New Directions in the Treatment of Multiple Myeloma: Reports on Carfilzomib-Based Therapy from ASH 2012*
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Publisher:  
Nicholas Englezos  
nick@engagehc.com  
732-992-1884

Editorial Director  
Dalia Buffery  
dalia@engagehc.com  
732-992-1889

Associate Publisher  
Maurice Nogueira  
maurice@engagehc.com  
732-992-1895

Associate Editor  
Lara J. Lorton  
732-992-1892

Editorial Assistant  
Jennifer Brandt  
jbrandt@the-lynx-group.com  
732-992-1536

National Accounts Manager  
Zach Ceretelle  
zach@engagehc.com  
732-992-1898

Executive Vice President  
Engage Managed Markets  
ccollins@engagehc.com  
732-992-1894

Senior Production Manager  
Lynn Hamilton

Quality Control Director  
Barbara Marino

Business Manager  
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Robert E. Henry

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Contact Information: For subscription information and editorial queries, please contact: editorial@engagehc.com; tel: 732-992-1892; fax: 732-992-1881.

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Multiple myeloma (MM) accounts for 10% to 15% of all hematologic malignancies, and is the cause of 20% of the deaths that result from blood and bone cancers. In 2012, the American Cancer Society estimated that there would be 21,700 patients newly diagnosed with MM, and 10,710 who will die from this type of cancer. The median survival for patients with MM was less than 1 year before the introduction of alkylating agents in the 1960s, and that rate increased with the introduction of high-dose chemotherapy and autologous stem-cell transplant (ASCT) in the 1980s. The advent of hematologic cell growth factors, the use of bisphosphonates, and the improved treatment of fractures have also contributed to increased survival for patients with MM. This increase in survival since approximately the year 2000 can be largely attributed to the development of novel, targeted therapies, including the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, and the first-in-class proteasome inhibitor bortezomib (Velcade).

Even with these new treatments, MM almost always relapses, and the duration of remission in patients with relapsed MM becomes shorter with each successive treatment regimen. Patients are likely to require treatment with one agent after another as their disease progresses and becomes resistant to chemotherapy. Therefore, there remains a need for additional therapies.

On July 20, 2012, the US Food and Drug Administration granted accelerated approval for carfilzomib (Kyprolis), which is indicated for the treatment of patients with MM who have received at least 2 previous therapies, including bortezomib and an IMiD (ie, thalidomide or lenalidomide), and have demonstrated disease progression on or within 60 days of completion of the last therapy. The approval of carfilzomib was based on the response rate determined in a single-arm, multicenter clinical trial, and was not based on survival. Furthermore, a clinical benefit (ie, increased survival or improved symptoms) has not been confirmed.

Clinical Trial Updates on Carfilzomib-Based Treatment for Patients with MM
Oral presentations and posters based on carfilzomib clinical trials were presented at the 2012 American Society of Hematology meeting, which was held December 8-11, in Atlanta, GA. These presentations included reports on the safety and the efficacy of single-agent carfilzomib; the use of carfilzomib as part of a combination therapy for patients who are newly diagnosed with MM, as well as those with relapsed and/or refractory disease; and dosing and administration modifications related to carfilzomib. In addition, interesting preclinical studies of carfilzomib were presented, as well as an initial report on oprozomib—an orally bioavailable structural analog of carfilzomib.

Epidemiology of Cardiac Events in Patients with MM
Patients with MM are at risk for cardiac adverse events (AEs) as a result of their age, their disease, or their treatment regimen. Kristen D. Kistler, PhD, of United BioSource Corporation, Lexington, MA, and colleagues conducted a retrospective cohort study of commercial and Medicare supplemental insurance claims from January 1, 2006, through December 31, 2011, to determine the incidence and prevalence of cardiac AEs in US patients with MM. This analysis was presented in a poster and included 22,076 patients with newly diagnosed MM and 1723 patients with relapsed MM. Nearly 75% of the patients had a cardiac AE during the study period, most frequently arrhythmias (24% in patients with newly diagnosed MM, 29% in relapsed MM), congestive heart failure (15% in each group), and ischemic heart disease (19% and 14%, respectively), independent of anti-MM treatment and whether the MM was newly diagnosed or relapsed. Other cardiac events included cardiomyopathy and conduction disorders. The incidence of cardiac AEs was associated with older patient age (particularly those aged ≥75 years) and with a history of cardiac events.
Cardiac and Pulmonary Safety

A poster presentation by Sagar Lonial, MD, Professor, Emory School of Medicine, Director, Translational Research, B-cell Malignancy Program, Winship Cancer Institute, Atlanta, GA, and colleagues summarized the cardiac and pulmonary events occurring in 526 patients with relapsed and/or refractory MM in 4 phase 2 trials of carfilzomib, including PX-171-003-A0 (N = 46), PX-171-003-A1 (the pivotal registration trial; N = 266), PX-171-004 (N = 164), and PX-171-005 (N = 50).10 Most patients received carfilzomib at the approved dose and schedule (20 mg/m² for cycle 1, escalated to 27 mg/m² for subsequent cycles, dosed on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle). The patients in the PX-171-005 study, who had various degrees of renal insufficiency, received carfilzomib 15 mg/m² in cycle 1, 20 mg/m² in cycle 2, and 27 mg/m² in cycle 3 and beyond. At baseline, 70% of the patients had a cardiac risk factor, defined as taking ≥1 cardiac medication. As in the epidemiology study,9 the most common cardiac AEs were arrhythmias (13.3% overall of any grade), and these were mostly low-grade, benign events. Grade 3 cardiac AEs were primarily cardiac failure.10 The rates of cardiac AEs generally remained stable over time.

