Carfilzomib—A Selective Proteasome Inhibitor for the Treatment of Relapsed and/or Refractory Multiple Myeloma

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Abstract

Multiple myeloma (MM) is a plasma cell malignancy characterized by overproduction of monoclonal immunoglobulins, hypercalcemia, renal injury, anemia, and osteolytic lesions. Despite markedly improved clinical outcomes since the introduction of first-generation immunomodulatory drugs and proteasome inhibitors, survival is very short in patients who relapse and are refractory to these therapies. Carfilzomib is a selective proteasome inhibitor currently being developed for the treatment of MM. In clinical studies, carfilzomib has achieved durable responses in relapsed and/or refractory MM and demonstrated acceptable tolerability with minimal peripheral neuropathy and no evidence of cumulative toxicity. Herein we summarize the key clinical data for single-agent carfilzomib in the relapsed and/or refractory disease setting and provide an overview of the current clinical development of the drug, both as monotherapy and in combinations.

Keywords

Multiple myeloma, proteasome inhibitor, relapsed/refractory, selective, safety, tolerability

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Multiple myeloma (MM) is a plasma cell malignancy characterized by the overproduction of monoclonal immunoglobulins and the presence of hypercalcemia, renal injury, anemia, osteolytic lesions, and frequent infections.[1,2] Other complications include hyperviscosity and amyloidosis.[1,2] It is the second most common hematologic malignancy after non-Hodgkin's lymphoma and will represent nearly 15 % of new hematologic malignancies diagnosed in 2012 in the US.[3]

MM is generally a disease of older individuals;[4] the median age at diagnosis is approximately 69 years.[5] With the approvals of the newer agents bortezomib, thalidomide, and lenalidomide, the median overall survival (OS) has improved from approximately two years in the late 1970s to 4.4–7.1 years in the decade since 2000.[6] However, in patients with relapsed disease that is refractory to the aforementioned agents, the median event-free survival and OS times are five and nine months, respectively.[7]

A number of factors may influence the course of disease in an individual patient with MM. Advanced age, poor performance status, the presence of specific cytogenetic markers (e.g., deletion 17p, t(4;14)), the presence of immunoglobulin (Ig)A isotype, serum creatinine ≥2 mg/dl, extramedullary disease, and renal insufficiency each independently predict worse outcomes.[1,8] Additional items of concern relate to the patient's treatment history and include prior therapy-associated toxicity and prior stem cell transplant. The newer agents (i.e., bortezomib, thalidomide, and lenalidomide) have distinct toxicity profiles (including myelosuppression, peripheral neuropathy, and venous thromboembolic events [VTEs]),[9] and the effective management of adverse events (AEs) associated with these agents is crucial to ensure that patients are able to receive the most effective treatment with minimal need for interruption.

While the median survival in patients with MM has increased due to the use of the newer agents, the duration of response (DOR) to post-relapse

therapies becomes progressively shorter with successive regimens.[7] The current goals of treatment in relapsed MM are focused on identifying optimal drug combinations and the optimal sequence of their use, and determining the place of new agents in the evolving treatment paradigm. Carfilzomib, a next-generation proteasome inhibitor (PI), has recently received approval by the US Food and Drug Administration for the treatment of relapsed and/or refractory MM in patients who have received at least two prior therapies including bortezomib and an immunomodulator (thalidomide or lenalidomide). Herein we provide a summary of the key data for single-agent carfilzomib in the relapsed and/or refractory disease setting.

Carfilzomib—Pharmacology and Preclinical Activity

Carfilzomib is an analog of epoxomicin and eponemycin, a pair of related natural products that were initially shown to inhibit tumors in animals and were later shown to inhibit the chymotrypsin-like (CT-L) activity of the proteasome.[10–14] At therapeutic concentrations, carfilzomib shows primary selectivity for CT-L activity of the proteasome and displays little activity against the trypsin-like or caspase-like activities.[15] In contrast to the approved boronic acid PI bortezomib, which is a reversible PI, the epoxyketone pharmacophore of carfilzomib forms an irreversible bond with the catalytic β5 subunit of the proteasome and with the analogous subunit β5i (LMP7) of the immunoproteasome (see *Figure 1*).[16]

