

Clinical potential of carfilzomib in the treatment of relapsed and refractory multiple myeloma

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Abstract: Treatment of refractory and/or relapsed multiple myeloma has been a challenging problem for over 20 years. However, we have made significant progress addressing this disease with the use of bortezomib, the first in class proteasome inhibitor, and the immunomodulatory agents, thalidomide and lenalidomide. Carfilzomib, the second-generation proteasome inhibitor, has also been approved for treatment of relapsed/refractory multiple myeloma. Carfilzomib is a highly selective and potent inhibitor of proteasome chymotrypsin-like activity. Phase I and II clinical trials have reported an acceptable toxicity profile, with manageable thrombocytopenia and anemia being the most common side effects. Peripheral neuropathy, a frequent dose-limiting side effect of bortezomib, was rare. Further, carfilzomib demonstrated encouraging single-agent activity and appeared to be effective even in patients refractory to bortezomib. Based on these promising data, carfilzomib is moving forward into Phase III trials for relapsed multiple myeloma and is also being investigated as front-line combination therapy for patients with newly diagnosed myeloma.

Keywords: proteasome inhibitor, bortezomib, pharmacology, safety, efficacy

Introduction

Proteasome inhibition has been shown to be an effective approach for the treatment of multiple myeloma. The introduction of bortezomib and the immunomodulatory agents, thalidomide and lenalidomide, have contributed to dramatic improvements in patient outcomes. In the decade since these agents were approved, the median overall survival for patients with myeloma has increased from 29.9 months to 44.8 months.¹ Moreover, induction regimens combining bortezomib and an immunomodulatory agent have achieved response rates of almost 100%, with more than half of patients obtaining a very good partial response or better.²⁻⁴ However, even among patients who experience long-term durable remissions, most will eventually die of refractory myeloma.

In relapsed/refractory myeloma, bortezomib, thalidomide, and lenalidomide each have single-agent clinical activity and are synergistic when used in combination, as reviewed in Lonial et al.⁵ However, their benefit is often limited by development of resistance and/or cumulative toxicity. For bortezomib, peripheral neuropathy is the primary concern. Therefore, the need for proteasome inhibitors with improved efficacy and tolerability continues to exist. This review focuses on the pharmacology, safety, and efficacy of the recently approved second-generation proteasome inhibitor, carfilzomib, in the setting of relapsed/refractory multiple myeloma.

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The proteasome

The sensitivity of myeloma to proteasome inhibitors is in part due to the unique properties of the plasma cells from which myeloma emerges. Both normal and malignant plasma cells are protein factories, synthesizing and secreting enormous amounts of antibody. Increased protein production inevitably results in accumulation of misfolded proteins, which can trigger apoptosis if not quickly eliminated. The proteasome system is one pathway by which plasma cells handle the increased burden of these dangerous protein byproducts.⁶

The proteasome is present in all cells and has multiple regulatory functions in cells that do not secrete protein. In addition to the ubiquitously expressed constitutive proteasome, a second immunoproteasome is present in cells of hematopoietic origin and is induced in nonhematopoietic cells by proinflammatory cytokines, as reviewed in Groettrup et al.⁷ Both proteasomes consist of a 20S catalytic core and two 19S regulatory caps. Together these form the 26S proteasome. The catalytic core is made up of two outer rings with seven alpha subunits each and two inner rings with seven beta subunits each. The $\beta 1$, $\beta 2$, and $\beta 5$ subunits are catalytically active threonine proteases and are responsible for digesting protein targeted to the proteasome. Specifically, $\beta 1$ has caspase-like activity and cleaves at acidic residues, $\beta 2$ has trypsin-like activity and cleaves at basic residues, and $\beta 5$ has chymotrypsin-like activity and cleaves at hydrophobic residues. The corresponding subunits in the immunoproteasome are LMP2 ($\beta 1i$), MECL1 ($\beta 2i$), and LMP7 ($\beta 5i$).⁷ Hematopoietic cells contain mostly immunoproteasome, and in plasma cells LMP7 makes up 60%–90% of the chymotrypsin-like activity.⁸

Pharmacology and preclinical data

Carfilzomib is a peptide epoxyketone derived from epoxomicin, a naturally occurring microbial protease inhibitor that is highly selective for the proteasome. This selectivity is mediated by covalent and irreversible binding to the proteasome catalytic subunits. Varying the peptide lengths and amino acid side chains of epoxomicin produces the tetrapeptide YU-101, which shows significant activity against the chymotrypsin-like subunit of the proteasome, but little activity towards the trypsin and caspase-like subunits.⁹ Addition of an amino-terminal morpholino moiety to YU-101 improves its aqueous solubility and results in PR-171 or carfilzomib (Figure 1).¹⁰

Carfilzomib has an IC_{50} of 6 nM for the chymotrypsin activity of purified constitutive 20S proteasome and 33 nM for the chymotrypsin activity of the immunoproteasome.