Overall, 1.1% of patients had their carfilzomib dose reduced and 4.4% of patients discontinued carfilzomib in response to cardiac AEs. There were 5 deaths resulting from cardiac events: 3 patients in the PX-171-003-A1 study died from cardiac arrest and 1 from dyspnea, and 1 patient in the PX-171-004 study died of a cardiac disorder. In addition, 3 patients in the PX-171-003-A1 study died of disease progression, which was considered to have a cardiac component.10

Respiratory AEs occurred in 69% of patients, most frequently dyspnea (42.2%), of which 4.8% had grade 3 dyspnea. This resulted in a dose reduction for 1.9% of patients, and for discontinuation in 2.3% of patients for all respiratory events and in 1.5% of patients with dyspnea. Dyspnea resolved in all but 1 patient and tended to occur in earlier cycles, with a median duration of 8 days. Respiratory infections occurred in 18.8% of patients, resulting in 2 deaths that were not considered to be related to carfilzomib. These rates of cardiac and pulmonary AEs are considered to be comparable to those reported for patients with relapsed and/or refractory MM. These events are being studied further in ongoing clinical trials.

Updated Results of Carfilzomib as a Replacement for Bortezomib

James R. Berenson, MD, Medical and Scientific Director, Institute for Myeloma & Bone Cancer Research, and Chief Executive Officer of Oncotherapeutics, both in West Hollywood, CA, and colleagues investigated the safety and efficacy of replacing bortezomib with carfilzomib in various regimens given to patients whose MM relapsed within 12 weeks of receiving a bortezomib-containing regimen or whose MM was refractory to the most recent bortezomib-containing regimen.12 This open-label, nonrandomized study has enrolled 33 patients, of whom 29 were evaluable for efficacy. Almost 66% of patients had a response of at least MR, almost 45% had at least MR for those receiving carfilzomib plus dexamethasone, and 75% had at least MR for those receiving carfilzomib with other agents, which included IMiDs, alkylating agents, and anthracyclines. The dose of carfilzomib was escalated and well tolerated up to 45 mg/m². There were 2 hematologic serious AEs, 12 nonhematologic serious AEs, and 1 death that resulted from pneumonia. Future enrollment in this ongoing study will focus on IMiD-containing regimens and on establishing the maximum tolerated dose (MTD) for additional carfilzomib-containing regimens.
Carfilzomib Combination Therapy in Patients with Newly Diagnosed MM

The carfilzomib combination therapy trials in patients with newly diagnosed MM are summarized in Table 1.

Carfilzomib, Lenalidomide, and Dexamethasone

Neha Korde, MD, Multiple Myeloma Section, National Cancer Institute, National Institutes of Health, Bethesda, MD, gave an oral presentation on the first interim analysis of a phase 2 study of carfilzomib, lenalidomide, and dexamethasone (CRd) in newly diagnosed patients with MM. Carfilzomib was administered at a dose of 20/36 mg/m² on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle, lenalidomide at 25 mg daily on days 1 to 21, and dexamethasone on days 1, 2, 8, 9, 15, and 16 at 20 mg for cycles 1 through 4, and at 10 mg thereafter. After at least 4 cycles, patients aged <70 years to 75 years could harvest stem cells. After 8 cycles, patients who had stable disease or better could receive extended-dose lenalidomide at 10 mg daily on days 1 to 21 for 12 cycles (ie, CRd-R). Correlative analyses included flow cytometry for minimal residual disease (MRD), positron emission tomography-computed tomography (PET-CT), proteasome assays, gene-expression profiling, and whole genome sequencing.

As of December 2012, 28 patients have been enrolled in the study, of whom 20 were evaluable. At a median of 7 cycles, no patients have developed grade ≥3 PN, and the second stage of accrual has begun. By cycle 2, mean M-protein levels dropped from approximately 2.75 g/dL to 0.5 g/dL. The best responses occurred after a median of 7 cycles, with ORR, 95%; every good partial response (VGPR), 85%; and near-complete response (nCR)/stringent complete response (sCR), 75%. Response was not affected by fluorescence in situ hybridization or by cytogenetics. The median time to sCR was 4.5 cycles.

The most common nonhematologic toxicities were elevated liver function tests (LFTs), fatigue, and rash. Lymphopenia was the most common hematologic toxicity. Standardized uptake value by [18F]-fluorodeoxyglucose (FDG)-PET-CT declined 49.3% (mean) in 6 patients who had active lytic lesions. After receiving 1 dose of carfilzomib, gene-expression profiling analysis showed an increase in proteasome gene-expression, and proteasome activity in MM cells (20s CT-L) was inhibited by 80%.

Table 1 Carfilzomib Combination Trials in Patients with Newly Diagnosed MM

<table>
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<tr>
<td><strong>Table 1</strong> Carfilzomib Combination Trials in Patients with Newly Diagnosed MM</td>
</tr>
<tr>
<td><strong>Patients in study</strong></td>
</tr>
<tr>
<td>CRd⁰¹</td>
</tr>
<tr>
<td>CCd⁰⁴</td>
</tr>
<tr>
<td>CYCLONE⁰⁵</td>
</tr>
<tr>
<td>CTD⁰⁶</td>
</tr>
</tbody>
</table>

ASCT indicates autologous stem-cell transplant; CCd, carfilzomib, cyclophosphamide, and dexamethasone; CRd, carfilzomib, lenalidomide, and dexamethasone; CTD, carfilzomib, thalidomide, and dexamethasone; CYCLONE, cyclophosphamide, carfilzomib, thalidomide (100 mg daily), and dexamethasone; MM, multiple myeloma.

Carfilzomib, Lenalidomide, and Dexamethasone

Antonio Palumbo, MD, Chief, Myeloma Unit, Department of Oncology, University of Torino, Italy, gave an oral presentation on the initial results of a multicenter, phase 2 trial of carfilzomib, cyclophosphamide, and dexamethasone (CCd), which included 58 patients aged ≥65 years or those who were ineligible for ASCT. Patients received 9 cycles of CCd induction therapy with carfilzomib at 20/36 mg/m² followed by carfilzomib maintenance therapy (infused on days 1, 2, 15, and 16 of a 28-day cycle) until disease progression. Of these
patients, 28% were aged ≥75 years and 35% had an unfavorable cytogenetic profile (t(4;14) or t(14;16) or del(17p)). At this early follow-up point (approximately 1 year), the response rates increased from cycle 1 through cycle 9; at cycle 9, the response rates were sCR, 23%; sCR/nCR/CR, 53%; ≥VGPR, 77%; and ORR, 100%. The best response was slightly lower for patients with International Staging System stage 2 or 3 disease and for those with higher-risk cytogenetics.