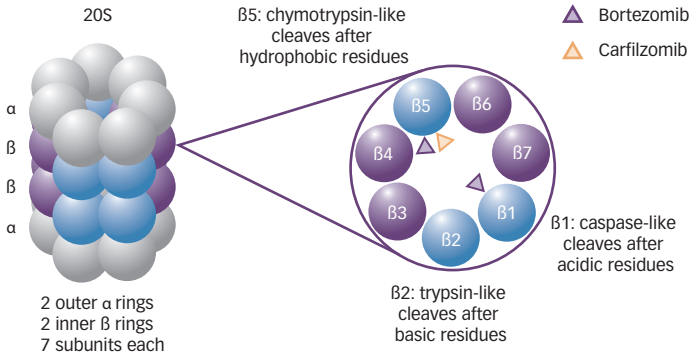
In preclinical models of MM, carfilzomib specifically inhibited the activities of both the proteasome and the immunoproteasome by 70–80 % in MM cell lines and primary MM cells, resulting in dose- and time-dependent inhibition of proliferation, leading to apoptosis.[17] Carfilzomib also overcame resistance to other agents including bortezomib and acted synergistically with dexamethasone to enhance apoptosis.[17] *In vivo*, carfilzomib demonstrated greater antitumor activity than bortezomib.[15,17] In these same models, carfilzomib showed substantially less off-target activity against non-proteasomal proteases than bortezomib, correlating with significantly less neurotoxicity and neurodegeneration,[15,17,18] which may be relevant to the different rates of peripheral neuropathy observed with both agents in the clinical setting.[19–24]

Clinical Studies

Phase I Studies

The open-label Phase I studies PX-171-001 (NCT trial number no longer available) and PX-171-002 (ClinicalTrials.gov identifier NCT00150462) in relapsed or refractory hematologic malignancies including MM helped define the clinical dose and consecutive-day dosing schedule for carfilzomib.[19,20] In the PX-171-001 study, patients received carfilzomib at doses ranging from 1.2 to 20 mg/m^2 intravenous (IV) infusion over 1–2 minutes on Days 1–5 every 14 days, and a maximum tolerated dose (MTD) was defined at 15 mg/m^2. The PX-171-002 study used a dosing schedule of two consecutive days per week. Carfilzomib doses ranged from 1.2 to 27 mg/m^2 IV infusion over 1–2 minutes on Days 1, 2, 8, 9, 15, and 16 of every 28-day cycle. In contrast to PX-171-001, an MTD was not reached. During dose expansion, an escalated dosing regimen was evaluated to improve tolerability of the regimen. Carfilzomib was administered at 20 mg/m^2 during the first week (Days 1 and 2) and then escalated to 27 mg/m^2 thereafter. At doses of 15–27 mg/m^2, there was evidence of activity among patients with MM and non-Hodgkin's lymphoma, including objective responses or stable disease (SD) in 14 of 36 evaluable patients. Based on these studies, an extensive clinical trial program of carfilzomib in MM, initially in the relapsed and/or refractory settings and then in earlier lines of treatment, was undertaken.

Figure 1: Active Sites of the 20S Proteasome and Sites of Inhibition by Carfilzomib and Bortezomib



PX-171-003-A0

PX-171-003-A0 (ClinicalTrials.gov identifier NCT00511238) was a Phase II pilot study that laid the groundwork for the larger PX-171-003-A1 study (see below). In the PX-171-003-A0 study, 46 patients with relapsed and refractory MM following at least two prior therapies received carfilzomib 20 mg/m^2 IV on days 1, 2, 8, 9, 15, and 16 every 28 days for up to 12 cycles (see *Table 1*). The best overall response was 16.7 % with a median DOR of 7.2 months (see *Table 2*).[21] The most common treatment-emergent AEs of any grade were anemia (73.9 %), fatigue (69.6 %), and thrombocytopenia (50.0 %).[21] Common grade 3/4 AEs were primarily hematologic and included anemia (37.0 %), lymphopenia (28.3 %), and thrombocytopenia (26.1 %) (see *Table 3*). Peripheral neuropathy and neuropathy-related AEs were generally mild and infrequent during the study. The encouraging efficacy and favorable safety profile observed in this pilot study provided the rationale to expand the protocol under an amendment to enroll approximately 250 additional patients and explore the feasibility of intrapatient dose escalation of carfilzomib from 20 to 27 mg/m^2.