The chymotrypsin inhibition is similar to that of bortezomib, but carfilzomib is less active against the trypsin and caspase-like subunits.¹⁰ At 10 nM, carfilzomib inhibits 80% of 20S proteasome chymotrypsin-like activity in cell lysates, but has a minimal effect on trypsin and caspase-like activity at concentrations up to 100 nM. In tissue culture, 10–100 nM carfilzomib preferentially binds to and inhibits $\beta 5$ and LMP7, but can also inhibit the other catalytic subunits at concentrations greater than 1 μM .^{8,11,12} Further, carfilzomib does not affect the activity of other serine proteases, such as cathepsin A, cathepsin G, chymase, and DPPII, that are inhibited by bortezomib. The specificity of carfilzomib appears to be a property of the epoxyketone pharmacophore. Keeping the carfilzomib peptide backbone, but replacing the epoxyketone with the boronate from bortezomib, results in potent inhibition of serine proteases.¹³ Of note, the increased promiscuity of bortezomib for proteases may explain the higher incidence of peripheral neuropathy seen in bortezomib-treated patients. In an in vitro model of neurite degeneration, 24 hours of bortezomib treatment induced a 40% reduction in neurite length. Equimolar concentration of carfilzomib had no effect on neurite length despite similar inhibition of proteasome activity. Bortezomib, but not carfilzomib, also inhibited the mitochondrial protease HtrA2/Omi, which may play a role in neuronal protection.¹³

Proteasome inhibitors exert their cytotoxic effects by disrupting the multiple pathways regulated by the proteasome. Inhibition of nuclear factor- κB , effects on angiogenesis and the tumor microenvironment, and induction of the unfolded protein response, are all thought to contribute to proteasome inhibitor-induced cell death.^{6,14,15} Carfilzomib has shown activity in a number of transformed human cell lines. A one-hour pulse of carfilzomib induced greater apoptosis and cell cycle arrest in multiple myeloma, Burkitt's lymphoma, acute lymphocytic leukemia, and non-Hodgkin's lymphoma cells compared with equivalent doses of bortezomib. Solid tumor cell lines and nontransformed cells were less sensitive to both compounds.^{10,11} Carfilzomib more effectively inhibited proliferation of patient-derived purified CD138⁺ myeloma cells as well as samples from patients with diffuse large B-cell lymphoma, chronic lymphocytic leukemia, and acute myeloid leukemia.^{11,16} It also partially overcame resistance to bortezomib in cell lines and primary samples resistant to bortezomib and other agents.¹¹ Carfilzomib-induced cell death correlates with increased accumulation of polyubiquitinated chains, caspase activation, poly(ADP-ribose) polymerase cleavage,

