Review

Carfilzomib: a novel agent for multiple myeloma

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Abstract

Objectives Carfilzomib is a new agent for the treatment of relapsed and refractory multiple myeloma (MM). This article presents a comprehensive overview of the pharmacokinetics, pharmacodynamics, dosing schedule, safety, efficacy, preparation and administration of carfilzomib, and its role in treating MM patients.

Key findings Carfilzomib is a selective proteasome inhibitor that differs structurally and mechanistically from bortezomib. In patients' whole-blood and peripheral-blood mononuclear cells, carfilzomib inhibited proteasomal and immunoproteasomal activity by 70–80%. Approved carfilzomib dosing is based on body surface area, and is given on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle (20 mg/m^2 in cycle 1; 27 mg/m^2 in cycle 2+). Premedication with dexamethasone and adequate hydration are recommended to reduce the risk of adverse events. The median $t_{1/2}$ of carfilzomib is short (0.29–0.48 h), with no accumulation detected between doses. In clinical studies in relapsed and refractory MM. and in combinations in newly diagnosed MM, single-agent carfilzomib demonstrated significant durable activity, good tolerability and a favourable safety profile, supporting its extended use.

Conclusions Carfilzomib represents an important addition to the treatment armamentarium for patients with relapsed and/or refractory MM, and studies are underway evaluating the role of single-agent carfilzomib in additional clinical settings as well as in different combinations.

Introduction

Multiple myeloma (MM) is a malignant, progressive B-cell tumour characterized by overproduction of monoclonal immunoglobulin, osteolytic bone lesions, renal dysfunction and immunodeficiency.[1] According to estimates from the American Cancer Society, 22 350 new cases will be diagnosed and 10 710 Americans will die from MM in 2013.[2] MM will represent nearly 15% of new haematologic malignancies diagnosed in 2013.[2] The incidence of MM is slightly greater in men than in women and ~2-fold greater in African Americans than in Caucasians.[1,3] In general MM is a disease of older individuals,[3] with a median age at diagnosis of 69 years.[1,4–6] The majority of patients with MM present with bone pain or fractures of unknown aetiology, renal failure, recurrent infections,[6] anaemia and fatigue.[5]

Over the last decade, the median overall survival (OS) following treatment for patients with MM has ranged from 4.4 to 7.1 years,[6] and nearly all patients experience eventual relapse and progression.[7] Therapeutic options for patients with advanced stage disease, including those relapsed after multiple prior lines of therapy and those with refractory disease, are limited, often including experimental agents and three- and four-drug combinations. For patients with relapsed or progressive disease, National Comprehensive Cancer Network (NCCN) guidelines recommend transplantation (in eligible patients), or salvage therapy on or off clinical trials.[8] However, the majority of the preferred regimens for salvage treatment are limited by drug toxicity and transient responses.

Carfilzomib (Kyprolis™, Onyx Pharmaceuticals, South San Francisco, CA) is a selective proteasome inhibitor (PI) that is US Food and Drug Administration (FDA) approved as single-agent treatment for relapsed or refractory multiple myeloma (RRMM).[9] It differs structurally and mechanisti-
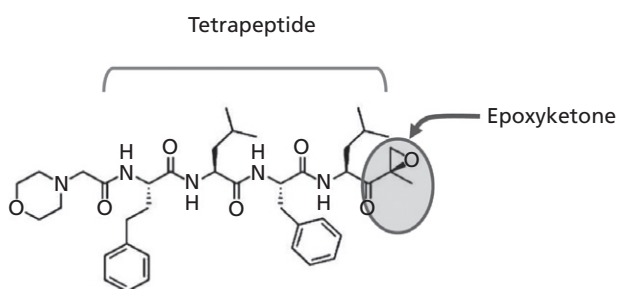
Tetrapeptide

Figure 1 Structure of carfilzomib. Carfilzomib consists of a tetrapeptide backbone with an active epoxyketone moiety or 'warhead' that is reactive with the N-terminal threonine active sites of the proteasome.

cally from bortezomib. It is a tetrapeptide bearing an epoxyketone moiety (Figure 1) and functions by irreversibly inhibiting chymotrypsin-like (CT-L) activity of the proteasome, thereby eliciting more sustained inhibition than the reversible PI, bortezomib and greater target specificity, which may explain the ability of carfilzomib to overcome resistance to bortezomib both in vitro and in vivo. Carfilzomib has been evaluated in clinical studies in patients with RRMM, and NCCN currently lists it as a preferred regimen in this population. Carfilzomib has also been studied in the frontline setting. The goal of this article is to present pharmacists with a complete overview of the pharmacokinetics (PK), pharmacodynamics (PD), dosing schedule, safety, efficacy, preparation and administration guidelines of the drug.

Pharmacology

Carfilzomib is an analogue of epoxomicin and eponemycin, related natural products initially shown to inhibit tumours in animals and later to specifically inhibit the CT-L activity of the 20S proteasome.[10–14] It is structurally and mechanistically distinct from the dipeptide boronic acid PI bortezomib, which forms a slowly reversible bond with the proteasome's catalytic $\beta 5$ subunit.[15] In contrast to bortezomib, carfilzomib forms an irreversible dual covalent bond with the catalytic $\beta 5$ subunit of the proteasome and with the analogous subunit $\beta 5_i$ (LMP7) of the immunoproteasome.[16] At therapeutic concentrations, carfilzomib shows primary selectivity for CT-L activity of the proteasome and is equipotent to bortezomib,[17] but displays little activity against the trypsin-like or caspase-like activities of the proteasome.[17] The selectivity coupled with the irreversible nature of the inhibition gives carfilzomib a potential advantage both in efficacy and tolerability over bortezomib.