PX-171-003-A1

The PX-171-003-A1 trial (ClinicalTrials.gov identifier NCT00511238) was an open-label, single-arm, multicenter Phase II study in 266 patients with relapsed and refractory MM following at least two prior therapies including bortezomib and an immunomodulator (thalidomide or lenalidomide). In this study, single-agent carfilzomib was administered intravenously over 2–10 minutes on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Patients received carfilzomib 20 mg/m^2 in Cycle 1 and then carfilzomib 27 mg/m^2 for up to 12 cycles (see *Table 1*). The primary endpoint was overall response rate (ORR; ≥partial response). Secondary endpoints included clinical benefit response (≥minimal response), duration of response (DOR), time to progression (TTP), progression-free survival (PFS), OS, and safety. The best ORR was 23.7 % with a median DOR of 7.8 months and median OS of 15.6 months (see *Table 2*).[22] The most common AEs were fatigue (48.9 %), anemia (45.9 %), nausea (44.7 %), and thrombocytopenia (38.7 %) (see *Table 3*), and there was no evidence of cumulative toxicity based on an analysis of the time

Table 1: Phase II Trials of Carfilzomib in Multiple Myeloma—Characteristics[21–25]

Study	MM Status	Prior Therapy	Carfilzomib Dosing
003-A0	Relapsed and refractory	≥2 regimens; responded to first-line and refractory to most recent	20 mg/m^2
003-A1	Relapsed and refractory	≥2 regimens; responded to ≥1 and refractory to most recent	20/27* mg/m^2
004	Relapsed or refractory	Responded to first-line; relapsed or refractory to ≥1 but ≤3	20 or 20/27* mg/m^2
005	Relapsed and refractory with various levels of renal insufficiency	≥2 regimens; achieved at least MR to ≥1	15, 20, 27 mg/m^2†

**20 mg/m^2 in Cycle 1, 27 mg/m^2 thereafter. †Increased in Cycles 1–3 as tolerated. MM = multiple myeloma; MR = minimal response.*

Table 2: Phase II Trials of Carfilzomib in Multiple Myeloma—Dosing Schedule and Efficacy Outcomes[21–25]

Study	Patients	Carfilzomib Dose (mg/m^2)[a]		ORR (%)	CBR (%)	DOR (mo)	TTP (mo)	PFS (mo)	OS (mo)
		C1	C2 and beyond						
003-A0	R/R MM	20	20	16.7	23.8	7.2	3.5	3.5	NE
003-A1	R/R MM	20	27	23.7	37.0	7.8	3.9	3.7	15.6
004 (BTZ-treated)	R-R MM	20	27	17.1	31.4	>10.6	4.6	4.6	29.9[b]
004 (BTZ-naive) Cohort 1	R-R MM	20	20	42.4	59.3	13.1	8.3	8.2	NR
004 (BTZ-naive) Cohort 2	R-R MM	20	27	52.2	64.2	NR	NR	NR	NR
005	R/R MM	15	20, 27[c]	21.3	21.3	4.2	6.4	4.4	NR

[a] Days 1, 2, 8, 9, 15 and 16 of a 28-day cycle. [b] Estimated. [c] 20 mg/m^2 in Cycle 2 and 27 mg/m^2 in Cycle 3 and beyond, if tolerated.
BTZ = bortezomib; C = cycle; CBR = clinical benefit response; DOR = duration of response; mo = months; NE = not estimated; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R/R = relapsed and refractory; R-R = relapsed or refractory; TTP = time to progression.

to onset of AEs in these patients. Thirty-three (12.4 %) patients experienced new or worsening peripheral neuropathy, primarily of grades 1 or 2 in severity despite 77 % having grade 1 or 2 peripheral neuropathy at study entry. The activity and tolerability of single-agent carfilzomib in this trial and the apparent lack of cross-resistance observed in patients with bortezomib- and immunomodulator-refractory disease underscores the potential for using carfilzomib in the treatment of relapsed and/or refractory MM.

PX-171-004

PX-171-004 (ClinicalTrial.gov identifier NCT00530816) was a Phase II, open-label, multicenter clinical trial that enrolled patients with relapsed or refractory MM after one to three prior lines of therapy. Results were analyzed and presented according to patients' bortezomib exposure status. Thirty-five patients exposed to at least one prior bortezomib regimen were enrolled and received carfilzomib 20 mg/m^2 in a twice-weekly, consecutive-day dosing schedule for up to 12 one-month cycles (see *Table 1*). These patients achieved a best ORR of 17.1 % (see *Table 2*), with a median DOR >10.6 months and a median TTP of 4.6 months.[25] The most common AEs were fatigue (62.9 %), nausea (60.0 %) (see *Table 3*), and vomiting (42.9 %). No exacerbation of baseline peripheral neuropathy was observed.