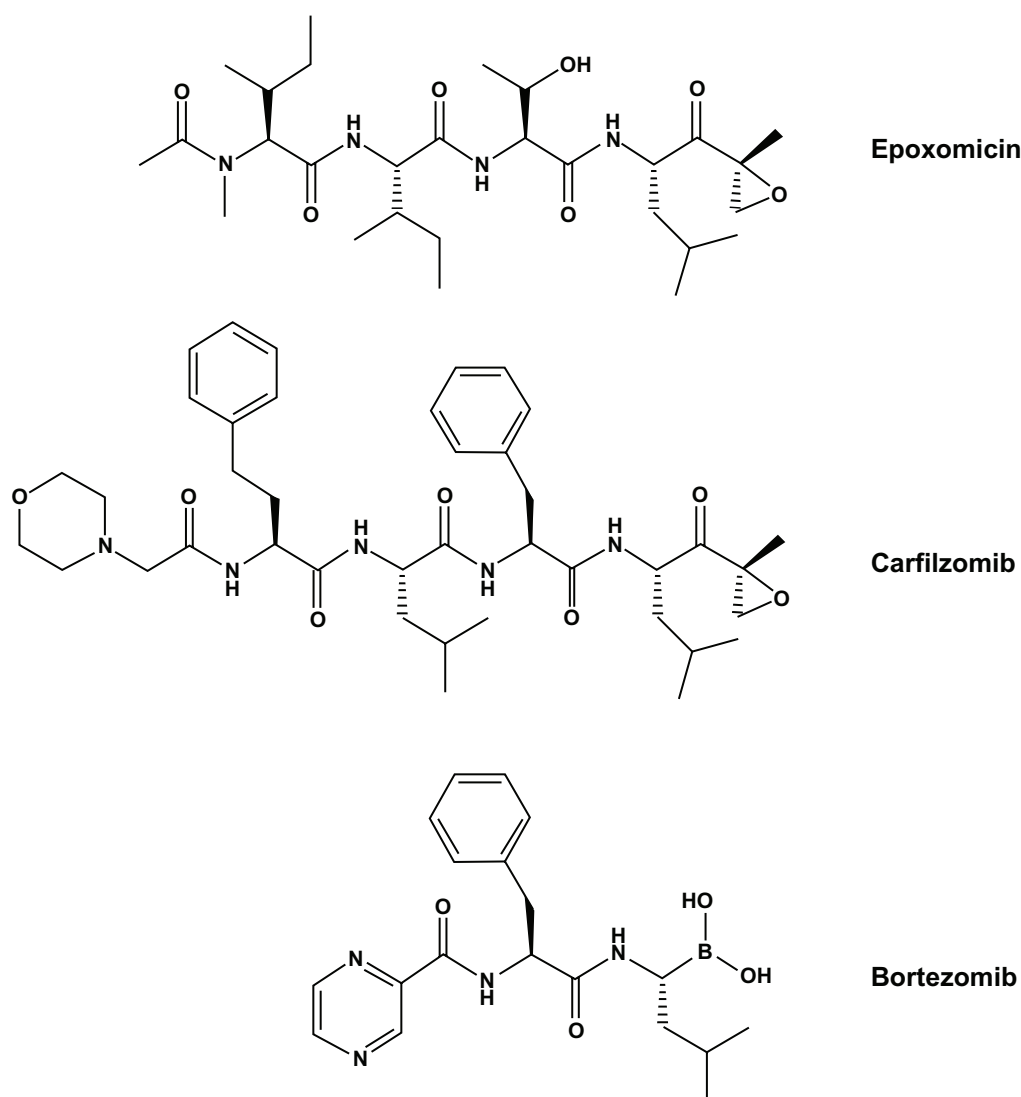


Figure 1 Structure of selected proteasome inhibitors.

Jun N-terminal kinase phosphorylation, and markers of the unfolded protein response.^{8,11,12}

Pharmacokinetics and pharmacodynamics

In rodents, carfilzomib is rapidly cleared from the plasma with a half-life of 5–20 minutes.^{10,17} This clearance is primarily extrahepatic, occurs via peptidase cleavage and epoxide hydrolysis, and does not appear to be determined by target binding.¹⁷ Similar kinetics were seen in two Phase I trials. Clearance occurred through multiple pathways, with an estimated elimination half-life of less than 30 minutes. The drug displayed a wide and rapid tissue distribution, which likely accounts for the short half-life, similar to bortezomib.^{18–20}

Dose-dependent inhibition of proteasome chymotrypsin activity occurs in all rat tissues, except the brain, one hour

after intravenous administration of carfilzomib. Despite irreversible binding of carfilzomib to the proteasome, proteasome activity recovers to approximately 50%–100% of baseline within 24 hours both in tissue culture and in vivo. These kinetics were only moderately slower compared with bortezomib, suggesting that recovery of activity is mediated by new proteasome synthesis. In rodents, the degree of inhibition and time to recovery of chymotrypsin-like activity was similar whether the drug was given as a one-time dose daily for 2 days (QD × 2) or daily for 5 days (QD × 5). However, in a xenograft model, weekly QD × 2 dosing was more effective than a weekly single dose or weekly doses given on days 1 and 4, as is done with bortezomib.¹⁰

Pharmacodynamics reported in Phase I trials varied slightly depending on the dose and dosing schedule. One hour after bolus doses of 15 mg/m² and higher, more than

75% of peripheral blood mononuclear cell proteasome activity was inhibited. In the QD \times 5 schedule, inhibition increased to greater than 90% after the fifth day. Proteasome activity returned to baseline during the nine days before the next cycle.¹⁸ With the higher 27 mg/m² dose given QD \times 2, 90% proteasome inhibition occurred at one hour. There was minimal recovery prior to the second dose, and at least similar if not greater inhibition after the second dose. Proteasome activity recovered to varying degrees during the 12-day rest period prior to the next cycle.¹⁹ Use of a 30-minute infusion allows doses up to 56 mg/m² to be administered without a significant increase in toxicity.²¹ Pharmacodynamic studies of patients receiving more than 36 mg/m² confirmed more than 90% inhibition of the proteasome. More immunoproteasome inhibition occurred with the 56 mg/m² dose compared with the 20 mg/m² dose.²² In both rats and human, a 30-minute infusion resulted in lower drug plasma concentrations compared with bolus dosing, suggesting that proteasome inhibition is a function of total dose rather than peak plasma concentration.^{17,21}

Safety and tolerability

The first two Phase I trials evaluated the safety and tolerability of different carfilzomib dosing regimens. In PX-171-001, 29 patients with relapsed/refractory hematologic malignancies were given carfilzomib consecutively on days 1–5 of a 14-day cycle. Dosing started at 1.2 mg/m² and was increased to 20 mg/m² before two patients experienced dose-limiting toxicity. At the 20 mg/m² dose, one patient developed grade 3 febrile neutropenia and a second had prolonged grade 4 thrombocytopenia. No dose-limiting toxicities occurred at any of the lower doses, so 15 mg/m² was deemed to be the maximum tolerated dose. The most common side effects of any grade were fatigue (48%), nausea (48%), diarrhea (35%), and respiratory symptoms, including cough (28%), dyspnea (28%), and exertional dyspnea (21%). Anemia was reported in 17% of patients and thrombocytopenia in 14%. Grade 3/4 adverse events were uncommon and only dyspnea and thrombocytopenia occurred in two patients each. Although the most common reason for treatment discontinuation was progressive disease, among patients who completed more than six cycles, inability to maintain the scheduled dosing was the main reason for discontinuation.