In preclinical models of MM, inhibition of the proteasome and the immunoproteasome by carfilzomib in cell lines and primary cells resulted in dose- and time-dependent inhibition of proliferation, ultimately leading to apoptosis.[18] Carfilzomib had greater specificity than bortezomib in these models and also showed significantly less neurotoxicity and neurodegeneration.[15] Carfilzomib also overcame resistance to bortezomib and other conventional agents, and acted synergistically with dexamethasone.[18]

Pharmacokinetics/Pharmacodynamics

Carfilzomib is rapidly and extensively metabolized to inactive metabolites.[16] Cytochrome P450 pathways play only a minor role in carfilzomib metabolism.[19] Plasma clearance rates exceed hepatic blood flow rates,[20,21] suggesting a significant contribution of extrahepatic mechanisms to elimination.[16,17] There has been no apparent effect of renal dysfunction on carfilzomib PK noted to date.[22]

The PK profile of carfilzomib was evaluated in patients with MM at doses of 11, 15, 20 and 27 mg/m² (Table 1).[21,23] Carfilzomib concentrations declined rapidly in a biphasic manner, and the majority of the drug was eliminated from the plasma compartment within 30 min.[21–23] The $t_{1/2}$ of carfilzomib was short, with a median of 0.29–0.48 h, and accumulation of carfilzomib was not detected.[21,22] This rapid clearance may explain the favourable safety profile of the drug.

Area under the curve (AUC) and maximum concentration (C_{max}) both increased in non-dose-dependent fashion with increasing carfilzomib doses. The volume of distribution at steady state (V_{ss}) was large and quite variable across dose levels, suggesting wide tissue distribution.[21,23] Repeated administration did not appear to alter carfilzomib exposure, although PK parameters showed a large degree of interpatient variability.[21,22]

In whole-blood and peripheral-blood mononuclear cells (PBMCs) from patients with MM, carfilzomib inhibited the CT-L activity of both the proteasome and the immunoproteasome by 70–80%,[17,18] and at 27 mg/m² ~90% inhibition has been seen.[23] Cumulative inhibition of CT-L activity was observed with repeat dosing.[18] Prolonged inhibition is suggested by the minimal proteasome activity observed on day 2 of the first cycle.[23] Progressive recovery of activity has been demonstrated in whole blood and PBMCs within 24, 72 and 168 h,[15,17,18,21] with complete recovery seen at cycle 2 following a 12-day rest period.[23]

Drug interactions

A single drug interaction study was conducted in patients with solid tumours to determine whether carfilzomib administration would alter the PK of midazolam, a CYP3A substrate, following reductions of CYP3A and 1A2 *in vitro*.[19] In both a single and repeat dose evaluations, carfilzomib did not affect the PK of midazolam, and there were no safety signals indicative of drug interactions.[19]

Table 1 Pharmacokinetic parameters of carfilzomib following intravenous administration to patients with haematologic malignancies[21,23]

Carfilzomib dose	11 mg/m^2		15 mg/m^2		20 mg/m^2		27 mg/m^2
Study	001	002	001	002	001	002	002
n	$n = 2$	$n = 3$	$n = 5$	$n = 3$	$n = 4$	$n = 8$	$n = 5$
C_{max} (ng/ml)							
Mean	90.2	505	325.9	143	683.0	528	406
SD	84.9	485	217.8	97	598.5	406	517
$t_{1/2}$ (min)							
Mean	25.3	12.9	28.9	13.1	17.1	39.4	26.8
SD	14.1	6.5	37.4	3.6	7.7	28.8	4.7
CL (ml/min)							
Mean	5 062	10 437	7 054	30 342	4 127	10 979	74 575
SD	3 958	10 973	7 177	23 890	4 981	5 880	108 935
V_{ss}, L							
Mean	42.5	68.4	942	199.1	140	108.4	1 539
SD	65.2	79.5	2 046	116.6	231	71.2	2 862
AUC_{last} (ng·ml/h)							
Mean	4 457	4 049[a]	9 728	1 414[a]	23 123[a]	4 911	3 409[a]
SD	2 520	3 695	10 897	919	17 323	3 495	3 964

[a]AUC_{last} (ng·min/ml). AUC_{last}, area under curve to last measurable time point (includes C_0); CL, systemic clearance; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state.

Table 2 Dose-finding and safety studies of carfilzomib in relapsed and/or refractory haematologic malignancies: dosing schedule and efficacy outcomes[21–23,25]

Study	Patient population	Schedule	Carfilzomib dose (mg/m^2)	ORR (%)	CBR (%)
PX-171-001	R-R (MM, WM, NHL, HD)	Days 1–5 (14-day cycle)	1.2–20.0	7.1[a]	14.3[a]
PX-171-002 (escalation)	R-R (MM, NHL, HD)	Days 1, 2, 8, 9, 15, 16 (28-day cycle)	1.2–27.0	14.0[a]	18.6[a]
PX-171-002 (expansion)	R-R (MM, NHL, WM)	Days 1, 2, 8, 9, 15, 16 (28-day cycle)	20 (C1) 27 (C2 and higher)		
PX-171-005	R-R MM with renal dysfunction	Days 1, 2, 8, 9, 15, 16 (28-day cycle)	15, 20 or 27	25.5	31.9
PX-171-007	R-R MM	30 min infusion Days 1, 2, 8, 9, 15, 16 (28-day cycle)	20 (C1, D1 and 2) 36, 45, 56 or 70	57.1	67.9

[a]Only for patients with MM. CBR, clinical benefit response rate; HD, Hodgkin's disease; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; QD, once daily; R/R, relapsed and refractory; R-R, relapsed or refractory; WM, Waldenström's macroglobulinemia.

