New Directions in the Treatment of Multiple Myeloma

Reports on Carfilzomib-Based Therapy from ASCO® and EHA*

Faculty
Elizabeth Bilotti, MSN, BSN, APN-C
John Theurer Cancer Center
Hackensack University Medical Center

Supported by funding from Onyx Pharmaceuticals, Inc.

© 2012 Green Hill Healthcare Communications, LLC provides information to healthcare professionals through independent conference coverage.
*This publication is not sponsored by, endorsed by, or affiliated with the American Society of Clinical Oncology or the European Hematology Association in any way.
Table of Contents

3 Clinical Trial Updates on Carfilzomib-Based Treatment for Patients with Multiple Myeloma

9 Nursing Perspectives on Carfilzomib-Based Therapy in Multiple Myeloma
   Elizabeth Bilotti, MSN, BSN, APN-C

Faculty

Elizabeth Bilotti, MSN, BSN, APN-C
John Theurer Cancer Center at Hackensack University Medical Center
Multiple Myeloma Division, Hackensack, NJ
Clinical Trial Updates on Carfilzomib-Based Treatment for Patients with Multiple Myeloma

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States. Approximately 21,700 new cases will be diagnosed in the United States during 2012 and 10,710 patients will die from this disease. Over the past decade, the development and use of several targeted therapies have revolutionized the treatment of myeloma, and many patients are now experiencing prolonged progression-free survival (PFS) and overall survival (OS). These therapies include the first-in-class proteasome inhibitor bortezomib and the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide. In addition to these therapies, numerous investigational agents are now being studied in clinical trials for MM and may soon enter the clinical arena.

One such agent is carfilzomib, a next-generation proteasome inhibitor. On July 20, 2012, the US Food and Drug Administration granted accelerated approval to carfilzomib injection (Kyprolis™, Onyx Pharmaceuticals) for the treatment of patients with MM who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy. Approval was based on results of the open-label, single-arm phase 2b study, PX-171-003-A1.4

Poster and oral presentations focusing on encouraging results from clinical trials of carfilzomib use in MM were presented at both the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting, held June 1-5, 2012, in Chicago, Illinois, and the 17th Congress of the European Hematology Association (EHA), held June 14-17, 2012, in Amsterdam, the Netherlands.

Carfilzomib Mechanism of Action

MM tumor cells express both the constitutive proteasome (c20S) and the immunoproteasome (i20S). It has been shown that targeted inhibition of the immunoproteasome overcomes resistance to conventional chemotherapies and nonspecific proteasome inhibitors. Using a validated assay (ProCISE) that differentiates between inhibition of the 2 proteasome types as well as individual active sites, Susan J. Lee and colleagues measured and characterized the proteasome inhibition by carfilzomib in whole blood and peripheral blood mononuclear cell samples from 41 patients with solid tumors and 73 patients who were refractory or intolerant to both bortezomib and an IMiD. These patients showed >80% total i20S inhibition. In contrast, an 11% ORR was observed in patients receiving lower doses of carfilzomib, and their samples demonstrated <50% total i20S inhibition. However, it should be noted that these samples were from multiple studies that enrolled patients with solid tumors as well as MM.

Relapsed, Refractory, and Intolerant MM

The Pivotal Study, PX-171-003-A1

The pivotal open-label, single-arm phase 2b study, PX-171-003-A1, was designed to assess single-agent carfilzomib in patients with relapsed and refractory MM who were refractory or intolerant to both bortezomib and an IMiD. The primary efficacy end point was best ORR, and secondary end points included duration of response (DOR), clinical benefit response rate (CBR), duration of CBR, time to progression (TTP), PFS, OS, and safety.

David S. Siegel, MD, PhD, presented efficacy data at both ASCO and EHA for 266 patients enrolled in study PX-171-003-A1. Patients had a median age of 63 years and a median time since diagnosis of 5.4 years, with 69% of patients having International Staging System stage II or III disease and 28% with unfavorable cytogenetic features by metaphase cytogenetics or fluorescence in situ hybridization. Carfilzomib was dosed on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. During cycle 1, patients received carfilzomib 20 mg/m², escalating to 27 mg/m² in subsequent cycles. Patients could be treated for up to 12 cycles. Responses were assessed by International Myeloma Working Group uniform response criteria.