In order to address the difficulty of the 5-day dosing schedule, a second Phase I study, PX-171-002, was initiated to evaluate the tolerability of carfilzomib administered on 2 consecutive days. Forty-eight patients with relapsed or refractory hematologic malignancies were enrolled. Carfilzomib

was given on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (QD \times 2). Dosing started at 1.2 mg/m² and increased to 27 mg/m². At 27 mg/m², only one patient experienced grade 3 hypoxia that met the criteria for dose-limiting toxicity. Based on the preliminary safety and efficacy data, the study was amended to allow a dose escalation approach from 20 mg/m² to 27 mg/m² on day 8. Six patients received this dosing schedule without any dose-limiting toxicity. Anemia and thrombocytopenia were the most common hematologic adverse events. At the 20/27 mg/m² dose, 36% of patients experienced a grade 3 or greater hematologic adverse event. In addition, transient thrombocytopenia was observed in patients at doses of 20 mg/m² or greater that recovered before the next cycle. Most nonhematologic events were grade 1 or 2 and included nausea, fatigue, pyrexia, and vomiting. All subsequent trials adopted this dosing schedule.

Additional safety data have been collected and compiled from four Phase II trials conducted in relapsed/refractory multiple myeloma (Table 1). PX-171-003-A0 and PX-171-003-A1 enrolled patients who had received at least two prior regimens and required previous treatment with bortezomib and an immunomodulatory therapy;^{23,24} PX-171-004 included patients who had received 1–3 prior regimens;^{25,26} and PX-171-005 evaluated the use of carfilzomib in patients with varying degrees of renal insufficiency.²⁷ PX-171-003 and PX-171-004 were initiated at 20 mg/m² QD \times 2, but the investigators later amended both trials to allow the carfilzomib dose to be increased to 27 mg/m² with cycle 2. In PX-171-005, dosing started at 15 mg/m² QD \times 2 with cycle 1, increased to 20 mg/m² with cycle 2, then 27 mg/m² with cycle 3 and beyond if tolerated. A total of 526 patients from these four trials were assessed. The most common adverse events of any grade were fatigue (55%), anemia (47%), nausea (45%), thrombocytopenia (36%), dyspnea (35%), diarrhea (33%), and pyrexia (30%). The most common grade 3/4 adverse events were thrombocytopenia (23%), anemia (22%), lymphopenia (18%), pneumonia (11%), and neutropenia (10%). Notably, treatment-emergent peripheral neuropathy was not a significant adverse event despite 72% of patients entering these studies with baseline peripheral neuropathy. Only 13% of patients reported worsening peripheral neuropathy, of which 1.3% was grade 3 and none were grade 4. Overall, five (1.0%) patients required dose modification or treatment discontinuation.²⁸ These results compare favorably with the rates of peripheral neuropathy seen with both subcutaneous (38%) and intravenous (53%) bortezomib.^{29,30} Further, in a subset analysis of PX-171-003-A1, pre-existing peripheral neuropathy did not affect the depth or duration of response.³¹

Table I Summary of adverse events in Phase II studies of carfilzomib

	PX-171-003 PX-171-004 PX-171-005	PX-171-007	IST-CAR-512	PX-171-010
Patients reported	526	24	41	100
Carfilzomib dose (QD × 2)	20–27 mg/m ² IV over 2–10 minutes	20/56 mg/m ² IV over 30 minutes	20/56 mg/m ² IV over 30 minutes	11–56 mg/m ²
Thrombocytopenia	37.8% (24.9%)	38% (38%)	37%	13%
Anemia	46.8% (22.4%)	38% (21%)	20%	16.3% (13%)
Neutropenia	22.6% (11.9%)	2% (2%)		(15%)
Fatigue	55%	54% (8%)	5%	17.3%
Nausea	45%	54%		
Pyrexia		54%		5.1%
Dyspnea	42.2% (5%)	54% (8%)	5%	8%
Pulmonary infection	18.8% (13.4%)	13% (13%)	15%	17.3% (11%)
Cardiac arrhythmia	13.3% (2.3%)			
Heart failure	7.2% (5.7%)		10%	
Hypertension		42% (13%)	20%	
Elevated creatinine	13% (<5%)			
Renal failure	7.2%			5.1%
Peripheral neuropathy	13% (1.3%)	4%		6.1% (1%)

Note: % all grades (% grade 3/4).

Abbreviations: IV, intravenously; QD × 2, days 1, 2, 8, 9, 15, and 16 of a 28-day cycle.

Although many of the patients entered these trials with pre-existing anemia and thrombocytopenia, dose-limiting hematologic adverse events were infrequent. In total, 70.3% of patients experienced a hematologic adverse event. The most common hematologic adverse event of any grade was anemia (46.8%), followed by thrombocytopenia (37.8%), lymphopenia (25.9%), and neutropenia (22.6%). The incidence of grade 3/4 thrombocytopenia was 24.9%, anemia 22.4%, lymphopenia 19.8%, and neutropenia 11.9%. A transient thrombocytopenia often occurred after the first dose of carfilzomib, reaching a nadir at day 8, but normalized prior to the start of the next cycle. A similar effect was observed with bortezomib, possibly due to reversible inhibition of thrombopoiesis.³² No cumulative thrombocytopenia or clinically significant bleeding episodes were observed. Febrile neutropenia occurred in approximately 1% of patients.³³

In addition to hematologic adverse events, respiratory adverse events were also common. Dyspnea was reported in 42.2% of patients. The majority of these episodes were grade 1 or 2 and lasted less than 2 weeks. The frequency with which dyspnea was reported decreased with later cycles, arguing against any cumulative toxicity. Pulmonary infection occurred in 18.8% of patients. Pneumonia was the most common adverse event (12.7%) and the most serious (9.9%). Cardiac adverse events occurred less frequently. Cardiac arrhythmia occurred in 13.3% of patients, congestive heart failure in 7.2%, and ischemic heart disease in 3.4%.