In clinical trials conducted to date, there have been no restrictions on concomitant medications, including cytochrome P450 substrates, inducers, or inhibitors.[9,24] Based on the metabolic pathways for carfilzomib and the results of clinical trials to date, significant drug–drug interactions are not predicted. Continued clinical experience will serve to confirm this prediction.

Clinical trials

Dose finding and safety studies

Carfilzomib trials PX-171-001 and PX-171-002 were phase 1 open-label dose-finding studies. Study PX-171-001 enrolled 29 patients with relapsed or refractory haematologic malignancies after two or more prior therapies

(Table 2).[21] Patients received carfilzomib at doses up to 20 mg/m^2 IV infusion over 1–2 min on days 1–5 every 14 days until evidence of unacceptable toxicity or progressive disease. The maximum tolerated dose (MTD) with the 5 consecutive-day dosing schedule was defined at 15 mg/m^2. The most common treatment-emergent events of any grade were fatigue (48%), nausea (48%) and diarrhoea (35%). Grade 3 and 4 events were reported at 15 and 20 mg/m^2 and included thrombocytopenia, anaemia, unspecified pain, increased aspartate aminotransferase, febrile neutropenia, neutropenia, chills and dyspnea. Grade 1 and 2 hypoesthesias and paresthesias were reported, but Grade 3 and 4 peripheral neuropathies (PN) were not. Of the 28 patients evaluable for response, 4 patients, all treated at doses of 11 mg/m^2 or higher, had

objective responses (Table 2), including 2 patients with MM.[21]

PX-171-002 evaluated a patient population similar to 001 and enrolled 48 patients with relapsed or refractory haematologic malignancies after two or more prior therapies (Table 2).[23] Patients received carfilzomib doses up to 27 mg/m^2 IV infusion over 1–2 min on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle until unacceptable toxicity or disease progression. Single-agent dose escalation ($n = 37$, MTD not reached) was followed by a dose expansion ($n = 11$) that comprised two cohorts (carfilzomib or carfilzomib + dexamethasone). During dose expansion, an escalated regimen was evaluated for a possible decrease in observed 'first-dose effects' associated with tumour lysis and/or cytokine release. Cycle 1 day 1 and 2 doses were 20 mg/m^2, followed by escalation to 27 mg/m^2 thereafter. Dosing in the expansion cohort was well tolerated with the majority of adverse events (AEs) Grades 1 or 2.

Notable haematologic AEs ≥ Grade 3 were anaemia and thrombocytopenia. There were no observations of ≥ Grade 3 PN. At doses of 15–27 mg/m^2, there was evidence of efficacy among patients with MM and non-Hodgkin's lymphoma (NHL) in 14 of 36 evaluable patients. The results of this trial demonstrated preliminary safety and efficacy of the escalated dosing regimen and served as the basis for subsequent studies.

In the phase 2 PX-171-005 study, single-agent carfilzomib was evaluated in 50 patients with varying degrees of renal dysfunction, including 8 patients on chronic dialysis (Table 2).[22] Carfilzomib was administered by IV infusion over 2–10 min on days 1, 2, 8, 9, 15 and 16 every 28 days. Patients received 15 mg/m^2 in cycle 1, 20 mg/m^2 in cycle 2 and 27 mg/m^2 in cycle 3 and beyond. Renal function did not affect carfilzomib clearance, peak exposure or total exposure, or AE profile.[22] The most common Grade 3/4 AEs (≥10%) were anaemia, thrombocytopenia, lymphopenia, fatigue, pneumonia and pain. Serious AEs (SAEs) occurred in 33 patients. Partial responses (PR) or better were reported in 25.5% of patients, and 44.7% had a best response of (stable disease) SD.[22] The results of this trial

suggest that dosage adjustments are not necessary for patients with varying degrees of renal function.

Higher doses and an alternative infusion time were evaluated in the phase 1b/2 PX-171-007 study (Table 2). Thirty-three patients with MM received carfilzomib as a 30-min IV infusion on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle. Cycle 1 day 1 and 2 doses were 20 mg/m^2, followed by escalation to 36, 45, 56 or 70 mg/m^2.[25] MTD was defined as 56 mg/m^2. Dose-limiting toxicities (DLTs) occurred in 2 patients treated at 70 mg/m^2; both patients continued carfilzomib at reduced doses. This trial further confirmed the safety and efficacy of an escalated regimen, while indicating the need for further study and evaluation of higher doses and alternative infusion strategies.

Single-agent studies in RRMM

Two phase 2 studies of single-agent carfilzomib in patients with RRMM, including those who were heavily pre-treated, were each analysed by cohorts (Table 3) (PX-171-003 (003-A0, 003-A1); PX-171-004 (004 bortezomib treated, 004 bortezomib naïve)). In the first cohort of both studies, carfilzomib was dosed at 20 mg/m^2, and in higher cohorts at 20 mg/m^2 in cycle 1 followed by 27 mg/m^2 in subsequent cycles.

