Original Study

Relationship Between Carfilzomib Dose and Efficacy Outcomes in Patients With Relapsed and/or Refractory Multiple Myeloma

Pierre Squifflet,[1] Stefan Michiels,[2] David Siegel,[3] Ravi Vij,[4] Sundar Jagannath,[5] Everardo D. Saad,[1,6] Kanya Rajangam,[7] Sunhee Kwon Ro,[7] Marc Buyse[1]

Abstract

We examined the dose-response relationship of the proteasome inhibitor carfilzomib in multiple myeloma patients (n = 461) treated in phase II trials using logistic regression models. In the primary analysis, adjustment for covariates yielded an increase in the odds ratio for response for each 1 mg/m^2 increase in the average administered dose of carfilzomib per patient, which provides evidence for a dose-response relationship.

Background: Carfilzomib is approved by the US Food and Drug Administration for the treatment of patients with relapsed and refractory multiple myeloma (MM) who have received at least 2 previous treatments. The approval was based on phase II trials that used a starting dose of 20 mg/m^2 escalated to a target dose of 27 mg/m^2 in cycle 2. We examined dose-outcome relationships in MM patients who received these 2 carfilzomib doses. **Materials and Methods:** Patient data from 4 cohorts of MM patients treated with single-agent carfilzomib in phase II trials were examined post hoc. The relationship between administered doses and overall response rate (ORR) was assessed using logistic regression models. Secondary analyses were performed using Cox regression models to assess the association between administered doses and time to event outcomes and using generalized estimating equations for cycle-specific response status (CSRS). **Results:** A total of 476 intention to treat patients were enrolled, 461 of whom were evaluable for efficacy. In the primary analysis, adjustment for cohort and baseline covariates yielded an odds ratio for ORR of 1.28 (95% confidence interval, 1.16-1.41; $P < .001$) for each 1 mg/m^2 increase in the average administered dose of carfilzomib per patient (up to 27 mg/m^2). Qualitatively similar and statistically significant results were seen for the association between administered dose and CSRS, duration of response, time to progression, progression-free survival, and overall survival when adjusted for cohort and baseline covariates. **Conclusion:** This post hoc analysis provides evidence for a dose-response relationship between the administered dose of carfilzomib and efficacy.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 11, 680-6
Keywords: Clinical trials, Dose-response relationship, Hematologic malignancy, Overall response rate, Post hoc analysis, Proteasome inhibitor

Introduction

Carfilzomib is a novel proteasome inhibitor granted accelerated approval by the US Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma (MM) who have received at least 2 previous therapies (including bortezomib and an immunomodulatory agent), and who have shown disease progression during therapy or within 60 days of completion of the last therapy.[1] This approval was based on the results of a single-arm pivotal phase II trial (PX-171-003-A1), which included 266 patients and showed an overall response rate (ORR) of 23.7%, with a median duration of response (DOR) of 7.8 months.[2] Moreover, 3 additional phase II trials (PX-171-003-A0, PX-171-004, and

[1]International Drug Development Institute, Louvain-la-Neuve, Belgium
[2]Service de Biostatistique et d'Epidémiologie, Institut Gustave Roussy, Université Paris-Sud, Villejuif, France
[3]John Theurer Cancer Center at Hackensack University, Hackensack, NJ
[4]Washington University School of Medicine, St Louis, MO
[5]Mount Sinai Medical Center, New York, NY
[6]Dendrix Research, Sao Paulo, Brazil
[7]Onyx Pharmaceuticals, Inc, An Amgen subsidiary, South San Francisco, CA

Submitted: Mar 20, 2015; Revised: Sep 3, 2015; Accepted: Sep 11, 2015; Epub: Sep 25, 2015

Address for correspondence: Pierre Squifflet, MSc, International Drug Development Institute, Avenue Provinciale, 30 – 1340 Louvain-la-Neuve, Belgium
Fax: +32 (0) 10 61 88 88; e-mail contact: pierre.squifflet@iddi.com

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.09.005

PX-171-005) have been conducted among patients with MM, and confirmed the activity and safety profile of carfilzomib in this population.[3-6] The latter of these trials was conducted among MM patients with renal impairment.[6] In phase I and II trials of single-agent carfilzomib in relapsed and/or refractory MM, Grade 3/4 adverse events were predominantly hematologic.[7-9] Of note, a low incidence of treatment-emergent peripheral neuropathy (14%) was observed, which is a major dose-limiting toxicity for the first-in-class, older proteasome inhibitor bortezomib, although lower rates of peripheral neuropathy have been observed with the use of weekly or subcutaneous administration of bortezomib.[10-12] Carfilzomib does not target nonproteasomal proteases to a significant extent[13] and thus, there is great interest in further development of carfilzomib in the treatment of MM. Results of phase III trials of this agent, alone and in combination therapy, will further define its role in the management of patients with relapsed or newly diagnosed MM.