Eight (1.5%) deaths had a contributing cardiac component, but seven of these eight patients had underlying cardiac risk factors. Cardiac adverse events resulted in six (1.1%) dose reductions and 23 (4.4%) treatment discontinuations.³⁴

Of the patients enrolled in these Phase II trials, 71% had renal dysfunction at baseline. Renal function remained stable in the majority (87%) of patients. Thirty-one (6%) patients experienced a transient increase in creatinine; in 37 (7%) patients the increase was not transient, and eight (2%) patients permanently discontinued treatment due to renal adverse event. Creatinine levels increased from grade 1/2 to grade 3/4 in less than 5% of patients.³⁵ Of note, patients in trial PX-171-005 with varying degrees of renal insufficiency did not appear to have a different spectrum, frequency, or severity of adverse events compared with patients with normal renal function.²⁷ Most cases of irreversible renal impairment in this trial were associated with progression of myeloma.

Although the trials above administered carfilzomib as a 2–10-minute bolus, preclinical rodent data suggested a 30-minute infusion was better tolerated and allowed higher doses to be administered.¹⁷ Two Phase I/II studies were designed to study the safety and efficacy of this approach. In PX-171-007, carfilzomib was given at 20 mg/m² on days 1 and 2 of the first cycle and then increased to 36, 45, 56, or 70 mg/m² (20/36, 20/45, 20/56, or 20/70) for days 8, 9, 15, and 16 of cycle 1 and all subsequent cycles. Dexamethasone (4–8 mg) was given prior to each infusion to prevent infusion reactions. The two patients

receiving 20/70 mg/m² experienced dose-limiting toxicities. One patient developed grade 3 reversible renal failure after the first dose. The second patient experienced grade 3 fatigue with fever after four doses.²² Twenty-four patients were treated at the maximum tolerated dose of 20/56 mg/m². The most common adverse events of any grade were fatigue, nausea, pyrexia, and dyspnea (54% each), and hypertension (42%). Most of these were grade 1 or 2. The most common grade 3/4 adverse events were thrombocytopenia (38%) and anemia (21%).²¹ In an expansion cohort of PX-171-007, 40 mg of weekly dexamethasone was added to either 20/45 mg/m² or 20/56 mg/m² of carfilzomib. In the 22 patients treated, reported adverse events of any grade were similar to those in previous studies with the exception of headaches (36.4%). Grade 3/4 thrombocytopenia occurred in 36% of patients and grade 3/4 anemia in 27%.³⁶ An additional 41 patients have been treated at 20/56 mg/m² QD × 2 in the IST-CAR-512 trial. Treatment-emergent grade 3/4 adverse events included thrombocytopenia (37%), anemia (20%), hypertension (20%), and pneumonia (15%).³⁷

Extended treatment with carfilzomib in PX-171-010 has not identified any evidence of cumulative or late-onset toxicity with prolonged administration. This trial enrolled patients who had received carfilzomib in any previous Phase I or II trial. The carfilzomib dose could be increased or decreased based on disease progression or toxicity. Other approved myeloma agents could be added as well. In all, 100 patients have been enrolled and have received a median of 22 cycles or 89 weeks of carfilzomib when including both the prior and current studies. The carfilzomib regimen was changed in 9.2% of patients and discontinued in 11.2% because of adverse events. The most common adverse events were upper respiratory tract infection (17.3%), fatigue (17.3%), and anemia (16.3%). Only 6.1% of patients reported worsening peripheral neuropathy. The most common grade 3/4 adverse events were neutropenia (15%), anemia (13%), thrombocytopenia (13%), and pneumonia (11%).³⁸

Efficacy

Results from the Phase II PX-171-003 and PX-171-004 trials indicate that carfilzomib has very good activity as a single agent which has led to its approval for use in relapsed/refractory multiple myeloma (Table 2). As described earlier, inclusion criteria for these two parallel trials were based on number of previous lines of therapy. PX-171-003-A0 and PX-171-003-A1 enrolled patients with at least two previous lines of therapy and required prior treatment with bortezomib, while PX-171-004 enrolled patients with 1–3 previous lines

