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Carfilzomib: a novel second-generation proteasome inhibitor

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Abstract

Carfilzomib (formerly PR-171) is a novel epoxyketone-based irreversible proteasome inhibitor. In preclinical studies, carfilzomib demonstrated irreversible binding to the proteasome and minimal off-target inhibition of other proteases. In clinical studies carfilzomib has demonstrated substantial antitumor activity in hematologic malignancies while exhibiting a well-tolerated side-effect profile. Painful neuropathy was minimally reported, suggesting a possible advantage over other proteasome inhibitors. With single-agent carfilzomib, dose-limiting toxicity was hematologic and included thrombocytopenia and neutropenia. In patients with relapsed or refractory multiple myeloma, twice-weekly consecutive-day single-agent carfilzomib 20 mg/m² for 3 weeks every 28 days, escalating to 27 mg/m² the second cycle was associated with a 54% overall response rate in bortezomib-naïve patients and a 26% overall response rate in bortezomib and immunomodulatory drug refractory patients.

Keywords

bortezomib; carfilzomib; chymotrypsin-like; multiple myeloma; PR-171; proteasome Inhibitor

Multiple myeloma is a malignant plasma cell disorder that accounts for approximately 10% of all hematologic cancers [1,2]. The availability of the immunomodulators (thalidomide and lenalido-mide) and the first in-class proteasome inhibitor, bortezomib (BTZ), has significantly improved survival in patients with myeloma [3]. Targeting the proteasome has led to further advances in the treatment of myeloma.

The proteasome is a multicatalytic protease complex that is responsible for ubiquitin-dependent turnover of cellular proteins [4–6]. Inhibition of the proteasome leads to an accumulation of substrate proteins and cell death [7]. The proteasome consists of a core 20S particle with four stacked rings of seven subunits each. The inner two rings contain β -subunits that encode the three major catalytic activities of the proteasome [8]. Hematologically derived tumor cells have been found to express a variant, i20S, proteasome making them a target for the protease inhibitor drugs [9]. The proteolytic activities, chymotrypsin-like (CT-L), trypsin-like and caspase-like make up the catalytic core of the proteasome [10]. Of these, the CT-L activity is the rate-limiting step of proteolysis [11] and has thus become one of the primary targets for the proteasome inhibitor drug class. The

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ubiquitin-proteasome pathway has become a validated target for cancer therapy with the approval of the proteasome inhibitor BTZ [12].

Overview of the market

The novel proteasome inhibitor BTZ is the first in its class to be approved for treatment of multiple myeloma (MM) and mantle cell lymphoma (MCL). It is a dipeptide boronic acid analog that is a covalent, slowly reversible inhibitor of primarily the CT-L activity of the 20S proteasome [13,14]. While demonstrating substantial activity in both newly diagnosed and refractory myeloma, a significant fraction of patients are primarily refractory, develop resistance [15] or experience dose-limiting toxicity, particularly painful peripheral neuropathy and thrombocytopenia [16,17]. These toxicities, thought to be partially due to off-target activity, can restrict dose and duration of therapy [18,19], which has led to further investigation of additional proteasome inhibitor classes.

Carfilzomib (PR-171)

Carfilzomib (CFZ) is a novel second-generation proteasome inhibitor, manufactured by Onyx Pharmaceuticals, Inc. (CA, USA) (Figure 1).

Chemistry

Carfilzomib is a proteasome inhibitor of the epoxyketone class that is structurally and functionally distinct from BTZ [12]. CFZ is a potent and highly selective inhibitor of the CT-L activity of the 20S proteasome, which results in antiproliferative and proapoptotic effects in cell lines representative of hematologic malignancy, particularly MM [20]. In addition, it provides irreversible proteasome inhibition that leads to a more sustained response in preclinical studies than observed with the reversible proteasome inhibitor BTZ [12].

Functionally, the epoxyketone pharmacore demonstrates specificity for the NH₂-terminal threonine residue, allowing for a high degree of specificity to the proteasome leading to irreversible inhibition of enzyme activity [20,21]. This highly selective mechanism eliminates the potential for off-target activity with other cellular proteases [9], which may contribute to improved tolerability *in vivo*.

