Kyprolis (Carfilzomib) Received New Indications as Combination Therapy for Use in Relapsed and/or Refractory Multiple Myeloma

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Multiple myeloma is a cancer of plasma cells in the bone marrow that often leads to bone destruction and bone marrow failure.[1,2] According to the American Cancer Society, more than 26,800 new cases of multiple myeloma were diagnosed in 2015, and 11,240 deaths were attributed to multiple myeloma.[3]

Representing approximately 1% of all cancers, multiple myeloma is the second most common hematologic malignancy after non-Hodgkin lymphoma.[4] The incidence of multiple myeloma is higher among men than it is among women.[1] Individuals aged ≥65 years, those with a family history of multiple myeloma, and those with a history of monoclonal gammopathy of undetermined significance are at an increased risk for multiple myeloma.[1] Common complications of multiple myeloma include bone pain, kidney dysfunction, bone loss, impaired immunity, and anemia.[5]

Although the overall incidence of multiple myeloma continues to increase, the mortality rates associated with this malignancy have declined during the past 20 years.[1,6] Specifically, the advent of novel therapy options for multiple myeloma, and improvements in high-dose therapy and supportive care have contributed to extended survival for patients with multiple myeloma.[6]

New anticancer drugs and novel combinations have emerged in part because of improved understanding of the bone marrow microenvironment and the biology of multiple myeloma.[7] Immune modulators and proteasome inhibitors now represent the cornerstones of initial treatment for multiple myeloma based on their proven ability to enhance the overall response rates and survival.[2,7]

Because novel agents for multiple myeloma have had a considerable impact on the healthcare budget, understanding their relative cost-effectiveness is important for ensuring efficient use.[8,9] Overall, 2 recent evaluations of the economics of these new agents in multiple myeloma resulted in similar conclusions.[8,9]

One of the studies used claims data from more than 2600 US-based patients with multiple myeloma, and found that the 1-year costs of bortezomib-based therapy were similar to those of non-novel combinations (approximately $112,000 each), whereas the costs of thalidomide- and lenalidomide-based regimens were significantly higher (approximately $130,500 and $159,200, respectively) than non-novel combinations.[8] In addition, patients taking thalidomide and lenalidomide had higher out-of-pocket costs in light of Medicare Part D's coverage gap for outpatient drugs.[8]

The second study modeled the cost-effectiveness of novel agents combined with melphalan and prednisone in patients with newly diagnosed multiple myeloma who were ineligible for a transplantation.[9] The researchers concluded that adding bortezomib to melphalan and prednisone was more cost-effective than adding thalidomide or lenalidomide to this combination.[9]

Despite strides in treatment, patients with multiple myeloma will experience disease relapse after initial treatment, and several lines of therapy are typically required.[10] Specifically, resistance to bortezomib and to lenalidomide is being observed with increasing frequency; therefore, there remains a marked need for additional therapeutic options for this patient population.[10,11]

Carfilzomib Receives Expanded Indications as Combination Therapy

On July 24, 2015, the US Food and Drug Administration (FDA) approved a new indication for carfilzomib (Kyprolis; Amgen) for use in combination with lenalidomide (Revlimid) plus dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma who have received 1 to 3 lines of therapy.[12] The expanded indication was based on data from the ASPIRE clinical trial, a phase 3 study demonstrating that the combination of carfilzomib, lenalidomide, and dexamethasone improved progression-free survival compared with lenalidomide and dexamethasone alone.[12-14]

Carfilzomib was initially approved by the FDA in 2012 as monotherapy in patients with relapsed and/or refractory multiple myeloma who received at least 2 previous therapies, including bortezomib and an immunomodula-

tory agent, and whose disease progressed during or within 60 days after completing the previous therapy.[15]

On January 21, 2016, the FDA approved yet another indication for carfilzomib to be used in combination only with dexamethasone for patients with relapsed and/or refractory multiple myeloma who have received 1 to 3 previous therapies.[14,16] This decision also converted carfilzomib's monotherapy accelerated approval in this setting to a full FDA approval.[14,16]

Carfilzomib was approved for use in combination with dexamethasone alone based on data from the ENDEAVOR clinical trial, a phase 3 clinical trial demonstrating a progression-free survival advantage for carfilzomib plus dexamethasone compared with bortezomib plus dexamethasone.[16,17]

Mechanism of Action

Carfilzomib is a proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. In vitro studies demonstrated carfilzomib's antiproliferative and proapoptotic properties in solid and hematologic tumor cells.[14]

Dosing and Administration

Carfilzomib is administered intravenously in single-dose vials containing 60 mg of the drug. Carfilzomib must be refrigerated before use.[14]

Hydration can be provided before and after carfilzomib administration as needed. Premedication with oral or intravenous (IV) dexamethasone is appropriate before all cycle 1 doses, and if symptoms of an infusion reaction develop or reappear.[14]

Table 1 ASPIRE: Efficacy Results in Patients with Relapsed or Refractory Multiple Myeloma

Efficacy end point	Carfilzomib, lenalidomide, + dexamethasone (N = 396)	Lenalidomide + dexamethasone (N = 396)
Overall response rate, %	87	67
Stringent complete response, %	14	4
Complete response, %	18	5
Very good partial response, %	38	31
Partial response, %	17	26
Progression-free survival, median, mo	26.3 (95% CI, 23.3-30.5)	17.6 (95% CI, 15.0-20.6)
Hazard ratio	0.69 (95% CI, 0.57-0.83)	
P value (2-sided)	.001	

CI indicates confidence interval.