Table 2 Summary of carfilzomib activity in Phase II trials

	PX-171-003-A0	PX-171-003-A1	PX-171-004	PX-171-004 (BTZ-naïve)	PX-171-007	IST-CAR-512	PX-171-006	Car-Pom-d
Patients reported	46	266	35	67	24	34	50	32
Median lines of treatment (range)	5 (2–16)	5 (1–20)	3 (1–13)	2 (1–4)	4 (1–9)	5 (1–11)	2	6 (2–15)
Refractory to last line	Yes	Yes	No	No	No	No	No	Yes
Carfilzomib dose (QD × 2)	20 mg/m ²	27 mg/m ²	20 mg/m ²	27 mg/m ²	20/45–20/56 mg/m ²	20/56 mg/m ²	20/27 mg/m ²	20/27–20/56 mg/m ²
Other agents							Len 25 mg D1–21, Dex 40 mg weekly	Pom 3–4 mg D1–21, Dex 40 mg weekly
ORR, %	16.7	23.7	17.1	52.2	55	53	78	50
CR, %	0	0	2.8	1.5	0	3	18	13
≥ VGPR, %	0	5.1	5.6	28.4	25	27	40	NR
OS, months		15.6	29.9	NR		NR		7.4
PFS, months	3.5	3.7	4.6	NR		7.6		
DOR, months	7.2	8	10.6	NR		10		

Abbreviations: BTZ, bortezomib; CR, complete response; Len, lenalidomide; ORR, overall response rate; Pom, pomalidomide; VGPR, very good partial response; Dex, dexamethasone; NR, not reached; PFS, progression-free survival; OS, overall survival; QD × 2, days 1, 2, 8, 9, 15, and 16 of a 28-day cycle; D, day(s).

of therapy. PX-171-004 also included a subset of patients who were bortezomib-naïve.

The 46 patients in trial PX-171-003-A0 received carfilzomib at 20 mg/m² QD × 2. These patients had a median age of 63 years and had received a median of five previous therapies. All had received bortezomib, 91.3% had received prior lenalidomide, and 91.3% had received prior thalidomide. The overall response rate was 16.7%, all of which were partial responses. A further 7.1% of patients achieved a minimal response for a clinical benefit rate of 23.8%. The median duration of response was 7.2 months for the overall population and 13.8 months for patients with an minimal response or better. Median progression-free survival was 3.5 months.²³ After trial PX-171-002 established 27 mg/m² as a safe dose, the PX-171-003 protocol was amended to allow inpatient dose escalation. A further 266 patients were enrolled in PX-171-003-A1 and received 27 mg/m² QD × 2. These patients had received a median of five prior therapies. All but one (99.4%) received prior bortezomib and 73% were refractory. All of the patients had received an immunomodulatory agent; 73% had undergone autologous stem cell transplant, and 80% were refractory or intolerant to both bortezomib and lenalidomide. Sixty-nine percent of patients were International Staging System stage II or III at diagnosis and 28% had cytogenetic or fluorescence in situ hybridization (FISH) abnormalities associated with a poor prognosis. The overall response rate was 23.7% (5.1% very good partial response, 18.3% partial response) and the clinical benefit rate was 37.0%. The overall response rate was lower in patients who had received two or more lines of bortezomib-containing therapy (18.5% versus 29.5%) and in those refractory to bortezomib in their last line of therapy (18.6% versus 28.3%). Patients refractory to both bortezomib and lenalidomide had an overall response rate of 15.4%. The median duration of response was 7–8 months, median progression-free survival was 3.7 months, and median overall survival was 15.6 months.²⁴

The benefit of carfilzomib was slightly better in the less heavily pretreated patients enrolled in PX-171-004. Thirty-five patients with a median of three prior treatments and prior bortezomib exposure received 20 mg/m² of carfilzomib QD × 2. The overall response rate in these patients was 17.1%, the clinical benefit rate was 31.4%, and median duration of response was greater than 10.6 months.²⁵ A second analysis reported on the bortezomib-naïve patients (median of two prior treatments). In this group, 72.9% had International Staging System stage I or II disease and 79.8% had normal or favorable cytogenetics. Ninety-two percent had received

an immunomodulatory agent and 72.9% had undergone autologous stem cell transplant. Among the 59 patients who received 20 mg/m² of carfilzomib, the overall response rate was 42.4% (3.4% complete responses, 13.6% very good partial responses), the clinical benefit rate was 59.3%, the median duration of response was 13.1 months, and median progression-free survival was 8.2 months. For the 67 patients who received a 27 mg/m² dose, the overall response rate improved to 52.2% (1.5% complete responses, 26.9% very good partial responses) and the clinical benefit rate was 64.2%. Median duration of response and progression-free survival were not reached.²⁶

Efficacy improved with the higher doses of carfilzomib administered as a 30-minute infusion. In the expansion cohort of PX-171-007, 22 patients were treated with carfilzomib 20/45 mg/m² or 20/56 mg/m² QD × 2 and dexamethasone 40 mg weekly. The median number of prior therapies in this group was four, and 96% of patients had received prior bortezomib. The overall response rate was 55% (25% very good partial responses, 30% partial responses), and progression-free survival was 5.4–6.0 months.³⁶ Similar efficacy was seen in IST-CAR-512. In this study, carfilzomib was given as 20/56 mg/m² QD × 2 with 8 mg of dexamethasone prior to infusion. If patients did not achieve a partial response after two cycles or had progressive disease after initially responding, the dexamethasone could be increased to 40 mg weekly. Thirty-eight patients with a median of five prior treatments were evaluated for efficacy. Approximately 78% of patients were refractory to bortezomib. The overall response rate for the entire group was 53% (3% complete responses, 24% very good partial responses, 26% partial responses). In the subgroup of patients refractory to bortezomib, the overall response rate was 42%, and in those refractory to both bortezomib and lenalidomide was 39%. The median duration of response was 10 months for the entire group, and progression-free survival was 7.6 months. For bortezomib-refractory patients, the median progression-free survival was 3.7 months.³⁷