The rates of grade ≥3 hematologic AEs were low. Nonhematologic grade ≥3 AEs included cardiac effects, fatigue, and infection. Dose reductions and discontinuations were approximately 10% to 12% each, and no difference was seen in AEs between patients who were aged ≥75 years and those aged >75 years. No thromboembolic events or PN were reported. The 1-year progression-free survival (PFS) and overall survival (OS) rates were projected to be 88% and 87%, respectively.

Cyclophosphamide, Carfilzomib, Thalidomide, and Dexamethasone

An update of the results of the dose expansion of the cyclophosphamide, carfilzomib, thalidomide (100 mg daily), and dexamethasone (CYCLONE) trial were discussed in an oral presentation by Joseph R. Mikhail, MD, FRCPC, a hematologist/oncologist at the Division of Hematology and Medical Oncology, Mayo Clinic Arizona, Scottsdale.15 A total of 3 dose-limiting toxicities (DLTs) have occurred with the 20/45-mg/m² carfilzomib dose, and none with the 20/36-mg/m² dose; therefore, additional patients are being accrued in the cohort receiving the 20/36-mg/m² dose. This report included 38 patients, with a median follow-up of 11.6 months. One patient died of pneumonia during cycle 3; in 35 patients the disease has not progressed.

Overall, 27 patients were evaluable for response and received either 20/27 mg/m² or 20/36 mg/m² of carfilzomib. The ORR was 96%, and 74% of the patients reached ≥VGPR. As in the CRd and CCd trials,13,14 responses improved with increasing cycles of therapy.15 All 38 patients were evaluated for safety: 42% had grade 3 AEs, and 16% had grade 4 AEs. These included 4 patients with arrhythmia and 2 patients each with elevated LFTs, fatigue, or muscle weakness. Grade 4 thromboembolism occurred in 2 patients. Hematologic AEs included 18% grade 3 and 13% grade 4 events (eg, neutropenia and lymphopenia). Grade 1 PN occurred in 9 patients. Reductions in the dose of at least 1 drug occurred in 16% of the participants.

DLTs at the 20/45-mg/m² carfilzomib dose that were possibly or probably drug-related included infusion reaction, heart failure, dyspnea, atrial fibrillation, fatigue, and increased alanine aminotransferase. Stem-cell mobilization and collection were successful in all patients in which they were attempted. The MTD cohort receiving the 20/36-mg/m² carfilzomib dose will be completed with accrual of at least 20 additional patients.

Carfilzomib with Thalidomide and Dexamethasone

The updated results of a phase 2, open-label, dose-escalation trial combining carfilzomib, thalidomide, and dexamethasone (CTd) in transplant-eligible patients with MM were presented by Pieter Sonneveld, MD, PhD, Senior Staff Hematologist, Department of Hematology, Erasmus Medical Center, Rotterdam, the Netherlands, in an oral presentation.16 This trial investigated 4 cycles of CTd as induction therapy followed by high-dose melphalan and ASCT as intensification, followed by 4 cycles of CTd at a lower dose of thalidomide for consolidation. The induction dose of thalidomide was twice that of the dose that was used in the CYCLONE trial.

The results from 50 patients who were evaluable for response, safety, and PFS in the first dose level were reported; 41 had completed stem-cell harvest, 40 had undergone ASCT, and 39 had received consolidation therapy. Grade 3 AEs included skin toxicities (12%), gastrointestinal (GI) and cardiac events (6% each), tumor lysis syndrome (4%), and PN (2%). The ORR was ≥90% in each phase of treatment; the number of CR and ≥VGPR increased after ASCT and consolidation. Responses for patients with standard-risk versus high-risk cytogenetics were similar. A dose escalation to 20/36-mg/m² carfilzomib in induction and in consolidation has been completed; escalation to 20/45-mg/m² carfilzomib is ongoing, and escalation to a 20/54-mg/m² dose is planned. The median follow-up was 14 months, which is too short to assess PFS and OS.

Carfilzomib Dosing and Administration

Thirty-Minute Infusion and Dose Escalation

Ashraf Badros, MD, ChB, Professor of Medicine, Department of Hematology and Oncology at the University of Maryland Medical Center, Baltimore, presented a poster of a phase 1b study of 30-minute infusions of carfilzomib at doses of 20/45 mg/m² and 20/56 mg/m² in combination with weekly dexamethasone in patients with relapsed/refractory MM.17 The slower infusion rate was assessed as a means of increasing the tolerability of carfilzomib and of allowing a higher dose to be administered. Of the 14 patients receiving carfilzomib at 20/45 mg/m², 4 had 7 serious AEs (ie, obstructive airway disorder, blood culture positive, spinal cord compression, pneumococcal bacteremia, pneumonia, hermia, and pulmonary embolism); of the 8 patients receiving carfilzomib at 20/56 mg/m², 2 had 2 serious AEs (ie, diverticulitis and pneumonia).

The ORR was 55% in the 20 evaluable patients. The PFS was 5.4 months and 6.0 months, respectively, for
the 2 dose groups at a median follow-up of 8.4 months and 6.6 months, respectively. The combination of a 30-minute infusion of 20/56-mg/m\(^2\) carfilzomib plus low-dose dexamethasone was at least as well tolerated and as effective as single-agent carfilzomib. This dose and regimen of carfilzomib is being tested in a phase 3 trial in combination with low-dose dexamethasone versus bortezomib plus low-dose dexamethasone in patients with relapsed MM.