PX-171-003-A0 and 003-A1 were open-label, multicenter studies in patients with RRMM following two or more prior therapies that included bortezomib and an immunomodulator (thalidomide or lenalidomide) and disease refractory to the last treatment regimen preceding study entry (Table 3).[26] In 003-A0, patients received carfilzomib 20 mg/m^2 IV on days 1, 2, 8, 9, 15 and 16 every 28 days for up to 12 cycles. Patients enrolled in 003-A1 received carfilzomib 20 mg/m^2 IV in cycle 1, and then at 27 mg/m^2 for up to 12 cycles (Table 3). Forty-two patients were evaluable for response in 003-A0, with best overall response (ORR) of 16.7% (Table 3).[26] The median duration of response (DOR), based on 7 patients with PR, was 7.2 months. The most common treatment-emergent AEs of any grade were anaemia (73.9%), fatigue (69.6%), and thrombocytopenia

Table 3 Single-agent phase 2 studies of carfilzomib in relapsed or refractory multiple myeloma: dosing schedule and efficacy outcomes[26–29]

Study	Carfilzomib dose (mg/m²)[a]		ORR (%)	CBR (%)	DOR (months)	TTP (months)	PFS (months)	OS (months)
	C1	C2 and beyond						
003-A0 ($n = 46$)	20	20	16.7	23.8	7.2	3.5	3.5	ND
003-A1 ($n = 266$)	20	27	23.7	37.0	7.8	3.9	3.7	15.6
004 (BTZ-treated) ($n = 35$)	20	27	17.1	31.4	>10.6	4.6	4.6	29.9[b]
004 (BTZ-naïve) ($n = 129$)	20	27	47.6	61.9	>13.1	12.0	11.6	NR

[a]Days 1, 2, 8, 9, 15, 16 of 28-day cycle. [b]Estimated. BTZ, bortezomib; CBR, clinical benefit response rate; DOR, duration of response; MM, multiple myeloma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; R/R, relapsed and refractory; R-R, relapsed or refractory; TTP, time to progression.

Table 4 Adverse event profile across phase 2 studies analysed in an integrated safety anaylsis[31]

Adverse event	003-A0 (n = 46)	003-A1 (n = 266)	004 (n = 164)	005 (n = 50)	Total (n = 526)
Adverse events of all grades occurring in ≥25% of patients					
Patients with ≥1 AE	46 (100.0)	266 (100.0)	164 (100.0)	47 (94.0)	523 (99.4)
Fatigue	32 (69.6)	130 (48.9)	102 (62.2)	28 (56.0)	292 (55.5)
Anaemia	34 (73.9)	122 (45.9)	65 (39.6)	25 (50.0)	246 (46.8)
Nausea	16 (34.8)	119 (44.7)	83 (50.6)	18 (36.0)	236 (44.9)
Thrombocytopenia	23 (50.0)	103 (38.7)	50 (30.5)	15 (30.0)	191 (36.3)
Dyspnoea	13 (28.3)	90 (33.8)	65 (39.6)	14 (28.0)	182 (34.6)
Diarrhoea	15 (32.6)	86 (32.3)	53 (32.3)	18 (36.0)	172 (32.7)
Pyrexia	15 (32.6)	83 (31.2)	51 (31.1)	11 (22.0)	160 (30.4)
Upper respiratory tract infection	17 (37.0)	71 (26.7)	52 (31.7)	9 (18.0)	149 (28.3)
Headache	12 (26.1)	74 (27.8)	51 (31.1)	8 (16.0)	145 (27.6)
Cough	13 (28.3)	65 (24.4)	51 (31.1)	8 (16.0)	137 (26.0)
Adverse events of Grade 3/4 occurring in ≥10% of patients					
Patients with ≥1 AE	39 (84.8)	231 (86.8)	107 (65.2)	45 (90.0)	422 (80.2)
Thrombocytopenia	12 (26.1)	77 (28.9)	24 (14.6)	10 (20.0)	123 (23.4)
Anaemia	17 (37.0)	63 (23.7)	24 (14.6)	14 (28.0)	118 (22.4)
Lymphopenia	13 (28.3)	52 (19.5)	21 (12.8)	9 (18.0)	95 (18.1)
Pneumonia[a]	5 (10.9)	25 (9.4)	19 (11.6)	6 (12.0)	55 (10.5)
Neutropenia	2 (4.3)	29 (10.9)	20 (12.2)	3 (6.0)	54 (10.3)

[a]One Grade 5 event of pneumonia in 003-A1.

(50.0%) (Table 4).[26] Common Grade 3/4 AEs were primarily haematologic and included anaemia (37.0%), lymphopenia (28.3%) and thrombocytopenia (26.1%). PN and neuropathy-related AEs were generally mild and infrequent during the study. In 003-A1, 266 patients were evaluable for safety, while 257 were evaluable for efficacy.[27] Patients had received a median of five prior lines of therapy prior to study entry. Best ORR was 23.7% (Table 3).[27] The DOR was 7.8 months and median OS was 15.6 months. Subset analyses by number and type of prior therapies and by favourable vs unfavourable cytogenetic profile indicated similar rates of response. The most common AEs were fatigue (48.9%), anaemia (45.9%), nausea (44.7%) and thrombocytopenia (38.7%) (Table 4). There was no evidence of cumulative toxicities. New-onset PN was infrequent during the study, and only 2 patients experienced Grade 3 or higher neuropathy.