Pharmacokinetic characteristics

In Phase I studies, high variability in the plasma concentration of CFZ was observed when 11, 15 or 20 mg/m² was administered. A rapid clearance was noted with an elimination half-life of less than 30 min. A clearance higher than liver blood flow suggests multiple clearance pathways. The C_{max} and area under the curve increased with dose but was not thought to be dose proportional. CFZ demonstrated a large volume of distribution at steady state (42.5–942 ml/min) suggesting wide tissue distribution. The maximum tolerated dose was determined to be 15 mg/m² but has since been increased [22].

Pharmacodynamics & preclinical studies

Carfilzomib reveals high specificity *in vitro* and in cellular assays for the CT-L proteasome activity [20]. It induces apoptosis and inhibits proliferation in purified samples from patients with MM and demonstrated activity in preclinical models of diffuse large B-cell lymphoma, chronic lymphocytic leukemia and acute myeloid leukemia. In addition, in myeloma cell culture models and purified plasma cells derived from MM patients, CFZ demonstrated the ability to overcome resistance to BTZ and worked synergistically with dexamethasone to enhance antitumor activity [20].

Administration of CFZ in rat and mice models resulted in dose-dependent inhibition of the CT-L proteasome activity in all tissues except the brain. In addition, mice bearing human tumor xenografts demonstrated a dose- and schedule-dependant activity of CFZ, while studies in rats revealed that 2-day or 5-day consecutive daily dosing ($QD \times 2$ or $QD \times 5$) at doses of up to 2 mg/kg provided peak proteasome inhibition at 80% or more, prevented full recovery of proteasome activity between doses and was well tolerated with minimal adverse events [12].

Clinical efficacy

Potential clinical uses of carfilzomib in cancer: Carfilzomib currently has the following potential uses in the treatment of cancer [20,23–25]:

- Multiple myeloma
- Amyloidosis
- Non-Hodgkin's lymphoma (NHL)
- Waldenstrom's macroglobulinemia (WM)
- Patients who are unable to tolerate BTZ due to toxicity

Phase I trials with single-agent carfilzomib in hematologic malignancies: In a Phase I study, CFZ was administered as twice-weekly consecutive-day dosing (days 1,2, 8,9,15 and 16, with 12 days of rest) via intravenous push on a 28-day cycle [26]. Dose escalation from 1.2 to 27 mg/m² was administered to 37 patients with MM, NHL, including MCL, Hodgkin's disease (HD) and WM, if they had relapsed after at least two prior therapies. The minimal effective dose (MED) was 15 mg/m² and maximum proteasome inhibition (80%) was achieved at this dose. Dose limiting toxicity (DLT) was reported at 27 mg/m², including a hypoxic event and grade 2 thrombocytopenia worsening to grade 4. Other toxicities were mild. Cyclic thrombocytopenia was rapidly reversible and painful peripheral neuropathy was not reported. On the basis of this study, consecutive-day CFZ dosing leads to sustained proteasome inhibition and is well tolerated (Tables 1 & 2).

Another Phase I study by O'Connor *et al.* studied a total of 29 patients with MM, NHL, WM or HD who were treatment refractory or had relapsed after two standard therapies. CFZ was administered as an intravenous push in a dose-escalation fashion on 5 consecutive days, followed by 9 days of rest (14-day cycle) [22]. Doses ranged from 1.2 to 20 mg/m². MED was 11 mg/m², while maximum proteasome inhibition (80%) was observed at 15 mg/m². A total of five responses occurred in 14 patients enrolled in the MED, including one MM partial response (PR), two myeloma minimal responses (MRs), one WM MR and one macroscopic complete response (CR) in gastrointestinal MCL. Four NHL patients demonstrated stable disease. DLT was observed at the 20 mg/m² level, included neutropenia (reversible) and grade 4 thrombocytopenia. Fatigue and nausea were the most common reported adverse events. Grade 3 and 4 peripheral neuropathy was not reported.

