Clinical Pharmacology: Advances and Applications

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REVIEW

Incidence and management of adverse events in patients with relapsed and/or refractory multiple myeloma receiving single-agent carfilzomib

This article was published in the following Dove Press journal:
Clinical Pharmacology: Advances and Applications
8 May 2014
Number of times this article has been viewed

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Abstract: Carfilzomib, a selective proteasome inhibitor approved in the USA in 2012, is a single agent for relapsed and refractory multiple myeloma. Carfilzomib is administered as a 2–10-minute infusion on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle at a starting dose of 20 mg/m^2 for cycle 1 and a target dose of 27 mg/m^2 thereafter. In the pivotal Phase II study (PX-171-003-A1), carfilzomib 20/27 mg/m^2 provided durable responses in a heavily pretreated population with relapsed and refractory multiple myeloma (n=266), with an overall response rate of 22.9% and a median duration of response of 7.8 months. In an integrated safety analysis of four Phase II studies, common adverse events (32.7%–55.5%) included fatigue, anemia, nausea, thrombocytopenia, dyspnea, and diarrhea. Grade 3/4 adverse events were generally hematologic and included thrombocytopenia (23.4%), anemia (22.4%), and lymphopenia (18.1%). Serious adverse events included pneumonia (9.9%), acute renal failure (4.2%), pyrexia (3.4%), and congestive heart failure (3.4%). New or worsening peripheral neuropathy was infrequent (13.9% overall, 1.3% grade 3, no grade 4). This review discusses findings of the integrated safety analysis and provides practical experience from a single institution in managing treatment-related and disease-related adverse events. Individualized treatment with proactive management of side effects and complications allows patients with advanced multiple myeloma to remain on carfilzomib for extended periods.

Keywords: carfilzomib, relapsed, refractory, myeloma, safety, adverse events, toxicity

Introduction

Multiple myeloma (MM), the second most common hematologic cancer, is characterized by uncontrolled clonal proliferation of malignant plasma cells within the bone marrow, with associated monoclonal immunoglobulin and protein fragments in blood and urine. Patients often present with hypercalcemia, renal insufficiency, anemia, and/or bone lesions (mnemonically referred to as CRAB), and frequently experience hyperviscosity, fractures, fatigue, and recurrent infections, the leading cause of death in MM, particularly pneumonia.[1–3] The introduction of targeted therapies, including proteasome inhibitors and immunomodulatory drugs, over the past decade has improved outcomes and survival,[4–6] but nearly all patients relapse and die from progression of the disease.

At the time of disease progression, patients have usually received multiple treatments, and frequently experience cumulative toxicities, including myelosuppression, cardiac toxicities, and peripheral neuropathy.[7] Pulmonary and cardiac comorbidities are common[8] and may be exacerbated by chronic anemia and anti-MM therapies,[9]

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and patients with relapsed and refractory MM (RRMM) are predisposed to pulmonary infections.[2]

Carfilzomib (Kyprolis®, Onyx Pharmaceuticals, Inc., South San Francisco, CA, USA) is a selective proteasome inhibitor that received approval in the USA in 2012 for the treatment of patients with RRMM who have received at least two prior therapies (including bortezomib and an immunomodulatory agent) and have disease progression on or within 60 days of completion of the last therapy.[10] In the pivotal Phase II study (PX-171-003-A1), single-agent treatment with carfilzomib resulted in an overall response rate of 22.9% and a median duration of response of 7.8 months.[11] It was well tolerated, with low rates of dose reductions and discontinuations due to adverse events (AEs).

Recently, an integrated safety analysis for the four Phase II studies of carfilzomib in patients with RRMM was performed to better characterize the safety profile of carfilzomib.[12] This review highlights the results of the integrated safety analysis and provides practical recommendations for preventing and managing AEs in order to maintain dose intensity, prolong treatment duration, and support quality of life, including recommendations from a large myeloma center at the Winship Cancer Institute of Emory University that participated in these trials.

Phase II studies: design and carfilzomib dosing

Table 1[11–16] provides a brief overview of the study design and dosing schema for the four Phase II clinical trials included in the integrated safety analysis: PX-171-003-A0 (NCT00511238),[13,17] PX-171-003-A1 (NCT00511238),[11] PX-171-004 (NCT00530816),[14,15,18] and PX-171-005 (NCT00721734).[16,19] Similarities and differences among these studies are worth noting. The 003-A0 and pivotal 003-A1 studies required refractory MM and prior exposure to bortezomib and immunomodulatory drugs, while the others did not. The 005 study investigated the use of carfilzomib in patients with varying levels of renal impairment, including patients on chronic hemodialysis, while the other studies required patients to have a creatinine clearance ≥30 mL per minute.