PX-171-004 was a phase 2, open-label, multicenter clinical trial that enrolled patients with RRMM following one to three prior therapies (Table 3). The cohort of patients who had received prior bortezomib (n = 35) received carfilzomib 20 mg/m² IV on days 1, 2, 8, 9, 15 and 16 every 28 days for up to 12 cycles.[28] The ORR was 17.1% (Table 3). The median DOR was >10.6 months and the median time to progression was 4.6 months. More than 25% of patients completed 12 cycles of treatment. The most common AEs were fatigue (62.9%), nausea (60.0%) and vomiting (42.9%). No exacerbation of baseline PN was observed, and there were no dose reductions or discontinuations due to PN.[28] The 129 bortezomib-naïve patients were separated

into cohort 1 (carfilzomib 20 mg/m² for all cycles) and cohort 2 (carfilzomib 20 mg/m² for cycle 1 and 27 mg/m² for all subsequent cycles). ORR was 42.4% in cohort 1 and 52.2% in cohort 2. For cohort 1, median DOR was 13.1 months and median time to progression (TTP) was 8.3 months. Neither median DOR nor median TTP was reached in cohort 2. More than 35% of patients completed a full 12 cycles of treatment. The most common treatment-emergent AEs were fatigue (62.0%) and nausea (48.8%), and there was a low overall incidence of PN (17.1%; no Grade 4).[29]

Because these phase 1 and 2 studies demonstrated efficacy and acceptable tolerability, patients were eligible for inclusion in an extension study (PX-171-010).[30] As of June 2012, 89 patients with MM had enrolled and patients had received a median of 10.5 cycles of carfilzomib during the extension study (a median of 22 cycles in previous study + the extension study). There was no evidence of unique or late-onset cumulative toxicity.

Combination studies in relapsed multiple myeloma

An initial phase 1b/2 study (PX-171-006) evaluated a combination of escalating doses of carfilzomib and lenalidomide with low-dose dexamethasone in patients with RRMM.[24] The ranges for carfilzomib (IV infusion over 2–10 min) and lenalidomide were 15–27 mg/m² (D1, 2, 8, 9, 15, 16) and 10–25 mg (D1–21), respectively, and the dexamethasone dose was 40 mg (D1, 8, 15, 22), given in 28-day

cycles. MTD was not reached, and the combination of the highest doses tested was well tolerated. Most AEs were reversible and manageable, and prolonged administration did not uncover any new or overlapping toxicities. AEs ≥ Grade 3 were mainly haematologic. Responses ≥ very good partial response (VGPR) were seen at all dose levels, and ORR was 78% at the highest dose level.[24]

Adverse events

General safety and tolerability

Across all phase 2 studies, the majority of patients experienced at least one treatment-emergent AE during treatment (Table 4).[31] The most common AEs of any grade were fatigue, anaemia and nausea. The most common Grade ≥3 AEs were primarily haematologic and included thrombocytopenia (23.4%), anaemia (22.4%), lymphopenia (18.1%) and pneumonia (10.5%). SAEs were reported in 45% of patients.[9] The most common SAEs regardless of causality across phase 2 studies were pneumonia, acute renal failure, pyrexia, congestive heart failure, dyspnoea, hypercalcemia and pathologic fracture. AEs resulting in discontinuation of therapy occurred in 15% of patients.[9]

Warnings and precautions for use

First-dose effects, infusion reactions and tumour lysis syndrome

Symptoms including fever, chills, arthralgia and other related reactions have occurred during and up to 24 h following infusion. In a phase 1 study, at a dose of 27 mg/m², 3 of 5 patients had a reversible Grade 2 increase in creatinine associated with a rapid decline in M-protein without evidence of tumour lysis syndrome (TLS) noted on day 2 of treatment.[23] In phase 2 studies, the escalated regimen was used, along with premedication with dexamethasone to mitigate possible infusion-related reactions,[27,29] and this approach is recommended in the prescribing information.[9]

Carfilzomib has been associated with TLS in <1% of patients across phase 2 clinical trials;[9] but patients with relapsed MM and high tumour burden may be at higher risk. These patients should be well-hydrated and monitored closely for signs or symptoms of emerging TLS.[9] Other TLS prophylaxis strategies should also be implemented as indicated.

Haematologic events

Haematologic events comprise the majority of Grade 3/4 AEs occurring in >10% of patients (see Table 4). Complete blood counts should be monitored regularly during therapy. Specific recommendations for holding or reducing doses are included in the prescribing information.[9] Thrombocy-

topenia in phase 2 studies was transient and cyclic, with platelet counts predictably decreasing to a nadir by day 8 of the 28-day cycle and returning to normal by the first day of the subsequent cycle.[31] There has been no evidence of cumulative thrombocytopenia or clinically significant bleeding associated with thrombocytopenia. Febrile neutropenia was reported in only 1% of patients. Across the studies, dose reductions and discontinuations due to haematologic AEs were ≤1.1%.[32]

Peripheral neuropathy (PN)

A relatively low incidence of PN was reported (13.9% overall) across all phase 2 studies.[31] Of 526 patients only 1.3% had Grade 3 PN, and no ≥ Grade 4 PN was reported. Despite a large proportion (71.9%) of patients with active PN (Grade 1 or 2) at study entry, the majority (87.3%) did not report AEs of PN during treatment or within 30 days of the last dose of carfilzomib. Discontinuations and dose modifications in response to PN-related AEs were rare (0.2% and 0.8%, respectively).[33]