Phase II trials with single-agent carfilzomib in multiple myeloma: In preliminary findings from a multicenter Phase II trial, CFZ was administered at a dose of 20 mg/m² intravenously on a $QD \times 2$ consecutive-day schedule for 3 weeks, every 4 weeks, for up to 12 cycles in 39 patients with MM who had relapsed from at least two prior therapies and who were refractory (Tables 1 & 2) [27]. Patients were heavily pretreated with a mean number of prior therapies of 6.4. All patients had received prior treatment with BTZ, 91% prior thalidomide, 89% prior lenalidomide and 83% prior stem cell transplantation (SCT). After three cycles, clinical benefit response (CBR) was 26% with five PR and five MR and 16 additional patients with stable disease. Time to response was rapid, frequently occurring

in the first cycle. CFZ was generally well tolerated. The most common reported adverse events were nonhematological and included fatigue (65%) and nausea (37%). Worsening of hematologic parameters: anemia (65%), thrombocytopenia (46%) and neutropenia (20%) were largely grades 1 and 2. Grade 1 and 2 peripheral neuropathy was observed at baseline in 78% of patients, while exacerbation of peripheral neuropathy was rare and did not lead to dose reductions or discontinuation of the study.

Another ongoing Phase II study in patients with relapsed or refractory MM-stratified cohorts into BTZ naive, BTZ responsive (>6-month response) or BTZ nonresponsive (<6-month response) [28–31]. CFZ was administered at 20 mg/m² intravenously on days 1, 2, 8, 9, 15 and 16, every 28 days for up to 12 cycles. To date, 110 BTZ-naive and 39 BTZ-treated patients have been evaluated. In the BTZ-naive group, patients were heavily pretreated. A total of 23% completed 12 cycles while 24 patients remain on the study. A total of 20% have elected to continue CFZ on an extended treatment protocol. Overall response rate was 54%. Common adverse events were fatigue, nausea, dyspnea and anemia, which were primarily grade 2. Grade 3/4 events were less common but included thrombocytopenia, fatigue, neutropenia and lymphopenia. Peripheral neuropathy was rare and did not result in any study discontinuation. Patients with baseline impairment of renal function did not require dose modifications [28,30,31].

In the BTZ-treated cohort, CFZ was administered to 39 heavily pretreated patients. Mean number of cycles received was three (range: one to 12). Overall, CBR was 26%, including five PR and five MR. Time to progression (TTP) was greater than 6 months. Common adverse events were primarily grade 2 and were similar to the BTZ-naive cohort. Grade 3/4 events were less common and included thrombocytopenia and neutropenia. Peripheral neuropathy was rarely reported (<10%). As observed in the BTZ-naive group, patients with baseline renal impairment did not require dose modifications [28,29,32].

Phase I trials with carfilzomib-based combinations in the treatment of relapsed and refractory multiple myeloma: A Phase I multicenter dose-escalation trial evaluated CFZ plus lenalidomide and low-dose dexamethasone at six dose levels in patients with relapsed or refractory MM [33]. CFZ (15–27 mg/m² intravenous, twice-weekly consecutive day dosing), lenalidomide (10–25 mg *per os* days 1–21) and dexamethasone (40 mg *per os* days 1, 8, 15 and 22) was administered in 4-week cycles. A total of 26 patients were evaluable for safety and 20 for response. To date, five out of six cohorts have been reported on. The overall response rate was 55% and CBR was 65% including two CR, four VGPR and five PRs. Two patients had MR while six demonstrated stable disease. No DLTs have been reported and adverse events are similar to those previously reported.

This same regimen has now been used in a small number of newly diagnosed patients with 100% response rate and 63% CR after eight cycles [34].

safety & tolerability

Overall, CFZ has demonstrated that it is well tolerated (Table 2). It has been tested at different dose levels and schedules in preclinical models revealing tolerability of consecutive-daily dosing [12]. Acute and chronic administration in mice, rats and monkeys revealed mild transient thrombocytopenia and pre-renal azotemia that was not exacerbated by consecutive dosing, and at a cumulative dose in the range predicted for clinical use no histological apparent abnormalities were induced [35].