**Infusional Carfilzomib**

An oral presentation by Nikoletta Lendvai, MD, PhD, Hematologist/Oncologist, Myeloma/Lymphoma Service, Memorial Sloan-Kettering Cancer Center, New York, NY, summarized the results of a phase 2 study that was also based on the preclinical observations that slower infusion rates of carfilzomib permitted higher doses.\(^{18}\) This single-arm, open-label study included 41 patients with relapsed or refractory MM who had previously received bortezomib and an IMiD. The carfilzomib dose was 20/56 mg/m\(^2\), and low-dose (ie, 20 mg) dexamethasone was added for patients whose disease progressed after 2 cycles. Of the 38 evaluable patients, approximately 45% had MM refractory to bortezomib or to lenalidomide, and 39% had MM refractory to both of these agents. The ORR was 53% in 38 evaluable patients, with higher rates (71%) seen in patients with bortezomib-sensitive MM than in patients with double-refractory disease (39%). The median PFS was 7.6 months, the median duration of response was 10.0 months, and the median OS rate was not reached. Although the median PFS and the median duration of response were shorter in patients with bortezomib-refractory MM versus those with bortezomib-sensitive MM, these differences were not statistically significant.

Grades 3 and 4 hematologic AEs included anemia (20%) and thrombocytopenia (36%). Grades 3 and 4 nonhematologic AEs included hypertension (20%), pneumonia (15%), and pulmonary edema/congestive heart failure (CHF; 10%, occurring in the first cycle). Dose reduction occurred most frequently for hypertension, and 29 patients discontinued carfilzomib, mostly as a result of disease progression. As previously mentioned, this 20/56-mg/m\(^2\) dose of carfilzomib is under further investigation.

**Table 2 Carfilzomib Combination Trials in Relapsed/Refractory MM**

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Trial phase</th>
<th>Carfilzomib dose, mg/m(^2)</th>
<th>Other agents</th>
<th>Further treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib plus panobinostat</td>
<td>1/2</td>
<td>20/27 to 20/45</td>
<td>Panobinostat 20 mg-30 mg on days 1, 3, 5, 15, 17, 19</td>
<td>None</td>
</tr>
<tr>
<td>Carfilzomib plus panobinostat</td>
<td>1/1b</td>
<td>20/27 to 20/45</td>
<td>Panobinostat 15 mg-30 mg on days 1, 3, 5, 8, 10, 12; dexamethasone 4 mg on days 1, 2, 8, 9, 15, 16</td>
<td>None</td>
</tr>
<tr>
<td>Carfilzomib plus pomalidomide and dexamethasone</td>
<td>1/2</td>
<td>20/27 to 20/56</td>
<td>Pomalidomide 3 mg in cohort 1, 4 mg in cohorts 1-4 on days 1-21; dexamethasone 40 mg in cycle 1-4, 20 mg after cycle 4</td>
<td>Maintenance from cycle 7 and beyond with carfilzomib on days 1, 2, 15, 16; pomalidomide/dexamethasone as before</td>
</tr>
<tr>
<td>Carfilzomib plus ARRY-520</td>
<td>1</td>
<td>20/27</td>
<td>ARRY-520 escalated from 0.5 to 1.5 mg/m(^2)/day on days 1, 2, 15, 16; dexamethasone 4 mg on days 1, 2, 8, 9, 15, 16</td>
<td>None</td>
</tr>
</tbody>
</table>

MM indicates multiple myeloma.
safety and efficacy of carfilzomib at a dose of 20/45 mg/m² and panobinostat at a 30-mg dose.

Jatin J. Shah, MD, Assistant Professor of Lymphoma/Myeloma, Division of Cancer Medicine, M.D. Anderson Cancer Center, Houston, TX, presented another poster describing a phase 1/1b study of carfilzomib plus panobinostat in patients with relapsed and/or refractory MM.20 In this trial, panobinostat was administered at escalating doses of 15 mg, 20 mg, or 30 mg, and carfilzomib was administered at doses of 20/27 mg/m², 20/36 mg/m², and 20/45 mg/m²; unlike the other study of carfilzomib plus panobinostat,19 this study also included administration of dexamethasone 4 mg on the days of carfilzomib administration.21 Of the 21 patients enrolled in this study, I experienced a DLT of grade 4, which was thrombocytopenia with epistaxis. Other AEs included anemia and thrombocytopenia; no patients developed PN. The clinical benefit rate (response of ≥MR) was 38%. The MRD was 45 mg/m² of carfilzomib plus 20 mg of panobinostat. This is a lower dose of panobinostat than that which is being tested in the expansion phase of the other trial of carfilzomib plus panobinostat by Dr Berdeja and colleagues.19 Additional patients, who have bortezomib-sensitive or refractory MM will be enrolled in this trial.

Carfilzomib plus Pomalidomide

In an oral presentation, Dr Shah discussed the results of a phase 1/2 trial of carfilzomib, pomalidomide, and dexamethasone (ie, Car-Pom-d).21 Cohort 1 included 3 mg of pomalidomide; all subsequent cohorts received 4 mg of pomalidomide on days 1 to 21 of a 28-day cycle. Carfilzomib was escalated from 20/27 mg/m² to 20/56 mg/m², and patients received 40 mg of dexamethasone weekly for the first 4 cycles, followed by 20 mg for subsequent cycles. From cycle 7 and beyond, carfilzomib was dosed on days 1, 2, 15, and 16, and patients received pomalidomide and dexamethasone as in the previous cycle. All patients in this trial had to have MM that was refractory to lenalidomide; all but 2 of the enrolled patients also had MM refractory to previous therapy with bortezomib.

DLTs were reported in cohort level 1 (ie, febrile neutropenia [FN] and cohort level 2 (ie, grade 4 thrombocytopenia and grade 3 rash). The MTD was established as 20/27-mg/m² carfilzomib, 4-mg pomalidomide, and 40-mg dexamethasone; of the 32 patients who were enrolled, 20 were enrolled at the MTD. Hematologic AEs included FN (6%) and other cytopenias; non-hematologic AEs included fatigue, hypocalcemia, diarrhea, dyspnea, elevated creatinine, and rash. Serious AEs included grade 3 pneumonia, pulmonary emboli, and CHF. The ORR was 50%, and the clinical benefit response was 67%. The median PFS was 7.4 months, and the OS was estimated at 1 year to be 90%.