Renal events

Hydration is recommended to reduce the potential risk of renal AEs from carfilzomib treatment, particularly in cycle 1.[9] In the clinical trials to date, the majority of patients (63.1%) had some degree of renal dysfunction at the time of study entry.[31,34] The majority of renal AEs were Grade 1 or 2.[9] Transient worsening of renal function (defined as ≥2× increase in serum creatinine with a return to baseline) was reported in 6% of patients. Non-transient worsening of renal function was reported in 7% of patients. Thirty-eight patients (7%) experienced Grade 3/4 acute renal AEs, of which 31 were Grade 3. Overall, 1.5% of all patients discontinued treatment due to renal AEs, and 50% of patients with acute renal failure AEs required no change in carfilzomib therapy.[34] Additionally, a carfilzomib study involving patients with R/R MM demonstrated no difference in grade or frequency of AEs across groups with varying degrees of renal dysfunction.[22]

Cardiac and pulmonary events

Cardiac failure events (including congestive heart failure, pulmonary oedema and decreased ejection fraction) were reported in 7% of patients regardless of causality, and death due to cardiac arrest in patients with a history of cardiac conditions has occurred during carfilzomib treatment.[9] Cardiac events resulting in treatment discontinuation occurred in 23 patients (4.4%) and included congestive heart failure (1.7%), arrhythmia (1.1%) and ischemic heart disease (1.0%).[35] Patients should be closely monitored for

new or worsening cardiac symptoms. Patients with existing significant cardiac history were excluded from clinical trials and may be at higher risk.[9]

Dyspnoea (grouped by multiple dyspnea terms) occurred in 42.2% of patients.[35] The majority of the dyspnoea events were Grade 1 or 2, with 4.8% of patients reporting Grade 3 and one death occurring in the clinical setting of congestive heart failure. Patients who develop dyspnoea during treatment should not receive further doses until symptoms have resolved or returned to baseline.[9]

Carcinogenicity/mutagenicity and reproductive effects

Formal carcinogenicity or teratogenicity studies have not been conducted in humans, although carfilzomib has caused embryo-foetal toxicity in animal studies.[9] There have been no adequate or well-controlled studies of carfilzomib in pregnant or nursing mothers.

Preparation and administration

Carfilzomib for Injection (Kyprolis®, Onyx Pharmaceuticals, South San Francisco, CA) is supplied as a lyophilized powder in 60-mg single-use vials. Prior to administration, the lyophilized product is reconstituted with sterile water for injection to yield a 2 mg/ml solution[29] of carfilzomib. Lyophilized carfilzomib should be stored in a refrigerator (2–8°C); transient temperature excursion data are not available. Reconstituted solution is stable for 24 h refrigerated or 4 h at ambient room temperature. Prepared doses should be used immediately.

Per prescribing information, carfilzomib should be administered via IV infusion over 2–10 min and can be given without further dilution (as 2 mg/ml solution) or further diluted in 50 ml of 5% dextrose solution. Carfilzomib has also been administered IV over 30 min in some clinical trials.[25,36] Longer or alternative administration techniques may improve safety and tolerability. Carfilzomib may be administered via either central or peripheral access. There is no compatibility information available with other parenteral drugs, so patients should have a dedicated line or port for drug administration, and the line should be flushed before and after administration with either 0.9% NaCl or 5% dextrose solution.[9] Carfilzomib is not considered a vesicant, but the infusion site should be evaluated for local reactions.

Dosing

Carfilzomib is dosed based on body surface area (BSA), which should be capped at 2.2 m². Actual body weight and the same formula should be used to calculate BSA throughout dosing.

The approved dosing schedule for carfilzomib is on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle, at a dose of 20 mg/m² in cycle 1, escalating to 27 mg/m² in cycle 2 and thereafter. Premedication with dexamethasone is recommended for all doses in cycle 1 and the first doses of cycle 2 to reduce the incidence and severity of possible acute reactions. Adequate hydration beginning in cycle 1 and continuing throughout treatment is recommended to reduce the risk of renal toxicity and TLS. Alternative dosing strategies (described above) are being investigated, and these may allow escalation to doses of up to 56 mg/m² or higher.[25]

Future directions

Table 5 lists ongoing studies for single-agent and combination carfilzomib therapy. Combination regimens that include a PI are among the current NCCN category 1 recommendations for MM treatment and form the basis for exploring carfilzomib as part of novel combinations, with a goal of improving clinical responses without the need to manage overlapping or DLTs.[37] Immunomodulatory drugs sensitize MM to PI inhibitors, which may improve clinical activity in combination.[38] In addition, pharmacogenomic modelling studies are underway to help identify those patients most likely to benefit from PI therapy.[38] These results may help to further clarify the optimal use of carfilzomib in treating patients with MM.