The ORR for all 266 patients was 22.9%, with a DOR of 7.8 months. Median OS for these patients was 15.4 months. Consistency of benefit for all these measures was demonstrated across many clinically important subgroups as well, including those patients with disease refractory to either bortezomib or lenalidomide in any prior regimen, refractory to both bortezomib and lenalidomide, and refractory to all 5 approved classes of agents (corticosteroids, proteasome inhibitors, IMiDs, alkylating agents, and anthracyclines) (Table 1).

Hematologic Adverse Events

MM is a disease of the bone marrow. The risk of hematologic adverse events (AEs) is increased in many patients who are treated with myelosuppressive agents. Thus, the evaluation of treat-
Safety Profile in Patients with Renal Impairment

At diagnosis and during the course of the disease, patients with MM may have renal impairment, due to either the pathogenesis of disease, comorbidities, or medications and treatments. Up to 50% of newly diagnosed patients have a decrease in creatinine clearance (CrCl), and approximately 9% require dialysis because of severe renal impairment. Approximately 20% develop clinically significant renal dysfunction after diagnosis. Whereas the IMiD lenalidomide requires dose adjustments in MM patients with renal impairment, the proteasome inhibitor bortezomib does not. R. Donald Harvey, PharmD, presented an analysis of the renal safety profile for single-agent carfilzomib as determined from data for the 526 relapsed or relapsed/refractory MM patients treated in 4 phase 2 studies referenced above.

<p>| IMiD and Lenalidomide of A gents |<br />
|-----------------------------|---|
|</p>
<table>
<thead>
<tr>
<th>Overall response rate, %</th>
<th>N=266</th>
<th>N=180</th>
<th>N=169</th>
<th>N=228</th>
<th>N=214</th>
<th>N=44</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.9</td>
<td>15.6</td>
<td>15.4</td>
<td>20.6</td>
<td>20.1</td>
<td>20.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median overall survival, mo</th>
<th>N=61</th>
<th>N=28</th>
<th>N=26</th>
<th>N=47</th>
<th>N=43</th>
<th>N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.4</td>
<td>12.4</td>
<td>11.9</td>
<td>13.8</td>
<td>13.2</td>
<td>15.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median duration of response, mo</th>
<th>N=7.8</th>
<th>N=7.4</th>
<th>N=7.8</th>
<th>N=7.4</th>
<th>N=7.4</th>
<th>N=7.8</th>
</tr>
</thead>
</table>

**Table 1. Consistency of Benefit Across Subgroups in the Phase 2b PX-171-003-A1 Study**

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Refractory to Bortezomib and ≥1 IMiD</th>
<th>Refractory to Both Bortezomib and Lenalidomide</th>
<th>Refractory and/or Intolerant to Bortezomib and ≥1 IMiD</th>
<th>Refractory and/or Intolerant to Both Bortezomib and Lenalidomide</th>
<th>Refractory to All 5 Approved Classes of Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=266</td>
<td>N=180</td>
<td>N=169</td>
<td>N=228</td>
<td>N=214</td>
<td>N=44</td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>22.9</td>
<td>15.6</td>
<td>15.4</td>
<td>20.6</td>
<td>20.1</td>
</tr>
<tr>
<td>Median overall survival, mo</td>
<td>15.4</td>
<td>12.4</td>
<td>11.9</td>
<td>13.8</td>
<td>13.2</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>7.8</td>
<td>7.4</td>
<td>7.8</td>
<td>7.4</td>
<td>7.4</td>
</tr>
</tbody>
</table>

**ImiD indicates immunomodulatory drug.**

Peripheral Neuropathy

Many of the agents used to treat MM can exacerbate or cause painful, treatment-limiting peripheral neuropathy (PN). To further assess the PN safety profile of carfilzomib, a cross-trial analysis was conducted of the 526 patients treated in 4 phase 2 studies (PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005). Thomas Martin, MD, presented results of this analysis at the 17th EHA Congress.