The dose of carfilzomib used in the pivotal phase II trial was based on results from a phase I trial.[7] Carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. In the pivotal study, PX-171-003-A1, the starting dose was 20 mg/m^2; if tolerated, this dose was stepped up to a target dose of 27 mg/m^2 in cycle 2.[2] The pilot study (PX-171-003-A0) that preceded this pivotal trial evaluated the 20 mg/m^2 dose with no step-up in 46 patients with relapsed and refractory MM with 2 or more previous therapies (including bortezomib and an immunomodulatory agent).[5] The PX-171-004 study, which evaluated carfilzomib in patients without (n = 129) or with (n = 35) previous bortezomib, was originally designed to evaluate the dose of 20 mg/m^2; an amendment allowed dose escalation to 27 mg/m^2 in cycle 2.[3,4] Thus, the PX-171-004 study had 2 dosing cohorts; one preamendment scheduled to receive the 20 mg/m^2 dose throughout the study (enrolled bortezomib-naive patients and bortezomib-pretreated patients), and the other postamendment that followed the stepped-up 20- to 27-mg/m^2 dosing regimen from cycle 2 onward and enrolled bortezomib-naive patients only.[3,4] In an analysis of the bortezomib-naive patients of PX-171-004, the 20-mg/m^2 cohort was compared with the 20- to 27-mg/m^2 cohort.[4] Although the trial was not designed to make comparisons between the 2 carfilzomib dose levels, a nonrandomized comparison showed an increased ORR in the 20- to 27-mg/m^2 cohort, thus lending support to the hypothesis from preclinical studies that proteasome inhibition behaves in a dose-dependent fashion.[14,15] The other 2 phase II trials included patients scheduled to receive either the 20 mg/m^2 dose throughout the study[5] or the stepped-up 20- to 27-mg/m^2 dosing regimen,[2,3] which allowed us to further test the hypothesis of a dose-response relationship for carfilzomib. We present the results of this post hoc analysis, which included all of the patients enrolled in the PX-171-003-A0 (NCT00511238), PX-171-003-A1 (NCT00511238), and PX-171-004 (NCT00530816) phase II trials of single-agent carfilzomib in relapsed and/or refractory MM.

Materials and Methods

Characteristics of Trials Analyzed

The design, eligibility criteria, end points, and major efficacy results of the phase II trials included in the current analysis are summarized in Table 1.[2-5] All 4 cohorts of patients enrolled in these trials provided informed consent, therefore, no ethical approval was sought for the current analysis. The analysis was carried out independently at the International Drug Development Institute, Belgium, and was sponsored by Onyx Pharmaceuticals, Inc, an Amgen subsidiary (South San Francisco, CA).

Outcome Variables of Interest

For the phase II trials described, the primary end point was the ORR (ie, the sum of the proportions of patients with complete response [CR], stringent complete response CR [sCR], partial response [PR], and very good PR [VGPR]), as defined according to the International Myeloma Working Group Uniform Response Criteria.[16] In all of the included trials, ORR was assessed on day 15 of cycle 1, on day 1 of subsequent cycles, and at the end of the study. The analyses of planned doses were on the basis of response assessments made by the trial sponsor, using serum and/or urine M-protein levels and other measurements, such as serum free light chain (FLC) assay results or bone scans. Disease progression was defined as any of the following: (1) an increase in serum M-protein $\geq$ 25% above the lowest response level and an absolute increase of $\geq$ 5 g/L; (2) an increase in urine M-protein $\geq$ 25% above the lowest remission value and an absolute increase in excretion of $\geq$ 200 mg per 24 hours; (3) an increase in the size of soft tissue plasmacytoma by $\geq$ 50% or appearance of a new plasmacytoma; (4) the appearance of new bone lesions or an increase in size of existing bone lesions $\geq$ 50%; (5) an increase in serum FLC difference (involved and uninvolved) above the lowest value and an absolute increase $\geq$ 25%; or (6) unexplained hypercalcemia ($>$ 2.875 mM or $>$ 11.5 g/dL). Progression had to be confirmed in 2 consecutive assessments. Secondary efficacy end points included clinical benefit rate, DOR, time to progression (TTP), progression-free survival (PFS), and overall survival (OS). Safety end points have been reported previously and were not assessed in the current analysis.

The primary outcome variable for the present analysis was ORR. Secondary variables of interest were cycle-specific response status, DOR, TTP, PFS, and OS. Cycle-specific response status was analyzed as a dichotomous variable according to whether patients had at least a PR at the end of each cycle. DOR was defined as the time between a confirmed sCR, CR, VGPR, or PR and disease progression or death from any cause; TTP was defined as the time between treatment start and disease progression; PFS was defined as the time between treatment start and disease progression or death from any cause; and OS was defined as the time between treatment start and death from any cause.

Analysis Principles

Because the dose in the first cycle was always to be 20 mg/m^2, references to the 20-mg/m^2 dose and the 27-mg/m^2 dose in this analysis relate to the second cycle onward, unless specified otherwise. Reference to the administered dose of carfilzomib in this analysis might relate to either of 2 different variables that were analyzed separately: (1) the average dose received by a given patient during treatment (the average administered dose [AAD]); or (2) the maximum dose (20 mg/m^2 or 27 mg/m^2) a given patient received (the maximum administered dose [MAD]). The primary analysis, in which the relationship between the administered dose of carfilzomib (AAD and MAD) and ORR was examined, included the 461