Original Study

An Open-Label Single-Arm Pilot Phase II Study (PX-171-003-A0) of Low-Dose, Single-Agent Carfilzomib in Patients With Relapsed and Refractory Multiple Myeloma

Sundar Jagannath,[1] Ravi Vij,[2] A. Keith Stewart,[3] Suzanne Trudel,[4] Andrzej J. Jakubowiak,[5] Tony Reiman,[6] George Somlo,[7] Nizar Bahlis,[8] Sagar Lonial,[9] Lori A. Kunkel,[10] Alvin Wong,[11] Robert Z. Orlowski,[12] David S. Siegel[13]

Abstract

An open-label single-arm multicenter pilot phase II study of the next-generation selective proteasome inhibitor carfilzomib was conducted in 46 patients with relapsed and refractory multiple myeloma (MM) after ≥ 2 previous therapies. The best overall response rate (ORR) was 16.7%, with a median duration of response of 7.2 months. This pilot study was the first phase II single-agent trial conducted with carfilzomib.

Background: Carfilzomib is a next-generation selective proteasome inhibitor that irreversibly binds its target and has demonstrated single-agent activity in patients with bortezomib-resistant multiple myeloma (MM). PX-171-003-A0, an open-label single-arm multicenter pilot phase II study, enrolled 46 patients with relapsed MM after ≥ 2 previous therapies including bortezomib and an immunomodulator (thalidomide or lenalidomide) and disease refractory to the last treatment regimen preceding study entry. **Methods:** Patients received carfilzomib 20 mg/m^2 intravenously on days 1, 2, 8, 9, 15, and 16 every 28 days for up to 12 cycles. Responses in 42 evaluable patients were assessed per International Myeloma Working Group Uniform Response Criteria, with minimal response assessed per European Group for Blood and Marrow Transplantation (EBMT) criteria. **Results:** The primary endpoint of best ORR was 16.7%, including 7 partial responses. Median duration of response was 7.2 months. Clinical benefit response (CBR) rate was 23.8% with a median duration of response of 13.8 months. The most common treatment-emergent adverse events (AEs) of any grade were anemia (73.9%), fatigue (69.6%), and thrombocytopenia (50.0%). Notably, peripheral neuropathy and neuropathy-related AEs were generally mild and infrequent. **Conclusion:** This pilot study was the first phase II single-agent trial conducted with carfilzomib. Based on these findings, the study was amended to test a higher carfilzomib dose in an additional 250 patients (PX-171-003-A1).

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[1]Mt. Sinai Medical Center, New York, NY
[2]Washington University School of Medicine, St. Louis, MO
[3]Mayo Clinic College of Medicine, Scottsdale, AZ
[4]University of Toronto Princess Margaret Hospital, Toronto, ON, Canada
[5]University of Chicago, Chicago, IL
[6]Beatrice Hunter Cancer Research Institute, St. John Regional Hospital, St. John, NB, Canada
[7]City of Hope National Medical Center, Duarte, CA
[8]Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada
[9]Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA
[10]Independent Consultant, San Francisco, CA
[11]Onyx Pharmaceuticals Inc, South San Francisco, CA
[12]MD Anderson Cancer Center, Houston, TX
[13]John Theurer Cancer Center, Hackensack, NJ

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Address for correspondence: Sundar Jagannath, MD, Mount Sinai Medical Center, 1 Gustave Levy Place, New York, NY 10029
E-mail contact: sundar.jagannath@mssm.edu

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Introduction

Important advances have been made in the treatment of multiple myeloma (MM) over the past decade with the introduction of thalidomide and the development of novel therapies including lenalidomide and the proteasome inhibitor bortezomib.[1-6] Despite these advances, MM remains an incurable disease because patients eventually relapse or disease develops that is refractory to treatment. In the relapsed or refractory setting, a limited number of combination regimens appear to improve overall disease control and survival compared with monotherapy, but generally at a cost of greater toxicity.[1,5,6] Typically, once the patient's disease relapses and becomes refractory to approved agents, the prognosis is poor.[7] Novel treatments that can be used as single agents or as part of combination regimens to achieve durable responses while still being well tolerated are needed for relapsed and refractory disease.

Carfilzomib is a next-generation selective proteasome inhibitor that produces sustained target inhibition in the absence of off-target effects related to bortezomib.[8-10] Although both proteasome inhibitors have similar potencies against their primary target, there are important structural and mechanistic differences between the 2 drugs.[10-13] Carfilzomib irreversibly inhibits the proteasome, whereas bortezomib is a slowly reversible inhibitor.[11,14] Thus carfilzomib induces a longer duration of proteasome inhibition than does bortezomib, which may account for its antitumor activity in bortezomib-resistant tumor models.[9] Furthermore, carfilzomib demonstrates significantly less cross-reactivity with nonproteasomal proteases compared with bortezomib, which has been shown to correlate with a lack of neurotoxicity in preclinical models.[11,12,15,16]