A total of 129 bortezomib-naive patients with relapsed or refractory MM were enrolled as well and separated into Cohort 1 (IV carfilzomib 20 mg/m^2 for all treatment cycles) and Cohort 2 (IV carfilzomib 20 mg/m^2 for Cycle 1 and then 27 mg/m^2 for all subsequent cycles) (see *Table 1*).[23] The primary endpoint was best overall response. ORRs were 42.4 % in Cohort 1 and 52.2 % in Cohort 2 (see *Table 2*), with median DORs of 13.1 months for patients in Cohort 1 and not reached for patients in Cohort 2.[23] Median TTP was 8.3 months and not reached for Cohorts 1 and 2, respectively. The most common treatment-emergent AEs were fatigue (62.0 %) and nausea (48.8 %) (see *Table 3*). Single-agent carfilzomib elicited a low incidence of peripheral neuropathy (17.1 %) overall, primarily of grades 1 or 2. Overall the response data for single-agent carfilzomib in bortezomib-naive patients in the PX-171-004 trial are promising and noteworthy as some of the highest to date for a single agent in this patient population, comparing favorably with earlier data obtained with the first-in-class PI, bortezomib, in similar patient populations.[26–28]

PX-171-005

In the PX-171-005 (ClinicalTrial.gov identifier NCT00721734) study, carfilzomib monotherapy was evaluated in 50 patients with varying degrees of renal dysfunction, including some on chronic dialysis, with patients grouped into cohorts according to creatinine clearance (CrCl).[24] In this study, patients received single-agent carfilzomib intravenously twice weekly for three of four weeks for up to 12 cycles. The dose given during Cycle 1 was 15 mg/m^2, increased to 20 mg/m^2 in Cycle 2, and to 27 mg/m^2 in Cycle 3 and all subsequent cycles (see *Table 1*). Renal function as measured by CrCl did not affect carfilzomib clearance, exposure, activity, or tolerability across all cohorts. The ORR was 21.3 % with a median TTP of 6.4 months, and the median OS was not reached at the time of data cut-off (see *Table 2)*.[24] The most common treatment-emergent AEs were fatigue (56.0 %), anemia (50.0 %), and nausea (36.0 %) (see *Table 3*). The overall incidence of grade 1/2 peripheral neuropathy was 10 %. The findings from this study suggest that, similar to other PIs and in contrast to MM treatments such as lenalidomide, carfilzomib dose and schedule do not need to be adjusted in patients with baseline renal dysfunction, including patients on hemodialysis.

Future Directions

Carfilzomib is currently being evaluated in a number of combinations in relapsed and/or refractory disease (e.g., carfilzomib plus lenalidomide or pomalidamide plus dexamethasone [CRd or CPd], CRd plus vorinostat).

Table 3: Phase II Trials of Carfilzomib in Multiple Myeloma—Adverse-event Profile[21–25,37]