Across the Phase II studies, patients received single-agent carfilzomib at doses ranging from 15 to 27 mg/m^2 on a 28-day cycle. At the approved dose, carfilzomib is administered via a 2–10-minute infusion on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. During cycle 1, patients receive a starting dose of 20 mg/m^2, and if tolerated, the dose can be increased to a target of 27 mg/m^2 per infusion during cycle 2 and beyond.[10] Subtherapeutic dexamethasone (4 mg) can and should be administered prior to carfilzomib during cycle 1 to reduce infusion reactions and in subsequent cycles as indicated.

Patient population in Phase II studies

In the population included in the integrated safety analysis, patients were predominantly Caucasian (72.4%) and male (57.4%), with a median age of 64 (37–87) years and a median time since diagnosis of 4.8 (0.5–24.4) years.[12] The distribution of European Cooperative Oncology Group

Table 1 Overview of Phase II safety study designs[11–16]

	PX-171-003-A0 NCT00511238[17]	PX-171-003-A1 NCT00511238[17]	PX-171-004 NCT00530816[18]	PX-171-005 NCT00721734[19]
Key eligibility criteria				
Prior therapy	▪ Relapsed and refractory ▪ ≥2 prior regimens ▪ Responded to ≥1 regimen ▪ Refractory to most recent ▪ Prior tx with bortezomib, IMiD, anthracycline, and alkylating agents	▪ Relapsed and refractory ▪ ≥2 prior regimens ▪ Responded to ≥1 regimen ▪ Refractory to most recent ▪ Prior tx with bortezomib, IMiD, anthracycline, and alkylating agents	▪ Relapsed and/or refractory ▪ 1–3 prior regimens ▪ Responded to 1st-line regimen	▪ Relapsed, refractory, and/or progressive ▪ ≥2 prior regimens ▪ Responded to ≥1 regimen
Other	▪ ECOG PS 0–2 ▪ No significant CVD[a] ▪ No grade 3/4 PN or grade 2 with pain	▪ ECOG PS 0–2 ▪ No significant CVD[a] ▪ No grade 3/4 PN or grade 2 with pain	▪ ECOG PS 0–2 ▪ No significant CVD[a] ▪ No grade 3/4 PN or grade 2 with pain	▪ ECOG PS 0–2 ▪ No significant CVD[a] ▪ No grade 3/4 PN or grade 2 with pain
Lab values				
Platelets	≥50,000/mm^3	≥50,000/mm^3	≥50,000/mm^3	≥30,000/mm^3
Hb	≥8 g/dL	≥8 g/dL	≥8 g/dL	≥7 g/dL
ANC	≥1,000/mm^3	≥1,000/mm^3	≥1,000/mm^3	≥1,000/mm^3
AST/ALT	<3× ULN	<3× ULN	Adequate hepatic function	Adequate hepatic function
CrCl	>30 mL/min	>30 mL/min	>30 mL/min	Various levels of RI
Treatment				
Carfilzomib dose[b]	20 mg/m^2	20/27 mg/m^2[c]	20 or 20/27 mg/m^2[c]	15/20/27 mg/m^2[d]
Max planned cycles	12 cycles	12 cycles	12 cycles	12 cycles

Notes: [a]New York Heart Association Class III–IV heart failure or recent myocardial infarction/unstable angina were excluded; [b]administered as a 2–10 min intravenous infusion on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle; [c]starting dose of 20 mg/m^2 in cycle 1, target dose of 27 mg/m^2 thereafter; [d]starting dose 15 mg/m^2 for cycle 1, 20 mg/m^2 for cycle 2 with target dose of 27 mg/m^2 thereafter.

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CrCl, creatinine clearance; CVD, cardiovascular disease; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; IMID, immunomodulatory drug; min, minute; PN, peripheral neuropathy; PS, performance status; RI, renal insufficiency; ULN, upper limit of normal.

performance status was 29.7%, 58.4%, and 11.6% for scores of 0, 1, and 2, respectively. Patients were heavily pretreated with a median of four prior regimens, with many refractory to lenalidomide (69.6%), bortezomib (51.7%), and thalidomide (39.7%). At study entry, patients had a number of comorbidities and disease-related and treatment-related complications, the most common being hematologic, including anemia (89.3%), lymphopenia (65.4%), neutropenia (64.4%), and thrombocytopenia (37.4%).[20] Additionally, 73.6% of patients had a history of cardiovascular events, and 70.0% were receiving one or more cardiac medications at study entry. Most patients (84.8%) had a history of peripheral neuropathy.[12] Across the four Phase II studies, 23.8% of patients had moderate to severe renal dysfunction (creatinine clearance <50 mL per minute), and 39.4% had mild renal dysfunction (creatinine clearance 50 to <80 mL per minute).