In Phase I clinical studies, neutropenia, hypoxia and thrombocytopenia were the dose-limiting toxicities [22–26]. Other toxicities included fatigue, nausea, dyspnea and anemia,

which were primarily grade 2. Grade 3/4 events were less common but included thrombocytopenia, fatigue, neutropenia and lymphopenia [28–31]. Peripheral neuropathy was rare and did not require dose modification. Patients who had undergone extensive prior treatment and those with significant comorbidities, such as diabetes or baseline renal impairment, tolerated consecutive-daily dosing and did not require dose modification.

The first dose effect with noncumulative and reversible elevation of serum creatinine has been observed and tumor lysis has been reported. Therefore, oral hydration is recommended prior to study dosing and low-dose dexamethasone 4 mg intravenous or *per os* is recommended before each dose in the first cycle. Deaths on study have been reported, including tumor lysis with associated multisystem failure, and acute hepatic failure but appear rarely.

conclusion

Carfilzomib has demonstrated single-agent activity in MM with an acceptable toxicity profile. Preclinical studies have demonstrated success in other hematologic malignancies as well. The most common reported adverse events are nonhematological and included fatigue and nausea. The main grade 3/4 toxicities are hematological (primarily neutropenia and thrombocytopenia) but have not required dose modifications. Dose reduction or discontinuation owing to peripheral neuropathy is rare, suggesting CFZ may have a different side-effect profile than BTZ. CFZ has also been safely combined with other chemotherapy agents forming the basis for Phase III testing. In addition, in further Phase Ib studies, dose escalation up to 45–56 mg/m² has been successful [36].

Future perspective

Future studies will evaluate CFZ earlier in the disease course, at higher doses and in combination therapies. Comparative analysis with existing or new proteasome inhibitors will be required to evaluate toxicity and effectiveness more directly. For example, explorations of novel applications as an immunosuppressant are logical.

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Executive summary

Mechanism of action

- Carfilzomib is an irreversible proteasome inhibitor that induces apoptosis and inhibits proliferation in hematologic tumor cells.

Pharmacokinetic properties

- Carfilzomib has a rapid distribution to all tissues, except the brain, followed by rapid clearance through multiple clearance pathways. Volume of distribution at steady state is 42.5–942 ml/min. Elimination half-life ranges from 15 to 30 min.
- Carfilzomib is excreted in the form of metabolites is primarily renal and biliary.

Clinical efficacy

- Carfilzomib is an investigational drug being studied for use in the treatment of previously treated relapsed or refractory multiple myeloma as well as other hematologic malignancies. Overall response rates of 18–45% have been reported in multiple myeloma.

Safety & tolerability

- The hematological side effects involve febrile neutropenia and thrombocytopenia as dose-limiting toxicities. The nonhematological side effects are fatigue, nausea, vomiting, diarrhea, upper respiratory infections with transient increased creatinine as the most common.
- Complete blood counts are measured prior to each dose as a form of monitoring.
- Contraindications include hypersensitivity to carfilzomib.
- There are no reported specific drug interactions.
- Dosage and administration: adults: Phase I dose-escalation studies and Phase II trials recommend a carfilzomib dose of 15 mg/m² administered as an intravenous push on a twice-weekly consecutive day dosing on days 1, 2, 8, 9, 15 and 16, every 28 days for up to 12 cycles. Dose-limiting toxicities occurred at 20–27 mg/m² but have been escalated up to 45–56 mg/m² as a 30 min infusion. Pediatric dosage: the safety and efficacy of carfilzomib has not been established in pediatric patients.

Figure 1. Carfilzomib
Structure of carfilzomib is shown.²⁰

Table 1

Carfilzomib (PR-171) preclinical, Phase I and II trials.