Source: Kyprolis (carfilzomib) injection prescribing information; January 2016.

Carfilzomib plus Lenalidomide and Dexamethasone

When given in combination with lenalidomide and dexamethasone, carfilzomib is administered as a 10-minute IV infusion on 2 consecutive days weekly for 3 weeks, followed by a 12-day rest period. Each 28-day period is considered 1 treatment cycle.[14] The recommended starting dose of carfilzomib is 20 mg/m^2 in cycle 1 on days 1 and 2. If tolerated, the carfilzomib dose can be escalated to 27 mg/m^2 on day 8 of cycle 1. After cycle 13, the day 8 and day 9 doses of carfilzomib are omitted. Carfilzomib is discontinued after cycle 18.[14]

Lenalidomide (25 mg) is taken orally on days 1 to 21, and dexamethasone (40 mg) is taken orally or intravenously on days 1, 8, 15, and 22 of the 28-day cycles.[14]

Carfilzomib plus Dexamethasone

When given in combination with dexamethasone, carfilzomib is administered as a 30-minute IV infusion on 2 consecutive days weekly for 3 weeks followed by a 12-day rest period.[14]

Carfilzomib should be administered at a starting dose of 20 mg/m^2 in cycle 1 on days 1 and 2. If tolerated, the carfilzomib dose should be escalated to 56 mg/m^2 on day 8 of cycle 1.[14]

Dexamethasone 20 mg is taken by mouth or intravenously on days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle.[14] Dexamethasone should be given 30 minutes to 4 hours before the administration of carfilzomib.[14]

Clinical Trials

ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone

The FDA approval of carfilzomib for use in combination with lenalidomide and dexamethasone was based on results of ASPIRE, a phase 3, randomized, controlled, open-label clinical trial that enrolled 792 patients (median age, 64 years) with relapsed and/or refractory multiple myeloma who had received 1 to 3 previous therapies.[13,14]

Carfilzomib was administered for a maximum of 18 cycles unless disease progression or unacceptable toxicity occurred earlier. Lenalidomide and dexamethasone administration continued until disease progression or until unacceptable toxicity.[14]

The median progression-free survival in patients receiving carfilzomib plus lenalidomide and dexamethasone was significantly higher than in patients receiving lenalidomide plus dexamethasone (26.3 vs 17.6 months, respectively; hazard ratio, 0.69; *P* <.001; **Table 1**).[13,14]

The median duration of response was 28.6 months for 345 patients who achieved a response in the carfilzomib-containing arm compared with 21.2 months for 264 patients achieving a response with lenalidomide plus dexamethasone.[14] The median time to response was 1 month in both arms.[14]

According to the ASPIRE study investigators, the 3-drug combination resulted in durable responses, a substantially higher response rate, and longer progression-free survival compared with the 2-drug combination without carfilzomib among patients with relapsed disease.[13]

ENDEAVOR: Carfilzomib plus Dexamethasone

The approval of carfilzomib plus dexamethasone was based on data from ENDEAVOR, an open-label, multicenter clinical trial involving 929 patients (median age, 65 years) with relapsed and/or refractory multiple myeloma. Patients were randomized to carfilzomib plus dexamethasone (N = 464) or to bortezomib plus dexamethasone (N = 465).

Patients who received carfilzomib plus dexamethasone achieved a median progression-free survival of 18.7 months compared with 9.4 months for bortezomib plus dexamethasone (P <.001; **Table 2**).[14,16] Carfilzomib plus dexamethasone also demonstrated improved overall response rate compared with bortezomib plus dexamethasone (77% vs 63%, respectively; P <.001).[14,16] At the time of data analysis of the ENDEAVOR study, overall survival data were immature.[14]

Table 2 ENDEAVOR: Efficacy Results in Patients with Relapsed or Refractory Multiple Myeloma

Efficacy end point[a]	Carfilzomib + dexamethasone (N = 464)	Bortezomib + dexamethasone (N = 465)
Overall response rate, %	77 (95% CI, 73-81)	63 (95% CI, 58-67)
Stringent complete response, %	2	2
Complete response, %	11	4
Very good partial response, %	42	22
Partial response, %	23	34
Progression-free survival, median, mo	18.7 (95% CI, 15.6–unavailable)	9.4 (95% CI, 8.4-10.4)
Hazard ratio	0.53 (95% CI, 0.44-0.65)	
P value (2-sided)	<.001	

[a]At the time of data analysis, the overall survival data were immature.
CI indicates confidence interval.
Source: Kyprolis (carfilzomib) injection prescribing information; January 2016.