Overall analysis

Safety and tolerability of carfilzomib

The integrated safety analysis further defines the safety and tolerability of single-agent carfilzomib. The median number of cycles given was four (range 1–21), with 19.0% of patients starting ≥12 cycles and 51.0% discontinuing treatment prior to 12 cycles due to disease progression; 14.6% required a dose reduction due to an AE and 14.8% discontinued treatment due to an AE (Table 2).[12]

Table 3[12,21] summarizes AEs that emerged during treatment, and Table 4[12] provides rates for AEs grouped by organ system, including cardiac, pulmonary, and renal. The most common AEs overall included fatigue, anemia, nausea, dyspnea, and diarrhea (range 32.7%–55.5%).[12] AEs of grade ≥3 in severity were generally hematologic, and included thrombocytopenia, anemia, lymphopenia, and neutropenia (range 10.3%–23.4%). Nonhematologic AEs associated with carfilzomib were generally grade 1/2 in severity, although serious AEs did include pneumonia (9.9%), acute renal failure (4.2%), pyrexia (3.4%), and congestive heart failure (3.4%).

Overall, there were 37 deaths on study or within 30 days of the last dose. Of these, seven were the result of AEs deemed at least possibly related to carfilzomib, including cardiac arrest (n=2), hepatic failure (n=1), dyspnea (n=1), multiorgan failure (n=1), cardiac disease (n=1), and death from unknown cause (n=1).[12]

The following sections will discuss AEs of clinical interest in more depth, along with approaches to mitigate their incidence and severity in order for patients to maintain carfilzomib treatment and dose intensity (Table 5[10,22,23]).

Hematologic AEs

Among AEs considered related to carfilzomib treatment, hematologic events were generally the most common, with rates of 28.3% for thrombocytopenia, 26.8% for anemia, 17.7% for lymphopenia, and 16.0% for neutropenia.[12,20] Generally, these events were transient and manageable, and serious clinical sequelae, such as fever and bleeding events, were rare. In general, patients receiving carfilzomib should be closely monitored with a complete blood count before each dose in addition to standard supportive care, as discussed in the following subsections.

Thrombocytopenia

Thrombocytopenia was transient and cyclic, with platelets 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.[12,20] No clinically significant bleeding events associated with thrombocytopenia or cumulative thrombocytopenia were reported. Decrease in platelet count was generally managed with platelet transfusions as per institutional

Table 2 Patient disposition

PX-171	003-A0 n=46	003-A1 n=266	004 n=164	005 n=50	ISA n=526
Median cycles (n)	3	4	6	4	4
Dose reduced due to AE, n (%)	3 (6.5)	47 (17.7)	18 (11.0)	9 (18.0)	77 (14.6)
≥12 cycles or on therapy,* n (%)	4 (8.7)	40 (15.0)	55 (33.5)	16 (32.0)	115 (21.9)
<12 cycles, n (%)	42 (91.3)	226 (85.0)	109 (66.5)	34 (68.0)	411 (78.1)
Progressive disease	23 (50.0)	157 (59.0)	64 (39.0)	24 (48.0)	268 (51.0)
AE	13 (28.3)	33 (12.4)	26 (15.9)	6 (12.0)	78 (14.8)
Withdrew consent	2 (4.3)	22 (8.3)	9 (5.5)	4 (8.0)	37 (7.0)
Other	4 (8.7)	14 (5.3)	10 (6.1)	0 (0)	28 (5.3)

Notes: *At data cutoff. Obtained from Haematologica/the Hematology Journal website http://www.haematologica.org.[12]
Abbreviations: AE, adverse event; ISA, integrated safety analysis.

Table 3 Integrated analysis of adverse events from four Phase II studies of single-agent carfilzomib in patients with relapsing and remitting multiple myeloma (n=526)

	All grades n (%)	All grades related[a] n (%)	Grades 3/4 n (%)	SAE[b] n (%)
Hematologic				
Anemia	246 (46.8)	141 (26.8)	118 (22.4)	7 (1.3)
Thrombocytopenia	191 (36.3)	149 (28.3)	123 (23.4)	6 (1.1)
Lymphopenia	126 (24.0)	93 (17.7)	95 (18.1)	0
Neutropenia	109 (20.7)	84 (16.0)	54 (10.3)	2 (0.4)
Leukopenia	71 (13.5)	56 (10.6)	28 (5.3)	0
Nonhematologic				
Fatigue	292 (55.5)	218 (41.4)	40 (7.6)	0
Nausea	236 (44.9)	185 (35.2)	7 (1.3)	0
Dyspnea	182 (34.6)	107 (20.3)	26 (4.9)	11 (2.1)
Diarrhea	172 (32.7)	118 (22.4)	5 (1.0)	3 (0.6)
Pyrexia	160 (30.4)	79 (15.0)	9 (1.7)	18 (3.4)
Upper respiratory tract infection	149 (28.3)	38 (7.2)	17 (3.2)	5 (1.0)
Headache	145 (27.6)	83 (15.8)	7 (1.3)	0
Cough	137 (26.0)	39 (7.4)	1 (0.2)	1 (0.2)
Increased serum creatinine	127 (24.1)	93 (17.7)	14 (2.7)	7 (1.3)
Peripheral edema	126 (24.0)	56 (10.6)	3 (0.6)	0
Vomiting	117 (22.2)	85 (16.2)	5 (1.0)	2 (0.4)
Constipation	110 (20.9)	57 (10.8)	1 (0.2)	0
Back pain	106 (20.2)	12 (2.3)	15 (2.9)	1 (0.2)
Pneumonia[c]	67 (12.7)	24 (4.6)	55 (10.5)	52 (9.9)