Initial (frontline) therapy

All current category 1 NCCN recommendations for newly diagnosed patients involve at least two drug combinations.[37] Based on these recommendations and on the safety profile of carfilzomib, there are several phase 2 studies of frontline combination therapy with carfilzomib (Table 5). In the CRd trial, carfilzomib doses up to 36 mg/m² were given in an escalated approach, and results have shown the three-drug combination to be well tolerated and highly active in patients with both favourable and unfavourable cytogenetics.[36] Overall, progression-free survival (PFS) at 24 months was estimated at 92%. Patients who were eligible received autologous stem cell transplantation (ASCT) or went on to receive CRd and eventually lenalidomide alone as maintenance therapy. These results are supported by a similar study (NCT01402284) in which CRd followed by lenalidomide maintenance and delayed ASCT was effective and tolerable.[39]

The CARTHADEX (CTd) trial is evaluating carfilzomib in combination with thalidomide and dexamethasone in frontline induction and consolidation prior to ASCT, and analysis of the first cohort shows the combination is a rapidly effective induction regimen.[40] Preliminary results of the four-drug regimen being evaluated in the CYCLONE

Table 5 Selected carfilzomib studies in progress

Registration number	Study name and description	Phase	Treatment arms	Status
Relapsed and/or refractory (single agent)				
NCT00511238	PX-171-003	2	Carfilzomib	Active, not recruiting
NCT00530816	PX-171-004	2	Carfilzomib	Active, not recruiting
NCT00721734	PX-171-005; renal impairment	2	Carfilzomib	Active, not recruiting
NCT00531284	PX-171-007; MM and solid tumour	1b/2	Carfilzomib	Recruiting
NCT00884312	PX-171-010; extension protocol	2	Carfilzomib	Active, not recruiting
NCT00999414	Compassionate use	NA	Carfilzomib	Recruiting
NCT01302392	PX-171-011; FOCUS	3	Carfilzomib vs best supportive care	Active, not recruiting
NCT01351623	Study of infusional carfilzomib	2	Carfilzomib 56 mg/m^2	Active, not recruiting
NCT01568866	ENDEAVOR	3	Carfilzomib vs bortezomib	Recruiting
NCT01775553	High-dose carfilzomib	2	Carfilzomib 56 mg/m^2	Not yet recruiting
Relapsed and/or refractory (combinations)				
NCT00603447	PX-171-006	1/2	Carfilzomib with lenalidomide and dexamethasone	Active, not recruiting
NCT01365559	Treatment of bortezomib-RRMM	1/2	Carfilzomib and non-IMiD regimen; Drug vs carfilzomib and IMiD-containing regimen	Recruiting
NCT01372540	Safety and efficacy with ARRY-520	1	ARRY-520 + carfilzomib	Recruiting
NCT01301807	Dose escalation of carfilzomib plus panobinostat	1	Carfilzomib and panobinostat	Recruiting
NCT01496118	Safety and efficacy with panobinostat	1/2	Carfilzomib and panobinostat	Recruiting
NCT01549431	Combination effects of carfilzomib and panobinostat	1	Carfilzomib and panobinostat	Recruiting
NCT01246063	Safety and efficacy with PLD	1/2	Carfilzomib and pegylated liposomal doxorubicin	Recruiting
NCT01464034	Dose finding with pomalidomide	1	Carfilzomib, pomalidomide, dexamethasone	Recruiting
NCT01665794	Dose finding with pomalidomide	1/2	Carfilzomib, pomalidomide, dexamethasone	Recruiting
NCT01080391	PX-171-009; ASPIRE	3	Carfilzomib, lenalidomide, dexamethasone vs lenalidomide dexamethasone	Active, not recruiting
NCT01297764	QUAD	1/2	Vorinostat, lenalidomide, carfilzomib, dexamethasone	Recruiting
NCT01690143	Conditioning study	1/2	Carfilzomib+high-dose melphalan	Recruiting
NCT01677858	Weekly carfilzomib + dexamethasone	1/2	Carfilzomib + dexamethasone	Recruiting
First-line combinations				
NCT01029054	CRd	1/2	Carfilzomib, lenalidomide, dexamethasone	Recruiting
NCT01057225	CYCLONE (CCyTd)	1/2	Carfilzomib, cyclophosphamide, thalidomide, dexamethasone	Recruiting
NCT01279694	CARMYSAP (Elderly patients)	1/2	Carfilzomib, melphalan, prednisone	Recruiting
NCT01346787	CCD	2	Carfilzomib, cyclophosphamide, dexamethasone	Recruiting
NCT01402284	CRd	2	Carfilzomib, lenalidomide, dexamethasone	Recruiting
NCT01559935	Car-BiRD (Sequential treatment)	2	Carfilzomib, dexamethasone, clarithromycin, lenalidomide	Recruiting
NCT01660750	11-MM-01	1	Carfilzomib, cyclophosphamide, dexamethasone	Recruiting
NTR2422; EUCTR2009-014922-40-NL	CARTHADEX (CTd)	1/2	Carfilzomib, thalidomide, dexamethasone	Ongoing but not recruiting

(CCyTd) trial have shown a 96% response rate after four cycles, with manageable toxicities.[41]

A trial of carfilzomib, melphalan and prednisone (CMP) for frontline treatment in the elderly is currently underway. Preliminary results have shown an ORR of 92%, which compares favourably with other regimens evaluated in this population.[42] Another study in elderly patients is investigating carfilzomib, cyclophosphamide and dexamethasone; the combination has been well-tolerated in this population, and preliminary results show all response-evaluable patients achieving at least a partial response.[43]

Taken as a whole, the preliminary results of these and other frontline regimens show promise for combination therapies using carfilzomib. Questions remain, including the long-term tolerability and durability of clinical response, the role of maintenance therapy, and the optimal dose and regimen of each drug in the combination.