Patients with high-risk disease by the Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) responded similarly to those with standard or with intermediate risk, but the number of patients in all of these groups was small. Based on these results, enrollment is ongoing in a phase 2 clinical trial of 82 patients.

Carfilzomib plus ARRY-520

Dr Shah also presented a poster describing a phase 1 study of the novel kinesin spindle protein inhibitor ARRY-520 in combination with carfilzomib in patients with relapsed and/or refractory MM who have received previous ASCT and are intolerant of or whose MM is refractory to bortezomib and to lenalidomide.22 Carfilzomib was administered at a dose of 20/27 mg/m², and ARRY-520 was dose-escalated from 0.5 mg/m² (in cohort 1) to 1.5 mg/m² (administered on days 1, 2, 15, and 16 of a 28-day cycle); dexamethasone 4 mg was administered on the same days as carfilzomib. Enrollment in the trial is ongoing. In the 9 patients enrolled so far, 1 DLT occurred, in cohort 2, which was influenza pneumonia (with 1.00-mg/m² ARRY-520). Grade 3 or greater AEs included neutropenia, anemia, lung infection, diarrhea, fatigue, hyperglycemia, and hypotension. A preliminary clinical benefit response of 56% was reported.

Carfilzomib Preclinical Studies

Carfilzomib Induces Differentiation of Mesenchymal Stromal Cells

Yu Chen of the Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, presented a poster showing that carfilzomib induces differentiation of mesenchymal stromal cells toward osteoblasts via activation of the beta-catenin and T-cell factor pathway in patients with MM, the putative molecular mechanism that is underlying the bone anabolic effects of carfilzomib in myeloma bone disease.23

Antimyeloma Effects of Carfilzomib with Cyclophosphamide or Bendamustine

Eric Sanchez, Associate Director of Animal Research at the Institute for Myeloma and Bone Cancer Research, West Hollywood, CA, presented a poster describing the effects of carfilzomib administered with cyclophosphamide or with bendamustine in a xenograft model of mice bearing implanted MM tumors. Both carfilzomib combinations had anti-MM activity and provide the rationale for clinical trials evaluating these combinations in patients with MM.24

Oprozomib: Phase 1b Trial in Hematologic Malignancies

Michael Savona, MD, Director of Leukemia Research and Senior Investigator of Hematologic Malignancies
and Drug Development at the Sarah Cannon Research Institute in Nashville, TN, gave an oral presentation of a phase 1b dose-escalation study of split-dose oprozomib (ONX 0912) in patients with hematologic malignancies. Oprozomib is an orally bioavailable structural analog of carfilzomib that similarly irreversibly and selectively inhibits the proteasome. Oprozomib was administered at a total daily dose of 120 mg and was escalated to 210 mg daily in 2 doses that were 4 to 6 hours apart with antiemetics and 4 mg of dexamethasone on days 1 to 5 of a 14-day cycle. The MTD was not reached at the highest dose (ie, cohort 4).

Of 13 patients receiving treatment, 11 had MM. The AEs that were reported for the first 3 cohorts included GI disturbances, cytopenias (including grade 4 thrombocytopenia), fatigue, pyrexia, hypoalbuminemia, and cognitive disorder. Some anti-MM was seen in 9 evaluable patients with MM, with partial response being the best response that was achieved. Dose-dependent proteasome inhibition was seen, as is shown in the Figure. Dose escalation will continue to MTD in a phase 2 expansion trial of patients with MM and Waldenström’s macroglobulinemia.

**Conclusion**

Ongoing trials of carfilzomib as a single agent and in combination therapies continue to define the role of this agent in the treatment of newly diagnosed patients and in patients with relapsed and/or refractory MM. The continued development of oprozomib may provide patients with a more convenient, oral option.

**References**


Carfilzomib-Based Therapies for Multiple Myeloma: A Pharmacist’s Perspective

R. Donald Harvey, PharmD, FCCP, BCOP
Assistant Professor, Department of Hematology and Medical Oncology, and Director, Phase 1 Clinical Trials Section, Winship Cancer Institute of Emory University, Atlanta, GA

Novel therapies for patients with multiple myeloma (MM) continue to show improved outcomes for a population that as little as 8 years ago had few options. The evolution of new targets for therapy and improved agents in established classes shows that continued investigation into the mechanisms of inhibiting plasma-cell proliferation and activity yields better medications for patients across the disease spectrum.1 Traditionally, new drugs are introduced to the field in the relapsed and/or refractory setting, which has recently become a more difficult endeavor because of the availability of multiple lines of effective therapies that are approved for use.

Despite this evolving and challenging drug development landscape, carfilzomib (Kyprolis) data showing improved response rates in patients with MM led to the US Food and Drug Administration’s accelerated approval of the drug in 2012.2 The current use and evolution of carfilzomib’s place in therapy, along with other agents and combinations, are important for pharmacists to follow to ensure that we are knowledgeable and prepared to help patients with MM achieve maximum benefit from therapy.

Current and Future Safety Considerations for Carfilzomib Use

Patients with MM who are eligible for carfilzomib therapy will likely be at greater risk for selected adverse events (AEs), such as myelosuppression, because of previous treatment and their disease status compared with newly diagnosed patients. It is, therefore, reasonable to assume that single-agent and combination trials in patients with newly diagnosed MM will show reduced toxicity rates compared with previous and ongoing trials in relapsed and/or refractory disease. Cardiac events in patients receiving carfilzomib are of particular interest, because these AEs were seen in patients receiving this agent in phase 2 trials. As in the case of neuropathy or thrombotic events, it is helpful to understand the pre-treatment frequency of cardiac events to differentiate drug- versus disease-related causes. The data presented by Kistler and colleagues at the 2012 American Society of Hematology meeting helped to contextualize cardiac events in >23,000 patients with MM.3

Of note, the rates in newly diagnosed and relapsed disease were similar, with arrhythmias being the most common cardiac event for both groups (24% and 29%, respectively), followed by ischemic heart disease (19% and 14%, respectively) and cardiomyopathy (3% each). All AEs were more common in patients aged ≥75 years. The clinical implications of these data are that cardiac events are common in MM, and that causality may be difficult to assign. If an event should occur, the timing, relevant history (eg, smoking, hypercholesterolemia),
subsequent therapy for the event, and overall tolerability and response to anti-MM therapy should be taken into consideration when deciding how to proceed.