Poor-risk cytogenetics and FISH did not appear to have a significant impact on the efficacy of carfilzomib. Patients in PX-171-003 with normal/favorable features had an overall response rate of 22.8% compared with an overall response rate of 29.6% in those with unfavorable features.²⁴ In PX-171-004, the overall response rate in patients with favorable cytogenetics was 51% and 37% for those with unfavorable cytogenetics, but the latter group consisted of only 19 patients and seven responses.²⁶ Finally, IST-CAR-512 compared patients with standard-risk and high-risk FISH.

Patients with standard-risk FISH had an overall response rate of 64%, while patients with high-risk FISH had an overall response rate of 53%.³⁷

Combination therapy

In addition to trials investigating the efficacy of single-agent carfilzomib, a number of trials have combined this agent with other approved and experimental agents in the relapsed/refractory setting. The rationale for a combination approach comes from studies of bortezomib used with agents such as lenalidomide, doxorubicin, cyclophosphamide, and histone deacetylase inhibitors. Many of these trials have shown promising efficacy with reasonable tolerability.⁵ However, since bortezomib-induced peripheral neuropathy can be dose-limiting, carfilzomib may be a suitable alternative.

Carfilzomib in combination with lenalidomide and dexamethasone is being studied as part of the ongoing Phase II PX-171-006 trial. Fifty-two patients with relapsed myeloma received carfilzomib 20/27 mg/m² intravenously QD × 2, lenalidomide 25 mg orally daily for days 1–21, and dexamethasone 40 orally on days 1, 8, 15, and 22 of a 28-day cycle. No dose-limiting toxicities were reported, and 11.5% of patients experienced a serious adverse event. Grade 3/4 hematologic adverse events included neutropenia (23%), anemia (15.3%), and thrombocytopenia (15.3%). Of the 50 patients evaluable for response, 18% achieved a complete response, 22% a very good partial response, 38% a partial response, 2% a minimal response, and 8% achieved stable disease, for an overall response rate of 78%. Most responses occurred within the first two cycles and continued to improve with additional treatment. No new or overlapping toxicities were reported with prolonged administration (14–23 months).³⁹

Carfilzomib has also been combined with the next generation immunomodulatory agent, pomalidomide, in a Phase I/II trial. Eligible patients were refractory to prior lenalidomide and relapsed/refractory to their most recent regimen. Twelve patients were enrolled in the dose escalation phase of the trial. Most of the patients had prior bortezomib exposure and many had high-risk cytogenetic features. Carfilzomib dosing was started at 20/27 mg/m² intravenously over 30 minutes QD × 2, with pomalidomide 4 mg orally on days 1–21, and dexamethasone 40 mg orally on days 1, 8, 15, and 22 of a 28-day cycle. At 20/36 mg/m² of carfilzomib, two of six patients experienced a dose-limiting toxicity (grade 4 thrombocytopenia and grade 3 rash). One of six patients experienced a dose-limiting toxicity (febrile neutropenia) at 20/27 mg/m², and so 20/27 mg/m² was established as the maximum tolerated dose. A further 20 patients were enrolled

in an expansion cohort. The most common nonhematologic adverse events of any grade in these 32 patients included fatigue (56%), hypocalcemia (34%), diarrhea (31%), dyspnea (28%), elevated creatinine (26%), and rash/pruritus (21%). Grade 3/4 hematologic adverse events included neutropenia (56%), anemia (38%), and thrombocytopenia (28%). The overall response rate was 50%, with 13% of patients achieving a very good partial response and 37% achieving a partial response.⁴⁰

Two studies are currently investigating carfilzomib in combination with the histone deacetylase inhibitor, panobinostat.^{41,42} Cells exposed to proteasome inhibitors upregulate the aggresome pathway to maintain protein catabolism as a survival mechanism. Preclinical data suggest that histone deacetylase inhibitors block the aggresome pathway, so the combination of proteasome and histone deacetylase inhibitors may be synergistic. Both studies have reached doses of 20/45 mg/m² QD × 2 for carfilzomib and 30 mg for panobinostat in the dose escalation phase. Neither study has established a maximum tolerated dose. In a study by Shah et al, patients had received a median of five prior regimens, 94% had received bortezomib (47% refractory), and 100% had received prior lenalidomide (70% refractory).⁴¹ Of 21 reported patients, 52% developed grade 3/4 thrombocytopenia, 43% developed anemia, and 29% developed neutropenia. Two patients achieved a very good partial response and four patients achieved a partial response. Berdeja et al reported fewer grade 3/4 adverse events, but the 14 patients in this study may have been less heavily pretreated. The median number of prior therapies was three; all patients had received prior bortezomib and 10% were refractory.⁴² Of the 14 patients, two achieved a very good partial response and four achieved a partial response.