Notes: [a]Possibly or probably related to carfilzomib treatment; [b]hospitalization or prolongation of existing hospitalization, life-threatening, or led to death; [c]one grade 5 event in study 003-A1. Adverse events graded according to the National Cancer Institute Common Terminology Criteria.[21] Obtained from Haematologica/the Hematology Journal website http://www.haematologica.org.[12]
Abbreviation: SAE, serious AEs.

guidelines, and, rarely, dose reduction. Dose reduction and discontinuation rates due to thrombocytopenic AEs were low (1.1% and 1.0%, respectively).

In clinical practice, carfilzomib should be withheld for grade 4 thrombocytopenia,[10] and platelet transfusion should be considered as indicated (eg, active bleeding, asymptomatic platelet count $<10{,}000/mm^3$). The etiology of thrombocytopenia should also be considered, as its presentation may be related to disease where aggressive therapy may lead to improved platelet counts. At Emory, we treat patients with platelet counts $>25{,}000/mm^3$, recognizing the elasticity of platelet recovery following treatment. The carfilzomib treatment schedule allows for frequent assessment of blood counts, and therefore a greater understanding of an individual's nadir and peak platelet counts.

Table 4 Integrated analysis of AE by grouped-term organ system from four Phase II studies of single-agent carfilzomib in patients with relapsing and remitting multiple myeloma (n=526)

	Any AE n (%)	≥grade 3 n (%)	SAE n (%)
Any cardiac	116 (22.1)	50 (9.5)	41 (7.8)
Cardiac arrhythmia	70 (13.3)	12 (2.3)	11 (2.1)
Cardiac failure	38 (7.2)	30 (5.7)	26 (4.9)
Ischemic heart disease	18 (3.4)	7 (1.3)	5 (1.0)
Cardiomyopathy	9 (1.7)	3 (0.6)	2 (0.4)
Any respiratory	363 (69.0)	54 (10.3)	34 (6.5)
Dyspnea	222 (42.2)	26 (4.9)	11 (2.1)
Cough	137 (26.0)	1 (0.2)	1 (0.2)
Pneumonia	67 (12.7)	55 (10.5)	52 (9.9)
Any grouped renal impairment	174 (33.1)	38 (7.2)	32 (6.1)
Increased serum creatinine	127 (24.1)	14 (2.7)	7 (1.3)
Acute renal failure	28 (5.3)	23 (4.4)	22 (4.2)
Renal failure	20 (3.8)	6 (1.1)	7 (1.3)

Notes: Obtained from Haematologica/the Hematology Journal website http://www.haematologica.org.[12]
Abbreviations: AE, adverse event; SAE, serious adverse event.

Neutropenia

Neutrophil counts have also been shown to be cyclic with carfilzomib treatment, reaching a nadir at day 15, and returning to normal by day 1 of the next cycle.[20] In the integrated safety analysis, febrile neutropenia occurred infrequently (1.1%), dose reduction and discontinuation rates due to neutropenia were very low (1.1% and 0.2%, respectively), and a shift from grade 0 (absence) neutropenia at baseline to grade 3/4 was uncommon (7/187 patients, 3.7%).[12]

Carfilzomib dose reductions may be used to manage neutropenia. Similar to the management of grade 4

Table 5 Clinical practice recommendations for carfilzomib[10,22,23]