The safety of intravenous (IV) carfilzomib as a single agent was demonstrated in 2 separate phase I dose-escalation studies in patients with relapsed or refractory hematologic malignancies.[17,18] In the first study (PX-171-001), carfilzomib (at doses ranging from 1.2 to 20 mg/m^2) was administered daily for 5 days, followed by 9 days of rest on a 2-week cycle, and the maximum tolerated dose (MTD) was established at 15 mg/m^2.[17] The most common toxicities were grade 1/2 fatigue and gastrointestinal events. No grade 3/4 peripheral neuropathy was reported. In the second study (PX-171-002), 48 patients with relapsed or refractory hematologic malignancies received carfilzomib at doses ranging from 1.2 to 27 mg/m^2 given on 2 consecutive days weekly for 3 weeks (days 1, 2, 8, 9, 15, and 16) on a 4-week cycle.[18] The treatment was well tolerated, and the MTD was not reached. Primarily hematologic toxicities were observed, with some transient and noncumulative elevations in serum creatinine levels. Notably, grade 3/4 peripheral neuropathy was not observed. An interim analysis of the PX-171-002 study demonstrated clinical activity and tolerability of the 20 mg/m^2 dose, and dose escalation continued in this study.[18,19]

The next pilot study, the first phase II study of carfilzomib, was designed to support a preliminary futility analysis of the efficacy and safety of single-agent carfilzomib in patients with relapsed and refractory MM when administered at a dose of 20 mg/m^2 on 2 consecutive days per week for 3 weeks of a 4-week cycle. Final data from the PX-171-002 study[18,19] demonstrated that escalation to 27 mg/m^2 was tolerable and efficacious, and the current study was amended (003- PX-171-003-A1A1) to include intrapatient dose escalation from 20 to 27 mg/m^2. Because the dose and schedule used in the PX-171-003-A1 study are different, separate statistical analyses were planned, and thus the investigators chose to report those results separately. The results of the pilot phase II study are reported herein.

Patients and Methods

This phase II multicenter open-label single-arm pilot study was conducted in 11 centers in North America. Eligibility criteria included age $\geq$ 18 years; relapsed and refractory MM with disease measurable by serum M protein $\geq$ 1 g/dL, urine M protein $\geq$ 200 mg/24 h, serum free light chains (sFLC) $\geq$ 10 mg/dL with an abnormal ratio, or quantitative immunoglobulins (if serum protein electrophoresis [SPEP] or urine protein electrophoresis [UPEP] was unreliable for routine M protein measurement); $\geq$ 2 previous treatment regimens for relapsed disease, with induction therapy and stem cell transplantation ($\pm$ maintenance) considered 1 regimen; disease that was responsive (minimal response [MR] or better) to $\geq$ 1 previous therapy and refractory ($\leq$ 25% response, or progression during or within 60 days of completion of the last therapy). Previous treatment with bortezomib and lenalidomide or thalidomide was required. Other eligibility criteria included a life expectancy of $>$ 3 months, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate hepatic function, and a creatinine clearance (CrCl) of $\geq$ 30 mL/min. Laboratory entry criteria included serum aspartate aminotransferase or alanine aminotransferase concentration less than 3 times the upper limit of normal, serum total bilirubin concentration less than 2 times the upper limit of normal, platelet count $\geq$ 50,000/mm^3, hemoglobin concentration $\geq$ 8.0 g/dL, and absolute neutrophil count $\geq$ 1000/mm^3. Patients with IgM MM, significant cardiovascular disease (eg, class III/IV New York Heart Association congestive heart failure), active infection, or significant peripheral neuropathy (grade 3/4 or grade 2 with pain) were not eligible for enrollment.

The study was conducted in accordance with US Food and Drug Administration and International Conference on Harmonisation Guidelines for Good Clinical Practice, Declaration of Helsinki, Health Canada, and applicable local health authority and institutional review board requirements. All patients provided written informed consent in accordance with federal, local, and institutional guidelines. The trial was registered at http://ClinicalTrials.gov (NCT00511238).

Treatment

Patients received carfilzomib 20 mg/m^2 intravenously over 2 minutes on 2 consecutive days per week on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle for up to 12 cycles. Oral or IV dexamethasone 4 mg was administered before all carfilzomib doses during the first cycle and could be given in any other cycle as necessary for prevention of treatment-related fever, rigors, chills, and/or dyspnea occurring after dosing.

Patients who achieved responses of stable disease (SD) or better after the first 2 cycles of treatment were eligible to continue receiving treatment for up to 12 cycles or until disease progression or intolerable toxicity. Dose interruptions were permitted for significant hematologic toxicity (grade 3 neutropenia or grade 4 thrombocytopenia, lymphopenia, or anemia) or nonhematologic toxicity ($\geq$ grade 3) until resolution ($\leq$ grade 1), or for CrCl $<$ 30 mL/min until resolution to $\geq$ 30 mL/min. When restarting treatment, the carfil-