Carfilzomib

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This spotlight review focuses on the second-generation proteasome inhibitor carfilzomib, which was recently approved by the US Food and Drug Administration for treatment of relapsed and refractory multiple myeloma patients who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy. This review focuses on clinical trial data leading to drug approval and provides advice for treating physicians who are now accessing this drug for patients.

Introduction

Proteasome inhibition is highly effective treatment for multiple myeloma (MM), Waldenström macroglobulinemia, low-grade non-Hodgkin lymphomas, and primary amyloidosis.1 Almost 10 years ago, the US Food and Drug Administration (FDA) approved the dipeptidyl boronic acid derivative proteasome inhibitor bortezomib (BTZ) for the treatment of refractory MM and subsequently frontline therapy for MM, thus opening the door to a new era of improved MM therapy. Indeed, disease-free and overall survival for most MM patients has been significantly extended. Nevertheless primary or secondary BTZ resistance2 is common, and treatment is often limited by BTZ-induced, dose-limiting side effects, mostly consequent to peripheral neuropathy.3 Although less frequent BTZ administration at lower doses and using subcutaneous delivery4,5 may contribute to a lowered BTZ neuropathy incidence and severity without seemingly compromising efficacy, new proteasome inhibitors—the “second generation”—have now been developed and are aimed at being potentially more efficacious and less toxic. The FDA recently granted accelerated approval for carfilzomib (CFZ) injection for the treatment of patients with MM who have received at least 2 prior therapies, including BTZ and an immunomodulatory agent, and who have demonstrated disease progression on or within 60 days of the completion of last therapy. This spotlight review focuses on the data leading to drug approval and provides helpful management tips for treating physicians.

Ubiquitin-proteasome pathway inhibition in MM treatment

Proteasomes are present in all eukaryotic cells.6,7 They degrade proteins8,9 and influence a multitude of cellular processes,10-16 including proliferation and DNA repair.17-19 Proteasome inhibition leads to an unfolded protein stress response by accumulation of misfolded proteins in the cell,20-22 inhibits NF-κB,23 and thus induces cell-cycle arrest24,25 and apoptosis.26-28 The (malignant) plasma cell in particular is susceptible to proteasome inhibition, even to small changes,29 because of its inherent function in Ab production.30-32

The proteasome

The constitutive 26S proteasome consists of protein-recognizing 19S regulatory particles and a 20S proteolytic core33 that carries 3 protein-specific catalytic sites: the chymotrypsin, trypsin, and caspase-like sites.34,35 Blocking the chymotrypsin-like site is most effective in cellular growth inhibition in vitro, but coinhibition of other proteasome subunits further increases overall growth retardation.35-38 Unique immunoproteasomes exist in cells of immune or hematopoietic origin, where the catalytic sites differ from the constitutive proteasomes.39 These play an important role in generating antigens for MHC class I presentation.39 Both constitutive and immunoproteasomes are expressed in MM cells and are targeted by the available inhibitors BTZ and CFZ. It has not been fully elucidated whether the anticancer effects depend on inhibition of one or both proteasome types because study results are ambiguous.40-43

CFZ-specific inhibition of the proteasome

CFZ (also known as PR-171) is a cell-permeable tetrapeptide epoxyketone analog of epoxomicin.44,45 It primarily inhibits the chymotrypsin-like site of the proteasome (Figure 1); in high doses, it shows additional inhibitory effects on the trypsin-like and caspase-like site, but also with a multitude of serine proteases,49-51 potentially contributing to some of the neurotoxicity.

CFZ pharmacodynamics and pharmacokinetics

CFZ penetrates all tissues but the brain extensively. It is largely metabolized extrahaepatically and is rapidly cleared from the circulation by biliary and renal excretion (t1/2 = 15-30 minutes): less than 1% is excreted intact.46,52-54 Unlike BTZ, CFZ is not primarily metabolized by hepatic cytochrome P450,55,56 and therefore plasma levels are minimally dependent on liver function and concomitant medication.57 Because of irreversible binding of CFZ, proteasome function after therapy can only be regained by de novo proteasome synthesis.52 Consecutive daily dosing of CFZ is optimal for inhibition of the proteasome in preclinical studies, thus leading to the eventual clinical schedule.46


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CFZ resistance

A significant number of MM patients present with either primary or secondary proteasome inhibitor resistance. Interestingly, some BTZ-resistant cell lines and patients are responsive to CFZ therapy and some CFZ-resistant cell lines remain sensitive to BTZ treatment. Differences in underlying resistance mechanisms have not been convincingly elucidated. Recently, up-regulation of P-glycoprotein could be demonstrated after CFZ, suggesting that drug transport may contribute to resistance.