ARRY-520, a kinesin spindle protein inhibitor, has shown single-agent activity in myeloma and is also being studied in combination with carfilzomib in a Phase I trial. Eligible patients had relapsed/refractory myeloma, were not eligible for autologous stem cell transplant, refractory/intolerant to bortezomib, and had prior exposure to lenalidomide. All patients received carfilzomib 20/27 mg/m² intravenously over 30 minutes QD × 2 and growth factor support. ARRY-520 was dose-escalated starting at 0.75 mg/m². No dose-limiting toxicities were observed in the three patients who received this dose. One patient required admission for influenza pneumonia with non-neutropenic fever at the 1.0 mg/m² dose. A total of nine patients have now been enrolled in the dose escalation phase. Observed grade 3/4 toxicities include two cases of neutropenia and pneumonia, and one case each of

Table 3 Summary of carfilzomib activity in newly diagnosed multiple myeloma patients in Phase II trials

	CTd	CYCLONE	CRd	CCyd
Patients reported	46	38	35	67
Patient population	Transplant eligible	Transplant eligible	Transplant eligible	Transplant ineligible/ elderly
Carfilzomib dose (QD × 2)	20/27 mg/m ²	15–45 mg/m ²	20/36 mg/m ²	20/36 mg/m ²
Other agents	Thal 200 mg D1–28; Dex 40 mg weekly	Thal 100 mg D1–28, Cy 300 mg/m ² D1, 8, 15; Dex 40 mg weekly	Len 25 mg D–21; Dex 20 mg D1, 2, 8, 9, 15, 16, 22, 23	Cy 300 mg/m ² D1, 8, 15; Dex 40 mg weekly
ORR, %	94	96	95	100
CR, %	44	26	75	53
≥VGPR, %	84	74	85	77

Abbreviations: Thal, thalidomide; Len, lenalidomide; Pom, pomalidomide; Dex, dexamethasone; Cy, cyclophosphamide; QD × 2, days 1, 2, 8, 9, 15, and 16 of a 28-day cycle; ORR, overall response rate; CR, complete response; VGPR, very good partial response; D, day(s).

anemia, diarrhea, fatigue, hyperglycemia, and hyponatremia. At the data cutoff, one patient had achieved a complete response and another a partial response.⁴³

Conclusion and future directions

Based on the available Phase I and II data, carfilzomib appears to be a safe and effective therapy for relapsed and refractory multiple myeloma. It has a favorable hematologic and renal safety profile. Perhaps most importantly, the incidence of peripheral neuropathy is low, even with prolonged use. Carfilzomib is likely to be well tolerated in heavily pretreated patients with baseline neuropathy. Further, the lack of cumulative toxicity bodes well for the use of carfilzomib in extended maintenance regimens. Common side effects, such as thrombocytopenia and anemia, were manageable, but will need to be closely monitored as carfilzomib is combined with other agents. An additional note of caution is in order regarding prolonged carfilzomib treatment and combination with other therapies. Cell lines cultured in the presence of epoxomicin or carfilzomib acquired resistance to these drugs by upregulating expression of P-glycoprotein (multidrug resistance gene 1), a drug efflux pump.^{44–46} Drugs such as doxorubicin can also induce P-glycoprotein, and cell lines expressing P-glycoprotein are insensitive to carfilzomib and other epoxyketone-based proteasome inhibitors.^{11,46,47} Therefore, carfilzomib may be susceptible to or induce drug resistance mediated by P-glycoprotein.

Thus far, carfilzomib has shown activity in patients refractory to bortezomib as well as those with high-risk cytogenetics and poor features on FISH. In general, higher doses given as a 30-minute infusion have resulted in better responses. Although early data on the response to carfilzomib are encouraging, a formal test of efficacy will come from the three randomized Phase III studies in relapsed/refractory multiple myeloma that are currently underway. The ASPIRE study is investigating the benefit of

adding carfilzomib to lenalidomide and dexamethasone;⁴⁸ carfilzomib and bortezomib are being compared head to head in the ENDEAVOR trial;⁴⁹ and the European FOCUS trial is assessing overall survival in patients receiving carfilzomib versus best supportive care.⁵⁰ Not surprisingly, the promising results in relapsed/refractory myeloma have prompted trials of carfilzomib in combination with other agents for newly diagnosed myeloma. Preliminary results from these Phase II trials show toxicity profiles similar to those seen with single-agent carfilzomib and complete response rates as high as 75% (Table 3).^{51–56} Carfilzomib is currently approved by the US Food and Drug Administration for myeloma patients who have received at least two prior therapies, including bortezomib and an immunomodulatory therapy. Further studies that are underway will provide insight for further indications in newly diagnosed patients and efficacy versus other proteasome therapies. Cost-effectiveness may be a question that needs to be addressed in future studies. In summary, carfilzomib is a promising addition to the existing drugs for multiple myeloma and will likely play an important role as a single agent and in combination therapy for both newly diagnosed and relapsed/refractory disease.

Disclosure

LHB is a consultant for Onyx Pharmaceuticals. SL is a consultant for Celgene, Millennium, Onyx, Novartis, Johnson & Johnson, Bristol-Myers Squibb, and Sanofi. VAG and AKN have no disclosures to make.

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