With carfilzomib, cardiac and pulmonary safety was summarized and described in >500 patients with MM across 4 trials by Lonial and colleagues. More than 66% of the patients were receiving cardiovascular medications in these trials, and, although arrhythmias were the most common event, they were less frequent than the rate seen in the Kistler review. Fewer than 5% of the patients required discontinuation or dose reduction, suggesting that continued therapy is both safe and feasible. Dyspnea may occur in patients receiving carfilzomib; however, it is short-lived and has been shown to be associated with other clinical events (eg, pulmonary embolism, heart failure).

The safety of prolonged exposure was also reported by Siegel and colleagues, who suggested that in patients who continue to respond, the rate of neuropathy remains low, and most grade 3 or 4 AEs are either a result of cytopenias or pneumonia. These data indicate that carfilzomib therapy as a long-term strategy is worth pursuing because of its promising efficacy and safety profile.

Prolonged infusion strategies may also allow higher doses to be given while maximizing safety when compared with the current 2- to 10-minute recommended administration. The approved carfilzomib dose of 20/27 mg/m² has been surpassed in many clinical trials, and an evaluation of the specific tolerability of 30-minute infusions of higher doses was presented by Badros and colleagues in a phase 1b trial, in which the dose of 20/56 mg/m² was established as safe and will be compared with bortezomib in a phase 3 clinical trial setting. Additional efficacy data in 20 patients with MM showed that carfilzomib 20/40 and 20/56 mg/m² infused over 30 minutes with dexamethasone was beneficial and had an overall response rate of 55%.

The Evolution of Carfilzomib Use in Relapsed/Refractory MM and in Newly Diagnosed Patients

When considering the safety profile and previous efficacy data, the most intriguing application of carfilzomib and other novel agents is in combination. Building on single-agent activity, further studies of carfilzomib combinations with novel agents were presented at the meeting. Combination data from phase 1/2 clinical trials on the histone deacetylase inhibitor panobinostat, pomalidomide, and the kinesin spindle protein inhibitor ARRY-520 provided insight into the next generation of MM regimens. Each trial defined recommended (phase 2) doses and demonstrated activity in heterogeneous populations, while validating the benefit of combination approaches with novel agents.

When evaluating data with carfilzomib in the initial treatment setting, we must carefully review the regimens and schedules used. Many new regimens are reassessing the optimal dose of carfilzomib with the understanding that higher doses in patients with newly diagnosed MM may be well tolerated, with improved efficacy compared with the relapsed and/or refractory setting. When comparing these regimens, we have to be mindful of the carfilzomib dose and the schedule, as well as any concurrent agents. The doses and schedules of agents such as dexamethasone, lenalidomide, and cyclophosphamide may be unique and regimen-specific. The trial by Korde and Landgren (N = 20) showed that a 2 mg in cycle 2 and beyond dose of carfilzomib 36 mg/m², along with 21 days of lenalidomide and dexamethasone 20 mg on the day that carfilzomib was administered every 28 days, produced near complete remission (CR)/stringent CR in 75% of the patients, with most of the responses occurring by cycle 5. The regimen was generally well tolerated, with a median of 7 cycles delivered at the time of evaluation and no grade ≥3 neuropathy. This combination is based on previous data with the bortezomib, lenalidomide, and dexamethasone regimen, and an ECOG trial (E1A11) comparing the 2 regimens is planned.

Other carfilzomib-containing regimens may hold promise in patients with newly diagnosed MM, including combinations with the oral alkylating agent cyclophosphamide plus thalidomide. Palumbo and colleagues presented data of transplant-ineligible patients with MM (35% of whom had unfavorable cytogenetics) with accelerated carfilzomib (20 mg/m² cycle 1, days 1 and 2, 36 mg/m² thereafter) with weekly oral cyclophosphamide and dexamethasone. The rates of all CR categories were 53%, and the responses generally improved over time. The 4-drug phase 1 combination of cyclophosphamide, carfilzomib, thalidomide, and dexamethasone was also presented, with updated results from the 20/27-mg/m² carfilzomib cohort showing a 29% CR rate, with ongoing accrual to the 20/36-mg/m² cohort.

Back to the Future

As MM therapy evolves, it is clear that orally based regimens have shifted drug development. Much like the historical melphalan–prednisone regimen, we can envision standard therapy of an oral proteasome inhibitor, an immunomodulatory drug (IMiD), and a corticosteroid as initial therapy in many patients, regardless of their transplant eligibility. The remaining questions are—which proteasome inhibitor and which IMiD agent? Novel agents, including pomalidomide, ixazomib (MLN 9708), oprozomib (ONX 0912), and the humanized monoclonal antibody elotuzumab continue to show promising activity and predict a future of effective, convenient regimens for patients with MM.
Carfilzomib data continue to evolve, showing promise across all categories of MM treatment. Contextualizing the safety information in different populations, while expanding efficacious options for patients with MM, is critical to ensuring optimal outcomes. Pharmacists can continue to provide needed education and input on carfilzomib-based treatment strategies for other clinicians and patients.

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**Carfilzomib-Based Therapies for Multiple Myeloma: A Nurse’s Perspective**

Beth Faiman, PhD(c), MSN, APRN-BC, AOCN
Nurse Practitioner, Cleveland Clinic Taussig Cancer Institute, OH

Most of the illnesses that are encountered in medicine are incurable. Diabetes and heart disease are 2 of the common, chronic, and incurable health conditions that require diligent monitoring. In 2013, multiple myeloma (MM) joins diabetes and heart disease in the category of chronic health conditions. Because treatment is required on an ongoing and daily basis, patients with MM rely on the discovery of new drugs to improve survival, quality of life, and the possibility of a cure.