CFZ phase 1 clinical trials

In the first phase 1 trial, CFZ was administered in escalating doses on 5 consecutive days, followed by a 9-day rest period in a 14-day cycle. Sustained proteasome inhibition was achieved; common side effects were low-grade fatigue and nausea, but no significant peripheral neuropathy was observed. Two CFZ-associated dose-limiting toxicities (DLT) occurred (thrombocytopenia and febrile neutropenia). The minimal effective dose (MED) was determined to be 11 mg/m² and 15 mg/m² the maximal tolerated dose (MTD). In a second phase 1 trial, CFZ was given on a 4-week cycle, on days 1, 2, 8, 9, 15, and 16 to 37 patients with hematologic malignancies. Five responses were seen in 26 MM patients at doses above 15 mg/m² and an MTD was not reached. The highest dose administered was 27 mg/m². Of all of the patients included, 3 had serious adverse events (SAEs) during phase one (sepsis, elevated liver enzymes, and chemical pancreatitis), all considered possibly related to CFZ. Five patients in the expansion cohort had 9 SAEs, of which 1 was considered to be CFZ related (hypoxia); 1 patient with a preexisting grade 2 renal impairment developed grade 3 renal failure. Although 50% of the patients entered the study with preexisting peripheral neuropathy, no aggravation to grade 3/4 was reported.

CFZ phase 2 clinical trials

PX 171-003 was the primary trial used for registration purposes and addressed CFZ single-agent activity in a cohort of particularly poor prognosis and unmet medical need patients. Therefore, 266 heavily pretreated MM patients (82% had > 4 lines of therapy and 80% were double refractory) were treated with single-agent CFZ in the twice-weekly regimen (see previous paragraph) with a dose-reduced (20 mg/m²) first cycle to abrogate potential tumor-lysis syndrome. Dosing in cycle 2 was escalated to 27 mg/m². The overall response rate (ORR) was 23.7%, with a median duration of response of 7.8 months, a progression-free survival of 3.7 months, and an overall survival of 15.6 months. Clinical benefit was seen in one-third of the patients. Outcome was not influenced by adverse cytogenetics, renal impairment, disease stage, or Eastern Cooperative Oncology Group (ECOG) performance score. Five of the 24 deaths in the 266 patients on trial were considered possibly related to CFZ treatment, including 2 cardiac arrests. Drug-related AEs of all grades were most frequently fatigue (37%), nausea (34%), and thrombocytopenia. Hematologic AE grade 3/4 included anemia (24%), thrombocytopenia (29%), lymphopenia (20%), and neutropenia (11%). Nonhematologic AEs grade 3/4 included pneumonia (9%), hyponatremia (8.3%), fatigue (7.5%), and hypophosphatemia (6.0%). One-third of the patients experienced mild to moderate dyspnea without detectable lung injury, possibly because of extensive hydration patients received. Although 77% of patients had grade 1/2 peripheral neuropathy at study inclusion, treatment-emergent peripheral neuropathy was uncommon (12.4%) and considered to be CFZ related in only 8.3% of patients. Acute renal failure qualifying for an severe AE occurred in 5 of 266 patients and was considered likely to be related to CFZ.

Other supportive clinical trials for registration included a phase 2 trial in 129 relapsed but BTZ-naive MM patients. This trial showed an impressive single-agent ORR of 52%. The impact of renal insufficiency in CFZ treatment was investigated in a phase 2 trial in 39 relapsed MM patients with varying renal impairment. Toxicities were manageable and independent of renal status; dose adjustment was not necessary. In the PX-171-010 trial, the long-term safety of CFZ treatment was assessed. No cumulative toxicities, including late development of peripheral neuropathy or significant emerging renal dysfunction, were observed.