		Emory approach
Prophylaxis		
Hydration • Reduces the risk of renal toxicity and TLS	• Instruct the patient to drink 8 cups of water a day during dosing • 250–500 mL of normal saline should be administered before and after infusion (as needed)	• Use 500 mL normal saline before and after infusion, except in patients at risk for fluid overload (renal, cardiac) where 250 mL volumes are employed
Subtherapeutic dexamethasone • Prevents or alleviates flu-like infusion symptoms	• 4 mg (PO or IV) should be administered before infusion during Cycle 1 with the 20 mg/m^2 starting dose and before all doses during the first cycle of the target dose of 27 mg/m^2	• Use 4 mg before the dose for all infusions except when contraindicated
Allopurinol • Reduces the risk of renal toxicity and TLS	• 100–300 mg PO daily	• Used selectively in patients with high tumor burden (eg, elevated LDH, uric acid, >50% plasma cells on bone marrow examination)
Antivirals (eg, acyclovir, famciclovir, valaciclovir) • Prevents herpes virus infections	• Antiviral agent should be prescribed in patients at risk • Common regimen is acyclovir 400 mg PO BID	• Acyclovir 400 mg PO BID in all patients
Antibacterials (eg, ciprofloxacin, cotrimoxazole, levofloxacin, moxifloxacin) • Prevents infections related to immunosuppression, particularly in patients at risk of certain infections	• Appropriate antibacterial agent should be prescribed in patients at risk	• Co-trimoxazole double strength PO daily MWF in all patients except when contraindicated
Management of AEs		
Hematologic toxicity Neutropenia (grade 3/4) Thrombocytopenia (grade 4)	• Withhold the dose of carfilzomib • If the patient fully recovers before the next scheduled dose, continue at same dose level ○ Thrombocytopenia: if the patient recovers to grade 3 thrombocytopenia, reduce dose by one dose level ○ Neutropenia: if the patient recovers to grade 2 neutropenia, reduce the dose by one dose level[a] • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician	• Assess drug versus disease causes • Hold carfilzomib if ANC <1,000/mm^3, platelets <25,000/mm^3
Cardiac toxicity Grade 3/4 cardiac toxicity; new onset or worsening of congestive heart failure, decreased left ventricular function, or myocardial ischemia	• Withhold the dose of carfilzomib until the event resolves or returns to baseline • After resolution, consider whether the patient should restart at a reduced dose[a] • If reduced dose is tolerated, the dose may be escalated to the previous dose at the discretion of the physician	• Per product information
Pulmonary hypertension or Peripheral neuropathy (grade 3/4)	• Withhold the dose of carfilzomib until the event resolves or returns to baseline • Restart at the dose used before the event or reduce dose[a] at the discretion of the physician • If reduced dose is tolerated, the dose may be escalated to the previous dose at the discretion of the physician	• Per product information
Pulmonary complications (grade 3/4) or Other grade 3/4 nonhematologic toxicities	• Withhold the dose of carfilzomib until the event resolves or returns to baseline • Consider restarting at the next scheduled treatment with one dose level reduction[a] • If reduced dose is tolerated, the dose may be escalated to the previous dose at the discretion of the physician	• Per product information
Hepatic toxicity Grade 3/4 elevation of transaminases, bilirubin, or other liver abnormalities	• Withhold the dose of carfilzomib until the event resolves or returns to baseline • After resolution, consider if restarting carfilzomib is appropriate • If appropriate, reinitiate at a reduced dose[a] with frequent monitoring of liver function • If reduced dose is tolerated, the dose may be escalated to the previous dose at the discretion of the physician	• Hold for AST/ALT >5 times the ULN and bilirubin >3 times ULN • Assess other potential causes • Reinitiate following resolution per product information

(*Continued*)

Table 5 (*Continued*)

		Emory approach
Renal toxicity Serum creatinine ≥2× baseline	• Withhold the dose of carfilzomib until renal function recovers to grade 1 or to baseline; monitor renal function • If renal dysfunction is attributable to carfilzomib, restart the next scheduled treatment at a reduced dose[a] • If renal dysfunction is not attributable to carfilzomib, restart at the dose used before the event • If reduced dose is tolerated, the dose may be escalated to the previous dose at the discretion of the physician	• Assess cause and timing of renal insult • If stabilized, clearly due to myeloma, and early in treatment, consider continuing at same carfilzomib dose • Avoid concurrent nephrotoxins when possible, particularly in first two cycles

Note: [a]From carfilzomib 27 mg/m^2 to 20 mg/m^2 or from carfilzomib 20 mg/m^2 to 15 mg/m^2.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BID, twice daily; IV, intravenously; LDH, lactate dehydrogenase; MWF, Monday, Wednesday, Friday; PO, orally; TLS, tumor lysis syndrome; ULN, upper limit of normal.

thrombocytopenia, carfilzomib should be withheld for patients experiencing grade 3/4 neutropenia.[10] Granulocyte colony-stimulating factor products are also an option and should be used prophylactically in patients at high risk for febrile neutropenia.[24–26] If neutrophil recovery is incomplete or slower than predicted and/or other lineages are affected, differentiation of etiology of neutropenia (drug versus disease) through bone marrow evaluation may be required.

