further investigation of this combination for treatment of newly diagnosed MM.

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Disclosure

R.V.B. has served as a consultant for Amgen Inc, Celgene, Genentech, and Eisai, has received honoraria from Amgen Inc, Celgene, Genentech, and Eisai, and has participated in speakers' bureaus for Amgen Inc, Celgene, Genentech, Eisai, and Gilead. P.C. has received research funding from US Oncology Research and Amgen Inc. W.H. has served as a consultant for Amgen Inc. H.Y., D.P., and A.S.K. are employees of Amgen Inc and own stock in Amgen Inc. J.R.B. has served as a consultant for Amgen Inc and has received research funding and honoraria from Amgen Inc. A.B. and R.A. have stated that they have no relevant conflict of interest.

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