Adverse Reactions

The most common adverse reactions occurring in at least 20% of patients who received carfilzomib in the combination therapy clinical trials included anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, and hypokalemia.[14]

In the ASPIRE study, serious adverse reactions leading to the discontinuation of carfilzomib were reported in 12% of patients—pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%) were the most common adverse reactions leading to carfilzomib discontinuation.[14]

In the ENDEAVOR clinical trial, adverse reactions leading to the discontinuation of carfilzomib occurred in 20% of patients receiving carfilzomib—cardiac failure was the most common adverse reaction leading to carfilzomib discontinuation.[14]

Carfilzomib has no contraindications and no drug interactions.[14]

Warnings and Precautions

Cardiac toxicities. New onset or worsening of preexisting cardiac failure, restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction, including fatalities, have occurred after carfilzomib treatment. Carfilzomib should be withheld for grade 3 or 4 cardiac events until recovery. The total fluid intake should be adjusted in patients at risk for or with baseline cardiac failure.[14]

Acute renal failure. Monitor renal function regularly. The dose of carfilzomib should be reduced or withheld as appropriate.[14]

Tumor lysis syndrome (TLS). Cases of TLS, including fatalities, have occurred with carfilzomib.[14] Patients with a high tumor burden are at an increased risk for TLS. Adequate hydration is important before administration of carfilzomib in cycle 1, and in subsequent cycles as needed. Uric acid–lowering drugs can be considered in patients at risk. Carfilzomib should be interrupted until TLS resolves.[14]

Pulmonary toxicity. Acute respiratory distress syndrome, acute respiratory failure, pneumonitis, and interstitial lung disease can occur with carfilzomib therapy. Carfilzomib should be discontinued if drug-induced lung toxicity is observed.[14]

Pulmonary hypertension. Carfilzomib should be withheld for pulmonary hypertension until resolution.[14]

Dyspnea. Carfilzomib should be discontinued for grade 3 or 4 dyspnea until resolution.[14]

Hypertension. Hypertension, including hypertensive crisis and emergency, has been reported with carfilzomib.[14] Monitor blood pressure regularly. If hypertension cannot

be adequately controlled, carfilzomib should be withheld.[14]

Venous thrombosis. Patients receiving carfilzomib have experienced venous thromboembolic events, including deep-venous thrombosis and pulmonary embolism.[14] Thromboprophylaxis may be appropriate.[14]

Infusion reactions. Infusion reactions, including life-threatening events, have occurred up to 24 hours after the administration of carfilzomib. Dexamethasone should be administered before carfilzomib to reduce the incidence of infusion reactions.[14]

Thrombocytopenia. Approximately 40% of patients receiving carfilzomib had thrombocytopenia in clinical trials.[14] Monitor platelet counts frequently.[14]

Hepatic toxicity/failure. Liver enzymes should be monitored regularly.[14]

Thrombotic microangiopathy. Cases of thrombotic microangiopathy have been reported with carfilzomib. The drug should be discontinued if thrombotic thrombocytopenic purpura/hemolytic uremic syndrome is suspected.[14]

Posterior reversible encephalopathy syndrome (PRES). Carfilzomib should be discontinued if PRES is suspected.[14]

Use in Specific Populations

Pregnancy. Carfilzomib may cause fetal harm. Women of reproductive potential should avoid becoming pregnant while receiving carfilzomib.[14]

Lactation. There are no data regarding the presence of carfilzomib in human milk, the effects on the breastfed infant, or the effects on milk production.[14]

Reproductive potential. Women of reproductive potential should use effective contraception during treatment with carfilzomib, and for at least 30 days after completing therapy.[14]

Pediatric use. There are no data about the safety and effectiveness of carfilzomib in pediatric patients.[14]

Geriatric use. No overall differences in the effectiveness of carfilzomib were observed between older and younger patients in the ASPIRE and the ENDEAVOR clinical trials. The incidence of serious adverse events increased with age.[14]

Renal impairment. No adjustment to the starting carfilzomib dose is necessary in patients with baseline mild, moderate, or severe renal impairment, or in patients on long-term dialysis. Carfilzomib should be administered after the dialysis procedure.[14]

Conclusion

Carfilzomib, an IV proteasome inhibitor, now has 3 FDA-approved indications in relapsed and/or refractory multiple myeloma: as monotherapy, in combination with dexamethasone, and in combination with lenalidomide and dexamethasone. Carfilzomib-based combinations demonstrated significantly longer progression-free survival compared with active comparators based on the findings from the ASPIRE and ENDEAVOR clinical trials.

The promising clinical activity of carfilzomib continues to be evaluated in patients with multiple myeloma, as well as in other hematologic malignancies and in relapsed solid tumors.[18] ■

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