Anemia

Hemoglobin remained stable throughout treatment, and the mean and median nadirs remained at grade 1 in the clinical trials.[12,20] Dose reduction and discontinuation rates due to anemia were very low (0.4% and 0.6%, respectively). Patients should have hemoglobin levels monitored routinely; the dose of carfilzomib does not need to be withheld or modified for anemia that can be managed with standard measures, including red blood cell transfusion when indicated.[10] At Emory, these indications include increasing fatigue, shortness of breath, and/or tachycardia with low hemoglobin levels (≤8 g/dL).

Nonhematologic AEs

Infusion reactions and acute effects

Events within the first 24–48 hours of treatment with carfilzomib include infusion-related reactions, increases in certain laboratory values (ie, creatinine, transaminases), and increased blood pressure. These can occur immediately following or up to 24 hours after administration of carfilzomib. First-dose effects associated with carfilzomib refer to a constellation of symptoms, including fever, chills, and rigors. Infusion-related reactions were characterized by a spectrum of flu-like symptoms, including fever, rigor, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, dyspnea, hypotension, syncope, chest tightness, and angina. The incidence of infusion-related reactions for various symptoms occurring within the first day of dosing in cycle 1 were dyspnea (12%), fever (8%), chills (4%), arthralgia (3%), myalgia (2%), and flushing (1%) (data on file, Onyx Pharmaceuticals, Inc., 2013).

Many of the frequently reported AEs associated with carfilzomib, especially those associated with infusion-related flu-like symptoms, may be prevented or alleviated with proper prophylaxis.[10] Patients should receive subtherapeutic dexamethasone (4 mg) before administration of carfilzomib during cycle 1 with the starting dose of 20 mg/m^2, and before all doses during the first cycle of the 27 mg/m^2 target dose. Prophylaxis with dexamethasone should be reinstated if symptoms develop or reappear during subsequent cycles. Prior to treatment, patients should be educated about the symptoms associated with infusion reactions and instructed to report them should they occur.

Cardiac AEs

In assessing cardiac AEs in heavily pretreated patients with MM, it is important to be mindful of the prevalence of cardiovascular disease at baseline due to age-related and disease-related risks, including exposure to treatments associated with cardiotoxicity, such as anthracyclines, alkylators, proteasome inhibitors, and stem cell transplant.[27–30] In the four Phase II studies, 73.6% of patients had a history of cardiovascular events and 70.0% were receiving a cardiovascular or diabetic medication, although it should be noted that significant cardiovascular disease was an exclusion criterion in these studies (Table 1). Prior treatments in the integrated safety analysis population included bortezomib (75.5%) and anthracyclines (52.5%).[12,31]

Cardiac failure events (eg, congestive heart failure, pulmonary edema, decreased left ventricular function) were reported in 7.2% of patients, and the most common cardiac AEs were arrhythmias; most were low-grade, benign, supraventricular events (ie, tachycardia and palpitations).[12,31]

Cardiac AEs grade ≥3 included cardiac failure (5.7%), cardiac arrhythmia (2.3%), ischemic heart disease (1.3%), and cardiomyopathy (0.6%). The rate of on-study cardiac events did not increase over time. Cardiac AEs resulting in treatment discontinuation (4.4% overall) included congestive heart failure (1.5%), cardiac arrest (1.0%), and myocardial ischemia (0.6%).

Patients receiving carfilzomib should be closely monitored for new or worsening cardiac symptoms, and any symptoms should be managed promptly.[10] For those experiencing new or worsening congestive heart failure symptoms, decreased left ventricular function, or myocardial ischemia, carfilzomib treatment should be withheld until resolution or return to baseline, with subsequent treatment decisions based on careful risk/benefit assessment. At Emory, we have elected to treat patients with proteasome inhibitor-sensitive disease and New York Heart Association Class I–II heart failure with no more than 250 mL of hydration before and after each carfilzomib dose, with close monitoring.

Pulmonary AEs

Dyspnea was reported as a grouped term in 42.2% of patients treated with carfilzomib enrolled in the four Phase II clinical trials (Table 4).[12,31] Most events were mild (grade 1 or 2), transient, occurred within one day of dosing, and resolved without dose reduction or discontinuation. Grade 3 dyspnea was reported by 4.8% of patients; there were no grade 4 events, and one death occurred in the setting of concurrent congestive heart failure. Other pulmonary AEs of clinical importance included pleural effusion in 4% of patients and pulmonary arterial hypertension in 2% of patients.[10,12] Grade 3 pulmonary arterial hypertension was reported in <1% of patients and in three patients was considered possibly related to carfilzomib. No dose reductions due to pulmonary arterial hypertension were reported, but one patient discontinued carfilzomib due to pulmonary arterial hypertension. Cardiopulmonary evaluation (eg, cardiac imaging) to determine the underlying etiology is recommended for patients presenting with signs or symptoms of persistent dyspnea and/or pulmonary arterial hypertension.[10] For grade ≥3 pulmonary events, treatment should be withheld until signs and symptoms resolve or return to baseline. In our experience, dyspnea seen following carfilzomib is self-limiting, and requires no intervention other than patient education. For prolonged episodes, referral to pulmonologists and/or cardiologists may be necessary based on the constellation of symptoms.