Maintenance therapy

Continued or maintenance therapy after ASCT has been shown to reduce the risk of relapse, but the only current NCCN category 1 recommendation is for lenalidomide as monotherapy[37] and there are emerging safety concerns with long-term lenalidomide therapy.[44] Based on promising results from the frontline CRd study,[36] there may be a role for carfilzomib in combination in maintenance therapy, with or without ASCT. The results of the CARTHADEX trial show that when the carfilzomib combination is used as consolidation, there is a significant upgrade of responses.[40]

Long-term use of carfilzomib, either as a single agent or in combination, has been shown to be tolerable in an extension trial following previous use of carfilzomib. Dosing either twice a week or in a reduced regimen of once a week has been shown to be effective and tolerable.[30]

Salvage therapy

Studies are also in progress to evaluate carfilzomib in combination regimens in the relapsed populations. ENDEAVOR, a phase 3 trial comparing carfilzomib + dexamethasone to bortezomib + dexamethasone in relapsed patients, is underway (NCT01568866). The ASPIRE trial, a phase 3 randomized controlled study comparing CRd to lenalidomide + dexamethasone (Rd) in relapsed patients, is also currently enrolling (NCT01080391). FOCUS (NCT01302392) is a European registrational study evaluating single-agent carfilzomib in patients in comparison to a best supportive care regimen.[45]

Other agents, including the histone deacetylase (HDAC) inhibitors (panobinostat, vorinostat, tubacin) and the Akt inhibitor perifosine, have shown in-vitro synergy and MM cytotoxicity used in combination with PIs.[46,47] Combination therapy with CRd + vorinostat has shown promise in certain subpopulations of RRMM patients,[46] and recent results from two dose-escalation studies combining carfilzomib and panobinostat show the combination to have a manageable safety profile[48,49] and promising efficacy in very heavily pre-treated patients.[48] The novel kinesin spindle protein (KSP) inhibitor ARRY-520 has shown benefit in RRMM treatment, and a phase 1 study, in progress, combining ARRY-520 and carfilzomib, reports the combination to have limited haematologic toxicity and a manageable side-effect profile with early signs of efficacy.[50] A phase 1/2 study is also underway combining various doses of carfilzomib given in an escalated regimen with pegylated liposomal doxorubicin (NCT01246063). In addition, two studies are underway to determine safety, MTD and efficacy of carfilzomib in combination with pomalidomide and dexamethasone in patients with relapsed/refractory disease (NCT01464034 and NCT01665794), and early reports indicate the combination is well tolerated and achieves high response rates in heavily pre-treated patients.[51]

As with the frontline regimens, additional studies, including a phase 3 trial, will likely be necessary to answer questions regarding long-term durability of response, the role of carfilzomib combination regimens in maintenance therapy, and the optimal dose and regimen of drugs in the combination.

Optimal dosing strategies

Although an MTD of 56 mg/m^2 was defined in patients with RRMM in the PX-171-007 study, doses up to 70 mg/m^2 have been administered, with increased PD response.[25] It is possible that alternative dosing regimens (e.g. once weekly dosing) may prove to be well tolerated with improved outcomes.[30] Carfilzomib monotherapy in patients with RRMM has been well-tolerated when given as a 30-min infusion in escalated regimens up to 56 mg/m^2.[25,52] Combining this regimen with low-dose dexamethasone appears to decrease some carfilzomib-related AEs.[53] Additionally, based on results from the frontline CRd study, when used in combination, carfilzomib doses of 36 mg/m^2 in an escalated fashion are well tolerated.[36] Several trials will continue to evaluate similar or higher dosing regimens. The Car-BiRd study (NCT01559935) will employ carfilzomib doses of 45 mg/m^2, and the CCD study is evaluating 20/36 mg/m^2 escalated dosing of carfilzomib in combination with cyclophosphamide and dexamethasone (NCT01346787).

Other malignancies and diseases

Additional in-vitro and phase 1 studies of carfilzomib have suggested the potential for activity in other haematologic malignancies, including diffuse large B-cell lymphoma, Hodgkin's lymphoma, Waldenström's macroglobulinemia,

mantle-cell lymphoma and chronic lymphocytic leukemia.[17,21,23,54,55] Based on responses seen with bortezomib, carfilzomib may also have a role in organ transplantation and graft vs host disease.[56] In these settings, carfilzomib offers the potential advantage of higher doses or longer durations of therapy due to the lower incidence of dose-limiting PN relative to that seen with bortezomib.

Conclusions

Carfilzomib is an important new addition to the array of drugs available to treat patients with RRMM. It has shown rapid, durable responses and an acceptable tolerability profile in heavily pre-treated patients. There has been no evidence of cumulative or significant treatment-limiting toxicity, despite prior treatment with bortezomib and immunomodulatory drugs in the majority of patients. Additionally, carfilzomib has demonstrated potential for long-term use without the need for dose adjustment or interruption. Management measures exist to mitigate the risk for AEs, even in patients with advanced disease or otherwise considered to be at high risk. While questions remain regarding optimal dosing strategies, either alone or in combination, and utility in other populations and diseases, carfilzomib fills an unmet need in the treatment of RRMM, as it offers an important treatment option for patients who have either failed or cannot tolerate other treatments. In addition, carfilzomib shows promise in frontline MM treatment, as well as other malignancies.

Declarations

Conflict of interest

Kimberly Redic participated in an Onyx Pharmacy Advisory Board in January 2012 and is a member of the Onyx Speakers Bureau.

Acknowledgements

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