	003-A0 (n=46)	003-A1 (n=266)	004 BTZ-treated (n=35)	004 BTZ-naive (n=129)	005 (n=50)	Total (n=526)
Adverse events of all grades occurring in ≥25 % of patients						
Number of patients with ≥1 AE (%)	46 (100.0)	266 (100.0)	35 (100.0)	129 (100.0)	47 (94.0)	523 (99.4)
Fatigue	32 (69.6)	130 (48.9)	22 (62.9)	80 (62.0)	28 (56.0)	292 (55.5)
Anemia	34 (73.9)	122 (45.9)	12 (34.3)	54 (41.9)	25 (50.0)	247 (47.0)
Nausea	16 (34.8)	119 (44.7)	21 (60.0)	63 (48.8)	18 (36.0)	237 (45.1)
Thrombocytopenia	23 (50.0)	103 (38.7)	11 (31.4)	39 (30.2)	15 (30.0)	191 (36.3)
Dyspnea	13 (28.3)	90 (33.8)	13 (37.1)	50 (38.8)	14 (28.0)	180 (34.2)
Diarrhea	15 (32.6)	86 (32.3)	13 (37.1)	40 (31.0)	18 (36.0)	172 (32.7)
Pyrexia	15 (32.6)	83 (31.2)	9 (25.7)	44 (34.1)	11 (22.0)	162 (30.8)
Upper respiratory tract infection	17 (37.0)	71 (26.7)	12 (34.3)	40 (31.0)	9 (18.0)	149 (28.3)
Headache	12 (26.1)	74 (27.8)	9 (25.7)	42 (32.6)	8 (16.0)	145 (27.6)
Cough	13 (28.3)	65 (24.4)	8 (22.9)	44 (34.1)	8 (16.0)	138 (26.2)
Adverse events of grade 3/4 occurring in ≥10 % of patients						
Number of patients with ≥1 AE (%)	39 (84.8)	231 (86.8)	20 (57.1)	92 (71.3)	45 (90.0)	427 (81.2)
Thrombocytopenia	12 (26.1)	77 (28.9)	7 (20.0)	17 (13.2)	10 (20.0)	123 (23.4)
Anemia	17 (37.0)	63 (23.7)	5 (14.3)	19 (14.7)	14 (28.0)	118 (22.4)
Lymphopenia	13 (28.3)	52 (19.5)	2 (5.7)	21 (16.3)	9 (18.0)	97 (18.4)
Pneumonia*	5 (10.9)	25 (9.4)	3 (8.6)	16 (12.4)	6 (12.0)	55 (10.5)
Neutropenia	2 (4.3)	29 (10.9)	4 (11.4)	17 (13.2)	3 (6.0)	55 (10.5)

** One grade 5 event of pneumonia in 003-A1. AE = adverse event; BTZ = bortezomib.*

Encouraging efficacy data have been achieved with these combinations, with data regarding CRd combinations (PX-171-006, ClinicalTrial.gov identifier NCT00603447) being the most mature at the time of writing.[24] Many of these studies are also evaluating higher doses of carfilzomib and using longer infusion times (e.g., 30 minutes) in an effort to enable the delivery of higher doses for potentially greater efficacy and simultaneously improve tolerability.[29] The CRd combination has also been tested in 53 newly diagnosed patients in a Phase I/II study (ClinicalTrial.gov identifier NCT01029054) and achieved a 100 % ORR, including 78 % near complete response/complete response and 61 % stringent complete response in patients completing at least eight cycles, with an estimated 24-month PFS rate of 92 %.[30]

Other studies (e.g., CARMYSAP [ClinicalTrial.gov identifier NCT01279694], CARTHADEX [see: http://apps.who.int/trialsearch/trial.aspx?trialid=NTR2422], CYCLONE [ClinicalTrial.gov identifier NCT01057225]) are evaluating the use of carfilzomib in the frontline setting, both as monotherapy and in combination with other approved and investigational therapies.[31–33] Ongoing comparative trials of carfilzomib include ASPIRE (CRd versus Rd; ClinicalTrial.gov identifier NCT01080391), the European registrational study FOCUS (single-agent carfilzomib versus best supportive care in relapsed and refractory MM; ClinicalTrial.gov identifier NCT01302392),[34] and ENDEAVOR (head-to-head comparison of Cd versus Vd; ClinicalTrial.gov identifier NCT01568866). Phase I clinical studies of carfilzomib also suggested the potential for activity in several other hematologic malignancies (e.g., Waldenström's macroglobulinemia, non-Hodgkin's lymphoma).[19,20,35] Based on the precedent set with bortezomib, there exists the possibility for indications outside oncology as well (e.g., organ transplantation and graft-versus-host disease).[36]

Conclusions

MM remains an incurable disease, and although the prognosis has improved with the advent of new treatment options, there is room for further improvement. Carfilzomib has achieved durable responses in heavily-pretreated patients with MM and demonstrated an acceptable tolerability profile with no evidence of cumulative toxicity and minimal peripheral neuropathy, despite prior treatment with bortezomib and immunomodulatory drugs in the majority of patients. Additionally, carfilzomib has demonstrated its potential to be used for treatment for long periods of time without the need for dose adjustment or interruption. In summary, carfilzomib fills an unmet medical need and has the potential to offer meaningful clinical benefit to patients who have either failed or cannot tolerate other drugs. ■

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