Across the four studies, respiratory infections were reported in 18.8% of patients. Pneumonia was the most common respiratory AE (12.7%) and the most common serious AE (9.9%).[12,31] Respiratory infections contributed to the death of two patients on carfilzomib, but neither death was attributed to carfilzomib. A small percentage of patients who experienced pneumonia had dose reduction (0.4%) or discontinued therapy (1.9%).

Prophylaxis with antibacterials can be considered for patients at high risk for infections, including those with recurrences of sinusitis, pneumonia, or urinary tract infections, and patients with decreased immunoglobulins (other than the monoclonal protein) for prolonged periods may be at risk for recurrent infections. At Emory, we consider supplemental intravenous immune globulin for patients with two or more serious infections (eg, requiring hospitalization or two different antimicrobial regimens to resolve).

Renal AEs

In the 005 study, the pharmacokinetics and safety of carfilzomib were evaluated in patients with normal renal function and those with mild, moderate, and severe renal impairment, including patients on chronic hemodialysis.[16] Carfilzomib disposition and AE rate and severity in patients with various degrees of renal insufficiency were similar to patients without renal impairment, demonstrating the utility of carfilzomib in patients with renal insufficiency. Concurrent use of nephrotoxic agents such as bisphosphonates should be carefully considered in patients with renal insufficiency receiving carfilzomib. At Emory, we prefer to give two or more cycles of carfilzomib prior to use of a bisphosphonate for fracture prevention to assess stability of renal function. We give dose-adjusted zoledronic acid to patients with creatinine clearance as low as 30 mL per minute or pamidronate 60 mg over 4–6 hours in patients with creatinine clearance <30 mL per minute.

In the integrated safety analysis, renal function did not worsen during the course of carfilzomib treatment in 87% of patients with post-baseline creatinine values (447/515).[12,32] Among 68 patients with worsening renal function, the median reduction in estimated glomerular filtration rate was 41.99 mL per minute from baseline to the first day of worsening within a median time of 44.5 days. A distinction between drug-related and myeloma-related worsening was not possible. In 46% (31/68) of patients, the effect was transient (ie, serum creatinine resolved to within 20% of baseline values), with a median duration of 1.4 (0.29–21.1) weeks, and no patients discontinued treatment due to renal dysfunction. In 54% (37/68) of patients, the result was nontransient and did not resolve as of the last available creatinine

values, with eight patients discontinuing treatment due to renal dysfunction. Overall, renal AEs resulting in carfilzomib dose reduction or discontinuation were uncommon in the population.

In practice, carfilzomib should be withheld for patients with serum creatinine two or more times the baseline value until renal function has recovered to grade 1 or baseline, with subsequent increased monitoring of renal function.[10] Clinically, if creatinine increases by two or more times the baseline value, frequently the distinction between myeloma and drug causes is clear, ie, total protein values increase substantially in concert with creatinine, indicating disease progression. Clearance of carfilzomib has not been studied during hemodialysis, so it should be administered after the procedure.

Peripheral neuropathy

Across the four Phase II studies, carfilzomib was associated with a low rate of mild to moderate, nondose-limiting peripheral neuropathy and did not exacerbate pre-existing peripheral neuropathy.[12,33] Although the majority of patients (85%) in the Phase II studies had medical histories of peripheral neuropathy, new or worsening peripheral neuropathy occurred infrequently during treatment with carfilzomib (overall 14%, 1% were grade 3, and no grade 4 peripheral neuropathy). Among patients with active peripheral neuropathy at baseline (72% of the population, all grade 1/2), 87% did not report AEs related to peripheral neuropathy at any time during treatment with carfilzomib. Given that most of these peripheral neuropathy events occurred before cycle 6, there was no evidence of a cumulative peripheral neuropathy toxicity. Overall rates of dose modification and discontinuation due to peripheral neuropathy were low (0.8% and 0.2%, respectively).

If grade ≥3 peripheral neuropathy occurs following administration of carfilzomib, treatment should be withheld until it resolves or returns to baseline.[10] In our center's experience, patients with peripheral neuropathy of grade 2 with pain prior to initiating carfilzomib very rarely progress to grade 3 after starting treatment; patients who do experience a worsening of peripheral neuropathy usually have substantial prior thalidomide and/or bortezomib exposure, clouding the etiology of peripheral neuropathy. We have also safely treated patients on stable medication regimens for pain associated with peripheral neuropathy (eg, pregabalin, gabapentin) with carfilzomib.