At the time of the analysis, 21.9% of patients had received
Repeating Bortezomib with Carfilzomib

James R. Berenson, MD, and colleagues conducted a phase 1/2 trial to investigate the safety and efficacy of carfilzomib as a replacement for bortezomib in a combination regimen. Eligible patients had to have progressed while receiving their most recent bortezomib-containing combination regimen after at least 4 doses of bortezomib or within 12 weeks of completing their final dose. Combination regimens containing an alkylating agent, thalidomide, bortezomib, or lenalidomide; (2) their primary disease; or (3) another underlying cause; 71.9% had active PN at baseline. Dosing was repeated bortezomib and was administered intravenously (IV) on days 1, 2, 8, 9, 15, and 16 of each cycle. Treatment continued using the same dose(s) and schedule(s) of each drug administered in the previous bortezomib-containing regimen. In cycle 1, carfilzomib 20 mg/m² was given, escalating in cycles 2 to 4 (27, 36, and 45 mg/m², respectively) or until a maximum tolerated dose (MTD) was reached for that regimen. Twenty-seven patients were enrolled and 22 were evaluable at the time of presentation. After a median of 6 cycles, an ORR of 50% was observed. A complete response (CR) was observed in 22.7%, a very good partial response (VGPR) in 4.5%, and a partial response (PR) in 22.7%. An additional 13.6% showed a minor response (MR), and 27% had stable disease (SD). The median TTP was 9.8 months. The most common grade 3/4 hematologic AEs were thrombocytopenia (59%) and lymphopenia (41%). The authors concluded that carfilzomib is an effective and tolerable replacement for bortezomib in patients who are refractory to or intolerant of bortezomib-containing combination regimens.

Carfilzomib Plus the HDAC Inhibitor Panobinostat

Preclinical and clinical studies have demonstrated synergistic anti-MM activity of the combination of panobinostat, an oral pan-histone deacetylase (HDAC) inhibitor, and the proteasome inhibitor bortezomib through the dual inhibition of the aggravating and proteasome pathways. Jesus G. Berdeja, MD, presented the study schema of a single-arm, open-label, multicenter phase 1/2 trial that will be evaluating the safety and efficacy of the combination of panobinostat and carfilzomib in patients with relapsed/refractory MM. The phase 1 study will determine the MTD of the combination of carfilzomib and panobinostat and will follow a standard dose-escalation design. The phase 2 portion of this study will evaluate the ORR in patients with relapsed/refractory MM who will receive treatment with the optimal dose of panobinostat and carfilzomib established during phase 1. Secondary end points will include TTP, PFS, OS, and safety. To date, 7 of the planned 52 patients have been enrolled.

Newly Diagnosed MM

Carfilzomib/Melphalan/Prednisone

Melphalan/prednisone/thalidomide and bortezomib/melphalan/prednisone are 2 combination regimens that have become the standard of care for elderly patients with MM and for those patients with MM who are not eligible for autologous stem-cell transplant (ASCT). Both of these regimens have demonstrated significant benefit over melphalan/prednisone alone in terms of PFS and OS in randomized, phase 3 trials. Philippe Moreau, MD, presented initial results from a phase 1/2 study evaluating the combination regimen of carfilzomib plus MP (CMP) in elderly ASCT-ineligible patients during the Myeloma Oral Abstracts session of ASCO 2012.

This open-label, multicenter trial is recruiting patients aged >65 years. Phase 1 was designed to identify any dose-limiting

Table 2. Treatment-Emergent Grade 3 or 4 Adverse Events in the PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005 Studies

<table>
<thead>
<tr>
<th></th>
<th>Thrombocytopenia (%)</th>
<th>Lymphopenia (%)</th>
<th>Neutropenia (%)</th>
<th>Anemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PX-171-003-A0 (N=46)</td>
<td>28.3</td>
<td>28.3</td>
<td>6.5</td>
<td>37.0</td>
</tr>
<tr>
<td>PX-171-003-A1 (N=266)</td>
<td>30.1</td>
<td>21.1</td>
<td>12.8</td>
<td>23.7</td>
</tr>
<tr>
<td>PX-171-004 (N=164)</td>
<td>14.6</td>
<td>13.4</td>
<td>14.0</td>
<td>14.6</td>
</tr>
<tr>
<td>PX-171-005 (N=50)</td>
<td>28.0</td>
<td>26.0</td>
<td>6.0</td>
<td>28.0</td>
</tr>
<tr>
<td>All Patients (N=526)</td>
<td>24.9</td>
<td>19.8</td>
<td>12.0</td>
<td>22.4</td>
</tr>
</tbody>
</table>
Updates on Carfilzomib from ASCO and EHA

Figure 1. Response Rates in Phase 1/2 Studies of Carfilzomib-Based Therapy for Newly-Diagnosed Patients.