The extension of the infusion time from 2-10 minutes to 30 minutes allowed tolerance of higher doses of CFZ. DLTs were seen at a dose of 70 mg/m² and at 56 mg/m², an impressive
single-agent ORR of 60% was achieved. Grade 3/4 toxicities were thrombocytopenia (38%), anemia (21%), and hypertension (13%).75

**CFZ clinical trials combination therapy**

A phase 1 trial (PX-171-006) in relapsed MM patients examined CFZ with standard-dose lenalidomide and low-dose dexamethasone in a 28-day cycle (no DLTs were observed and the ORR was 78%).76 A phase 1/2 trial of this combination was then performed in newly diagnosed patients. CFZ was dose escalated in this study and a 36 mg/m² dose was found to be tolerable. After a median of 12 cycles of therapy, the ORR was 98%, with an impressive stringent complete remission rate of 42%.77

CFZ plus melphalan and prednisone (CMP) for elderly patients with newly diagnosed MM was administered on the usual schedule twice weekly with a 12-day rest in a 42-day cycle. The MTD was 36 mg/m² and 2 DLTs (fever and hypotension) occurred. The regimen was judged to be safe and effective. An ORR of 92% could be determined in an interim analysis.78

Other reported alkylator combination regimens include CYCLONE (cyclophosphamide, CFZ, thalidomide, and dexamethasone) for newly diagnosed MM patients, which, again, demonstrated efficacy, with an ORR of 100% and deep responses in many patients.79

**CFZ practical guidance**

The FDA-approved label dose and the dose being tested in phase 3 clinical trials is CFZ 20 mg/m² in the first 28-day cycle and, if tolerated in cycle 1, escalating to 27 mg/m² for cycle 2 and beyond. The current vial size of 60 mg is well suited to the 27 mg/m² dose. Higher doses up to at least 45 mg/m² were tolerable in limited phase 1/2 testing, but data on these doses are still accumulating and this treatment is not currently used outside of clinical trials.

CFZ is administered intravenously over 2-10 minutes on consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17-28). If signs of dose intolerance occur, a dose reduction down to 20 mg/m² or an extension of infusion time up to 30 minutes can be considered.

The staged dose escalation between cycles 1 and 2 reflects concerns from phase 1 testing about possible tumor lysis, early infusion reaction with fever and dyspnea, and increases in creatinine in the presence of high tumor burden and dehydration. Therefore, current advice is to maintain adequate fluid volume status throughout treatment and to monitor blood chemistries closely, particularly in cycle 1. In our practice, this currently means obtaining laboratory reports on days 1, 2, 3, 8, and 15 in cycle 1 and on days 1, 8, and 15 thereafter. Before each dose in cycle 1, it is currently recommended—and is our practice—to give 250 mL of IV fluid before each dose if the patient can tolerate such fluid. After hydration and routine allopurinol, tumor lysis on clinical extension of infusion time up to 30 minutes can be considered.

As with BTZ treatment, shingles or hepatitis reactivation has been reported so prophylaxis is recommended.

Table 2. CFZ studies that include survival data

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elderly, cardiac-compromised, or hypertensive patients. Although the consecutive daily dosing schedule may be less convenient, it is important to note that patient compliance has generally been high in our experience and a consensus opinion of physician clinical trial participants is that CFZ is a well tolerated drug in the majority of patients and offers the unique benefit of minimal neuropathy.

Summary

CFZ is a potent proteasome inhibitor and effective therapy in MM with an advantageous side effect profile characterized by low rates of peripheral neuropathy and potential use in other diseases as Waldenström macroglobulinemia, lymphoma, amyloidosis, and autoimmune diseases. In MM, CFZ is a welcome addition to BTZ, alkylators, corticosteroids, and the immunomodulatory drugs thalidomide and lenalidomide in the therapeutic arsenal. The results of ongoing phase 2 and multiple phase 3 trials will help to further define the role of CFZ in MM therapy and will help to establish the best dosing, schedule, and supportive care management that benefit these patients.

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Authorship

Contribution: K.M.K. and A.K.S. analyzed the data and wrote the manuscript.

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References


38. Arendt CS, Hochstrasser M. Identification of the yeast 20S proteasome catalytic centers and subunit interactions required for active-site formation.


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