The field of clinical research can be exciting when an agent is discovered and is as effective as (or more than) was anticipated. Much time and effort are required to see a clinical trial through from start to finish. Conducting a trial involves many difficult aspects, from writing the clinical protocol and ensuring scientific rigor to accruing patients and maintaining accurate records. The investigators must obtain funding and align themselves with a multidisciplinary team of physicians, nurses, and scientists. Each of these tasks can be daunting for the novice researcher. Even for the best researchers, the majority of the drugs that are developed in the laboratory do not make it to human trials for testing. The reasons for that include a lack of funding or a lack of researchers to carry out the necessary experiments.

Dr Lederman provides a comprehensive review of the clinical trials that feature one of the newest anti-MM agents that has successfully transitioned from the laboratory to the bedside—carfilzomib (Kyprolis). Carfilzomib is a proteasome inhibitor that selectively and irreversibly binds to its target, resulting in sustained inhibition absent of off-target effects. In July 2012, carfilzomib was approved in the United States for the treatment of relapsed and refractory MM. Despite only having phase 2, nonrandomized data, the US Food and Drug Administration (FDA) recognized the need for patients with MM to have access to all drugs that may provide some benefit. In the
PX-171-003-A1 clinical trial, carfilzomib has demonstrated an acceptable safety and efficacy profile in patients with relapsed and/or refractory MM.

Carfilzomib and bortezomib (Velcade) belong to the drug class of proteasome inhibitors. Proteasomes are important components of cellular degradation, and proteasome inhibitors prevent the proteasome from functioning properly and produce conflicting regulatory signals so that the myeloma cells cannot survive. Carfilzomib selectively and irreversibly inhibits the chymotrypsin-like activities of proteasomes via a binding mechanism that is distinct from that of bortezomib. The different mechanisms of the proteasome inhibition of carfilzomib and bortezomib are critical, because patients with MM who have not responded (or have stopped responding) to bortezomib will now have another treatment option with carfilzomib.1

According to the FDA indication, carfilzomib should be given to patients for the treatment of MM if the patient has received at least 2 previous therapies (including bortezomib and an immunomodulatory drug [IMiD], such as lenalidomide or thalidomide), with demonstrated disease progression on or within 60 days of completion of the last therapy. The starting dose of carfilzomib is 20 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle administered over a 2- to 10-minute period. The dose should be escalated to 27 mg/m² after the first cycle of therapy if no significant side effects—such as fatigue, cardiopulmonary, or infusion reactions—occur. Carfilzomib, when given according to the FDA indication, can be very effective in patients with previously treated MM.1

Providers should be aware of key considerations when patients begin carfilzomib therapy. In <1% of patients in a phase 2 clinical trial, tumor lysis syndrome occurred. Therefore, oral allopurinol should be given to patients with a high tumor burden. Infusion reactions were rare in the phase 2 registration trial. To minimize the risk of infusion reactions, dexamethasone 4 mg orally or intravenously should be given during the first 2 cycles of carfilzomib administration. Finally, patients with a history of herpes zoster infection should receive concomitant antiviral medications.1

Additional trials in patients with newly diagnosed and relapsed and/or refractory MM are necessary to clarify the role of carfilzomib in MM. It remains unclear in which patient population (newly diagnosed or relapsed and/or refractory MM), and with which drugs carfilzomib will be safe and effective to use. Dr Lederman provides an excellent overview of some of the trials that are currently under way in patients with newly diagnosed and relapsed and/or refractory MM.

Many oral and poster presentations featured carfilzomib at the 2012 meeting of the American Society of Hematology. Maturing safety data from the earliest carfilzomib trials were presented in an effort to provide insight into cardiac and pulmonary adverse events (AEs). As was discussed in a poster by Lonial and colleagues, in one analysis of 526 patients with relapsed and/or refractory MM in 4 phase 2 clinical trials of carfilzomib, the rates of cardiac and pulmonary events were considered to be comparable to the rates reported for patients with relapsed and/or refractory MM.2 In addition, Siegel and colleagues presented long-term data that highlighted the safety and tolerability of carfilzomib.1 As carfilzomib is being studied in patients with newly diagnosed MM, it is encouraging to see the long-term tolerability of carfilzomib reported.

Some exciting trials were presented in which carfilzomib was combined with an IMiD. Preliminary data from 2 clinical trials in patients with newly diagnosed MM involve the regimen of carfilzomib, lenalidomide, and dexamethasone (CRd),4 and cyclophosphamide, carfilzomib, thalidomide, and dexamethasone (CYCLONE).5 The CRd and CYCLONE trials use agents that are already available and approved by the FDA for use in MM. Using carfilzomib in combination with other agents, especially FDA-approved agents, provides an opportunity to optimize disease control. In the CRd and CYCLONE trials, improved responses to treatment were seen with a longer duration of therapy.

The side effects of the CRd and CYCLONE regimens were similar to many anti-MM therapies, although the incidence of elevated liver enzymes, fatigue, dyspnea, and arrhythmias seen in CYCLONE was possibly or probably related to the higher dose of carfilzomib (20/45 mg/m²). Therefore, the maximum tolerated dose in the next cohort of the CYCLONE study will be 20/36 mg/m². It is also important to note the low incidence of moderate-to-severe peripheral neuropathy. The low evidence of neurotoxicity allows the provider to combine carfilzomib with thalidomide, as in the CYCLONE study.5

The time of infusion for carfilzomib was the topic of 2 presentations. In the phase 1b clinical trial presented by Badros and colleagues, the carfilzomib dose of 20/56 mg/m², when given in combination with low-dose dexamethasone, was at least as well tolerated and effective as single-agent carfilzomib.5 These study results were consistent with a phase 2 clinical trial presented by Lendvai and colleagues, in which an increased infusion time allowed a higher dose of carfilzomib to be administered.7 The 2 study results are pertinent to providers, because it is a major goal of treatment to minimize AEs and enhance tolerance to the drug. Further evidence that the longer infusion time can improve tolerance may change the way we administer carfilzomib in the future.