A) Patients >65 years ineligible for transplant treated with carfilzomib/melphalan/prednisone (CMP). B) Patients eligible for transplant treated with carfilzomib/cyclophosphamide/thalidomide/dexamethasone (CYCLONE) in phase 2; median follow-up of 8.2 months. C) Patients who received carfilzomib/lenalidomide/dexamethasone (CRd) and did not proceed to transplant.

CR/nCR indicates complete response/near-complete response; MR, minor response; PR, partial response; VGPR, very good partial response.

Note: These are 3 separate trials, and data are not meant for making comparisons.

Figure 1A

Figure 1B

Figure 1C

toxicity (DLT) and determine the MTD of CMP. In phase 2, investigators assessed safety and evaluated the efficacy of this combination (ORR, PFS, event-free survival [EFS], and OS) in newly diagnosed MM patients. Carfilzomib was given IV on days 1, 2, 8, 9, 22, 23, 29, and 30 for nine 6-week cycles. All patients received 20 mg/m² on days 1 and 2 of cycle 1. Thereafter, cohort 1 (n=6) received 20 mg/m², cohort 2 (n=6) received 27 mg/m², and cohort 3 (n=6) received 36 mg/m². Oral melphalan 9 mg/m² and prednisone 60 mg/m² were given on days 1 to 4 of each cycle. When no MTD was observed, the study was amended to add cohort 4 (carfilzomib 45 mg/m²; n=6). Two patients in cohort 4 experienced DLT (fever and hypotension); thus, the MTD was determined to be carfilzomib 36 mg/m².

At the time of presentation, 43 patients had been enrolled: 6 in each of cohorts 1 to 4 and 19 of the planned 30 for the extension of phase 2. Thirty-five of these patients (median age 74 years) were evaluable for response. After a median of 8 cycles, ORR was 89% (3% CR, 40% VGPR, and 46% PR), with an additional 3% achieving MR (Figure 1A). Two patients had SD and 1 patient had progressed. At a median follow-up of 12 months, OS was 93.9% and EFS 80.7%. Toxicities experienced by these 35 patients included deep vein thrombosis (2), renal impairment (1), infections (5), pericardial effusion (1), fatigue (1), atrial fibrillation (2), cardiac failure (1), and toxic death (1). Of note, only 1 patient experienced any neurotoxicity, and this was at grade 1. Although longer follow-up is necessary, Dr Moreau concluded that these initial results indicate that frontline CMP was a tolerable and very effective combination in elderly MM patients.

Carfilzomib/Cyclophosphamide/Thalidomide/Dexamethasone

Recent investigations are attempting to determine the best combination of agents to use as induction therapy for newly diagnosed patients with MM. Combinations of an IMiD and a proteasome inhibitor, as well as IMiD- or proteasome inhibitor–based 2-, 3-, and 4-drug regimens, have demonstrated efficacy as induction regimens with manageable toxicity in previously untreated patients with MM eligible for ASCT. For example, the safety and efficacy of combining carfilzomib, cyclophosphamide, thalidomide, and dexamethasone (CYCLONE) for ASCT-eligible patients is being investigated in a phase 1/2 trial. Initial results were presented by Joseph R. Mikhael, MD, during the Myeloma Oral Abstracts session at ASCO 2012 and on a poster at the 17th EHA Congress.

The primary goal of the phase 1 portion of this trial was to determine the MTD of carfilzomib when used in this combination regimen. With no DLT observed in phase 1, dosing for phase 2 was set at carfilzomib 20 mg/m² IV on days 1, 2, 8, 9, 15, and 16 of cycle 1 and 27 mg/m² in subsequent cycles; cyclophosphamide 300 mg/m² orally on days 1, 8, and 15; thalidomide 100 mg orally daily; and dexamethasone 40 mg orally on days 1, 8, 15, and 22 of a 28-day cycle. A total of 27 patients were enrolled, 6 in phase 1 and the remainder in phase 2. Median age was 65 years.

At a median follow-up of 8.2 months, 26 of the 27 patients were still alive. The 1 death that occurred was felt to be unrelated to therapy, and 1 patient elected to leave the trial. ORR for the 24 patients treated in phase 2 was 96% (29% CR, 46% VGPR, and 21% PR), with an additional 4% achieving MR (Figure 1B).