Gastrointestinal AEs

Gastrointestinal AEs were common, with 72.4% of patients experiencing at least one gastrointestinal AE; the most common events were nausea (44.9%), diarrhea (32.7%), vomiting (22.2%), and constipation (20.9%).[10,12] The majority of gastrointestinal events were grade 1/2 and only 2.9% were considered serious. Gastrointestinal AEs rarely resulted in dose limitation or treatment discontinuation. The most common grade 3 gastrointestinal AEs were nausea (1.3%), vomiting (1.0%), diarrhea (0.8%), and constipation (0.4%).

In practice, frequency and severity of gastrointestinal AEs vary according to the individual patient and concurrent medications. Prophylaxis with antinausea medications (eg, ondansetron) is suggested before treatment with carfilzomib, but these may also contribute to constipation. In addition, patients receiving opioids for pain may be more likely to experience gastrointestinal AEs. Dexamethasone, which is used prophylactically with administration of carfilzomib, also has antiemetic activity. In our experience, the majority of patients typically require no additional antinausea medication.

Tumor lysis syndrome

Tumor lysis syndrome is a metabolic complication resulting from the rapid destruction of cancer cells and release of their intracellular contents.[34,35] The clinical manifestations of tumor lysis syndrome include increased lactate dehydrogenase, hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and renal failure. Patients with MM and a high tumor burden are considered to be at risk for tumor lysis syndrome.

In patients treated with carfilzomib, tumor lysis syndrome was observed in five patients in the Phase II trials,[10,12] with three cases occurring prior to the inclusion of prophylaxis guidelines within study protocols. Following implementation of the prophylactic guidelines in the protocols, tumor lysis syndrome was only reported in one of 613 patients and thus is no longer considered to be a major concern.

To reduce the risk of tumor lysis syndrome, patients should be well hydrated before and after receiving carfilzomib therapy (250–500 mL of intravenous fluid as indicated).[10] Euvolemia should be maintained throughout treatment and monitored to prevent fluid overload. Blood chemistries should also be closely monitored. If tumor lysis syndrome occurs, therapy should be interrupted until symptoms resolve.

Viral infections

Herpes simplex infection or herpes zoster reactivation associated with MM is due to impaired lymphocyte function from the disease and/or treatment-related myelosuppression.

In Phase II studies with carfilzomib, prophylactic oral antiviral therapy was recommended for all patients and required for patients with a history of herpes zoster or simplex in the 003 studies and all patients receiving subtherapeutic dexamethasone in the 005 study.[12] Overall, 62.7% of patients received prophylactic therapy across the Phase II studies, and there was a low rate of herpes virus infection (25 patients, 4.8%) with only one grade 3 event of "pain secondary to shingles". Antiviral prophylaxis is recommended prior to initiating carfilzomib for patients who have a history of herpes zoster infection.[10]

Emory approach

Based on our experience with carfilzomib throughout its clinical development, we have adapted its standard treatment protocol to meet the needs of our patients. We administer carfilzomib on Mondays and Tuesdays to ensure patients can easily access the clinic during the remainder of the working week, and have adopted a 30-minute infusion time for all doses of carfilzomib in all cycles, based on observations of lower AEs possibly attributed to carfilzomib, including dyspnea and fever. Additionally, we continue subtherapeutic dexamethasone prior to every infusion, again with potential benefits for prevention of infusion reactions, nausea, and drug-related fever, among other AEs. For patients in whom excessive hydration is a concern (eg, heart failure, renal dysfunction), we limit pre-hydration and post-hydration to 250 mL (500 mL total), and diurese as clinically indicated. We also initiate prophylactic oral acyclovir 400 mg twice a day and double strength oral cotrimoxazole once daily on Monday, Wednesday, and Friday in patients who are not already receiving these agents because of therapy or disease-related risks. Our experience and practice is based on multiple prior and ongoing clinical trial patients as well as post-approval standard treatment in patients with relapsed/refractory disease.

Summary

Single-agent carfilzomib has an acceptable safety and tolerability profile in patients with RRMM, including those who are heavily pretreated or refractory to bortezomib and/or immunomodulatory drugs. In addition, carfilzomib has low rates of peripheral neuropathy, without cumulative or late-effect toxicities. Carfilzomib provides a clinically significant advance in the treatment of RRMM.

Acknowledgment

Medical writing and editorial support were provided by Michael Raffin and Sabrina L Maurer, Fishawack Communications, Inc., North Wales, PA, and funded by Onyx Pharmaceuticals, Inc., South San Francisco, CA, USA.

Disclosure

The author reports no conflicts of interest in this work.

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