Carfilzomib is being studied in combination with
new drugs, such as panobinostat, pomalidomide, and the novel kinesin spindle protein inhibitor ARRY-520. In each of the early-phase trials, the maximum tolerated dose of the combinations and safety are being determined. Although more patients are needed to determine the safety, efficacy, and tolerability profiles of the combinations, the preliminary results are promising.

Conclusions

The accelerated FDA approval of carfilzomib is a benefit to patients who have exhausted many options to treat their MM. At this time, carfilzomib should only be given to patients who have relapsed and refractory MM unless they are enrolled in a clinical trial. We anxiously wait for the safety and efficacy data from previous and ongoing clinical trials to mature. Those results will shed light on the best way to use these drugs and in which combination for optimal benefit.

Author Disclosure Statement

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How Payers May Respond to the Evolving Pharmacologic Management of Multiple Myeloma: A Payer’s Perspective

Atheer A. Kaddis, PharmD
Senior Vice President, Sales and Business Development, Diplomat Specialty Pharmacy, Flint, MI

The past decade has given us several breakthrough treatment options for a complex and serious malignancy, multiple myeloma (MM). The next decade promises more breakthrough treatment options and may be the most important period for patients diagnosed with MM, as we learn more about this disease and offer treatment options that may lead to improved survival. We are currently on the cusp of this paradigm shift in the treatment of MM, and the excitement about newer therapies and combination regimens is palpable in the oncology community.

This publication provides an excellent summary of the 2012 American Society of Hematology meeting presentations on carfilzomib (Kyprolis), alone and in combination with other therapies. The proteasome inhibitor carfilzomib is one of the breakthrough drugs currently available for the treatment of MM that has progressed after treatment with bortezomib (Velcade) and an immunomodulatory drug (IMiD) (eg, thalidomide or lenalidomide). Although carfilzomib has not shown improved survival, the fact that patients have responded to this therapy after being treated with bortezomib and an IMiD is an important focus of future therapy for MM. It is known that MM almost always
relapses, and remission durations shorten with each relapse.¹ This is leading to the development of several additional treatment options for this malignancy, as well as to novel combination therapies, especially for patients at high risk for relapse.

Approximately 60 new medications are in development for the treatment of MM, with approximately 10 new medications in late-stage (phase 3 clinical trials) development.² Although much attention has been given to one of the leading candidates in new drug development for MM, notably pomalidomide, other agents will likely gain similar attention in the near future, including oprozomib, an oral proteasome inhibitor that is a structural analog of carfilzomib.

Not all new drug development for MM is being met with excitement; some of it is being met with anxiety. That anxiety is notably evident with payers, as we continually see rising prescription drug costs at minimal clinical and, in this case, survival impact. Payers are excited to see advancement in the treatment of serious illnesses such as MM; however, the costs of these therapies alone—and especially in combination—is being viewed as cost-prohibitive. The published annual cost of therapy with lenalidomide plus dexamethasone and that of bortezomib as a single-agent therapy in the treatment of relapsed and/or refractory MM ranges between approximately $109,000 and approximately $130,000 per patient.³ The same article notes that the acquisition costs of lenalidomide and bortezomib were comparable; therefore, combination therapy with these 2 agents could result in the annual cost of therapy exceeding $200,000 per patient. This could be the future of the treatment costs for patients with MM, because of the high rate of relapse of this disease, and the growing interest in combination therapies for patients with relapsed and/or refractory MM.

Payers will respond to the continuing increase in the costs to treat MM, regardless of the excitement related to the progress being made in the treatment of this disease. It will not be uncommon to see the inclusion of MM in pay-for-performance programs, further adoption of treatment guidelines for MM, the adoption of end-of-life care programs, and common managed care strategies, such as utilization management and formulary management, over the next decade.

One of the strategies that will coincide with the burgeoning pharmaceutical pipeline for MM is medical management, rather than only focusing on pharmacy benefit management. As treatment options cross the pharmacy benefit and the medical benefit for payers, there is increasing interest by payers in managing treatment across both benefits. This is consistent with the growth in the use of oral therapies, and injectable therapies in combination, for MM. Many payers are relying on health plans, pharmacy benefit managers, and specialty pharmacies to assist with this strategy, which will grow in popularity as more treatment options become available, especially given the high cost of these therapies.

Another strategy that will help payers to address their concerns about the cost of therapy for MM, as well as other oncologic conditions and specialty disease states, is that of patient-centered oncology medical homes and accountable care organizations. As these care-delivery models gain in maturity and processes are streamlined, payers will again work with physicians and other caregivers to manage disease states across all benefits and sites of care.

The hope is that these models will establish a continuum of care approach to the treatment of patients with chronic, complex illnesses using a payment model that incentivizes physicians to follow the latest treatment guidelines and to use cost-effective methods to keep rising costs in check, while providing best-in-class care. This is especially important in the treatment of conditions such as MM, which is a very expensive disease to treat, given its rate of relapse and the cost of treatment options currently available as well as those in development.

Specialty pharmacies will continue to play an important role in the treatment of patients with MM. Regarding oral therapies, specialty pharmacies will continue to ensure that patients with MM begin therapy as prescribed, and that patients continue their therapy, as long as they are achieving a positive response while mitigating potential side effects. Specialty pharmacies will also continue to see some shift of injectables from a “buy-and-bill” approach to one where specialty pharmacies will dispense medications to the physician’s office for administration of the drug in the office setting. This will create a stronger bond between specialty pharmacies and oncologists in the treatment of MM.

The future for the treatment of MM is exciting, given the advances in understanding the disease and the development of therapies to successfully treat patients diagnosed with this condition. The use of various strategies to ensure that the right patient receives the right treatment at the right time will help to mitigate the anxiety of payers regarding the rapidly increasing costs of treating MM.

Author Disclosure Statement

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