The most common low-grade AEs were fatigue, constipation, lethargy, thrombocytopenia, somnolence, neutropenia, increased creatinine, and malaise. Grade 3 AEs were reported in 50% of the patients, with another 21% reporting grade 4 events. Grade 3 nonhematologic AEs (38%) included arthralgias, increased liver function tests, fatigue, and muscle weakness; grade 4 throm-
basis was observed in 8% of patients. Grade 3 hematologic AEs were experienced by 13% of patients and included anemia, lymphopenia, and leukopenia; grade 4 hematologic AEs (17%) included neutropenia and lymphopenia. There were only 7 cases of grade 1 PN, and 1 case of grade 3 tumor lysis syndrome (in cycle 1). All stem cell collections that were attempted were successful.

An extended phase 2 trial has been initiated to explore higher doses of carfilzomib (up to 45 mg/m\(^2\)). The first cohort of patients has been enrolled and is receiving carfilzomib at 20/36 mg/m\(^2\). No DLT has yet been observed.

**Carfilzomib/Lenalidomide/Dexamethasone**

IMiDs and proteasome inhibitors in combination with each other and in combination with dexamethasone have provided rapid, deep, and more durable responses compared with standard treatment approaches. Depth of response has been shown to be associated with improved long-term outcomes for patients with MM. However, maintaining dose levels over the long-term can be limited by emerging and cumulative toxicities.

An interim analysis of a phase 2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd) for relapsed MM showed that 78% of 52 evaluable patients achieved at least a PR, 40% at least a VGPR, and 18% a CR or stringent CR (sCR). This prompted a phase 1/2 study in newly diagnosed patients with MM eligible for ASCT, designed to further improve the depth of response and DOR compared with established treatment approaches, improve tolerability, and minimize the impact on stem cell collection.

In this study (N=53), CRd showed high activity and good tolerability. Carfilzomib was administered IV at 20, 27, or 36 mg/m\(^2\) on days 1, 2, 8, 9, 15, and 16 (1, 2, 15, and 16 after cycle 8); lenalidomide orally at 25 mg/day, days 1 through 21; and dexamethasone at 40/20 mg weekly, cycles 1 through 4/5+ in 28-day cycles; for up to 8 cycles or until disease progression or unacceptable toxicity. After cycle 4, transplant-eligible candidates underwent stem cell collection, and then continued CRd for 4 more cycles with the option of deferred transplantation. CRd maintenance was given during cycles 9 through 24 at the same dose as received in cycles 5 through 8. It was recommended that patients in response continue lenalidomide maintenance past cycle 24 off protocol.

The primary objectives of this study were to determine the MTD of carfilzomib when added to Rd (phase 1) and to assess the safety and efficacy of CRd (combined phase 1/2). Patients ranged in age from 35 to 81 years, with 43% > 65 years (median, 59 years). Of 51 patients with available data, 33% had unfavorable cytogenetics, including 20% with del(13)/t(14), hypodiploidy, 10% t(4;14), and 15% del(17p). At median follow-up of 13 months, all patients had completed at least 1 cycle of therapy and 10 had discontinued therapy during induction (of those, only 1 was due to toxicity, 7 had proceeded to ASCT, and 2 were due to patient or investigator preference). Seven patients are still receiving CRd induction therapy. Thirty-six patients initiated CRd maintenance. At this time, 2 patients have discontinued CRd maintenance (1 due to disease progression and 1 due to patient or investigator preference), 29 are still receiving CRd maintenance, and 5 have proceeded to lenalidomide maintenance. Stem cell collection was possible in 35 of the 38 ASCT-eligible patients (3 declined for insurance reasons).

In the overall population, 42% of patients achieved sCR, 62% achieved ≥ near-complete response (nCR), 81% ≥VGPR, and 98% ≥PR. Responses were generally rapid and durable. In the 46 patients who did not proceed to ASCT, 67% achieved ≥nCR, 83% ≥VGPR, and 100% ≥PR after a median of 12 cycles (Figure 1C). Analysis of response in patients with unfavorable cytogenetics is hampered by the limited number of patients; time-to-event analyses are not possible due to the very low number of events (1 death and 2 progression).

During induction, the CRd regimen was well tolerated, with only 31% of patients requiring a dose modification; supportive measures were usually able to effectively manage AEs. Tolerability was maintained throughout CRd maintenance as well. Dose modifications were limited to 19% for carfilzomib, 28% for lenalidomide, and 31% for dexamethasone. The most common toxicities of any grade during maintenance were lymphopenia (30%), leukopenia (26%), and fatigue (25%). Only 11% of patients experienced any PN, all at grade 1 or 2.