Study (year)	Trial details	Outcome	Ref.
Kuhn <i>et al.</i> (2007)	Cell model and patient-derived neoplastic cells	Carfilzomib selectively binds CT-L proteasome activity leading to dose-dependent apoptosis and inhibited proliferation, and overcame bortezomib-resistant multiple myeloma cell lines	[20]
Demo <i>et al.</i> (2007)	Tumor cell lines, rats and mice with human tumor xenografts	Carfilzomib has greater selectivity for the CT-L proteasome activity leading to apoptosis. Consecutive day dosing is well tolerated and highly effective	[12]
Alsina <i>et al.</i> (2007)	Phase I in 37 patients with relapsed multiple myeloma, NHL, MCL, HD or WM	Twice weekly consecutive (QD × 2) day dosing at 15 mg/m ² intravenously is the recommended dose for Phase II trials	[26]
O'Connor <i>et al.</i> (2009)	Phase I in 29 patients with relapsed or refractory multiple myeloma, NHL, MCL, HD or WM	Consecutive (QD × 5) day dosing on 14-day cycle at 15mg/m ² intravenously is well tolerated but consecutive QD × 2 dosing is recommended to maintain patient adherence	[22]
Jagannath <i>et al.</i> (2008)	Phase II in 39 patients with previously treated relapsed or refractory multiple myeloma	Preliminary results at carfilzomib dose 20 mg/m ² intravenously on QD × 2 consecutive dosing. CBR: 26%. Median three cycles	[27]
Vij <i>et al.</i> (2008)	Phase II in 110 BTZ-naïve and 39 BTZ-treated patients with previously treated relapsed or refractory multiple myeloma	Preliminary results at carfilzomib dose 20 mg/m ² intravenously on QD × 2 consecutive dosing	[28]
Siegel <i>et al.</i> (2009)			[29]
Wang <i>et al.</i> (2009)		BTZ-naïve ORR: 54%	[30]
Jakubowiak <i>et al.</i> (2010)		BTZ-treated ORR: 26%	[31]
Niesvizky <i>et al.</i> (2009)	Phase Ib in 26 patients with previously treated relapsed or refractory multiple myeloma	Preliminary results in five out of six dose level cohorts with carfilzomib, LEN and low dose dex ORR: 55%; CBR: 65% CFZ 20 mg/m ² , LEN 25 mg, dex 40 mg is the established tolerated dose	[33]

BTZ: Bortezomib; CBR: Clinical benefit response; CFZ: Carfilzomib; CT-L: Chymotrypsin-like; dex: Dexamethasone; HD: Hodgkin's disease; LEN: Lenalidomide, MCL: Mantle cell lymphoma; NHL: Non-Hodgkin's lymphoma; ORR: Overall response rate; QD × 2: 2-day consecutive day dosing; QD × 5: 5-day consecutive day dosing; WM: Waldenstrom's macroglobulinemia.

Table 2

Safety outcomes in clinical trials.

Study (year)	Toxicities	Ref.
Alsina <i>et al.</i> (2007)	DLT was a hypoxic event and thrombocytopenia. Reversible grade 2 creatinine elevation	[26]
O'Connor <i>et al.</i> (2009)	Thrombocytopenia and neutropenia were DLT. Fatigue, nausea, diarrhea and cough	[22]
Jagannath <i>et al.</i> (2008)	No DLT. Fatigue, nausea, URI, diarrhea. Grade 1/2 anemia, thrombocytopenia and neutropenia	[27]
Vij <i>et al.</i> (2008)	Fatigue, nausea, vomiting, neutropenia, anemia, thrombocytopenia, increased creatinine, diarrhea and dyspnea	[28]
Siegel <i>et al.</i> (2009)		[29]
Wang <i>et al.</i> (2009)		[30]
Jakubowiak <i>et al.</i> (2010)		[31]
Niesvizky <i>et al.</i> (2009)	No DLT. Reversible thrombocytopenia, anemia and neutropenia	[33]

DLT: Dose-limiting toxicity; URI: Upper respiratory infection.