The clinical significance of these data was discussed by Andrzej J. Jakubowiak, MD, PhD, during ASCO 2012 and the 17th EHA Congress. Of the 22 patients with suspected CR, 20 (91%) had no evidence of minimal residual disease by multiparameter flow cytometry. The proportion of patients with ≥nCR and the proportion with sCR both increased with prolonged treatment. For those patients who had completed ≥4 cycles, 45% achieved sCR and 67% achieved ≥nCR (n=49). These rates increased to 61% sCR and 78% nCR for patients who had completed ≥8 cycles (n=36). All patients who achieved sCR maintained that response for a median of 9 months. Although the patient population was small and the number of events low, the 12-month and 24-month PFS rates were estimated to be 97% and 92%, respectively. After extended treatment, patients continued to tolerate treatment well, with limited dose modifications and PN. Dr Jakubowiak concluded that these data compare favorably to the best results with other frontline induction regimens and with sequential ASCT plus post-ASCT consolidation.

**Conclusion**

Taken together, data on carfilzomib-based therapy presented at ASCO and EHA demonstrated favorable safety and efficacy. Results from ongoing clinical studies will continue to delineate the role of this agent in the treatment of MM.

**References**


Nursing Perspectives on Carfilzomib-Based Therapy in Multiple Myeloma

Elizabeth Bilotti, MSN, BSN, APN-C
John Theurer Cancer Center at Hackensack University Medical Center
Multiple Myeloma Division, Hackensack, NJ

In the past decade, several targeted therapies have been approved for treating patients with multiple myeloma (MM). These agents have been associated with improved survival when used at the time of diagnosis or in the relapsed/refractory setting. Recently, the US Food Drug Administration approved another effective agent, carfilzomib, for the treatment of the disease. As mentioned in the main article, this approval was based on results of the single-arm, phase 2b PX-171-003-A1 study, and allows the use of carfilzomib in a narrowly defined patient population. When analyzing the results of this trial, it is important to recognize that relapsed and/or refractory patients eligible for carfilzomib-based therapy have an expected overall survival of less than 9 months. Now that this agent is available, being cognizant of effective adverse-event (AE) management strategies and the ways in which carfilzomib may be used are imperative.

Managing AEs in Pretreated Patients

Consideration of treatment-emergent AEs in patients with MM is always important, but in the heavily pretreated population it is crucial. The underlying disease state as well as prior therapies may contribute to the risk of certain toxicities, including renal impairment, myelosuppression, and peripheral neuropathy (PN). In the PX-171-005 trial, dose modification was not required for patients with renal dysfunction, including those needing dialysis. A cumulative analysis of patients enrolled in single-agent carfilzomib studies revealed changes in renal function, many of which were transient; only 8 patients required treatment discontinuation. Disease progression, hypercalcemia, and dehydration may be contributing factors to this condition, and require immediate intervention. Data from this study not only provide the rationale for monitoring renal function in all patients receiving carfilzomib, they also reiterate the need to maintain kidney health. Patients should be reminded to maintain adequate oral hydration (2-3 L/day), avoid nephrotoxic agents, and report any episodes of prolonged diarrhea or vomiting.

In patients with advanced myeloma who have been treated with multiple lines of therapy, baseline cytopenias are common. Although treatment-emergent grade 3 or 4 hematologic AEs were reported in recent trials, they rarely led to dose reductions or discontinuations. Platelet counts drop after the first week of each carfilzomib cycle and recover by the beginning of the next cycle. Monitoring blood counts, educating patients regarding the significance of cytopenias, and instructing them about signs and symptoms to report as well as providing growth factor and transfusion support will allow therapy to continue as scheduled.

Many patients with MM have preexisting PN at the time of treatment, which may be due to the disease itself, prior therapy with agents such as bortezomib or thalidomide, or specific comorbidities (eg, diabetes). PN can be a dose-limiting toxicity and may frequently affect both the patient’s quality of life and functional status. In the single-agent registration trial of carfilzomib, although 77% of patients had grade 1 or 2 PN at baseline, only 12.4% had treatment-emergent PN (new onset or worsening of preexisting PN). Only 1.1% of patients had grade 3 PN, and none had grade 4 PN. The analysis of the 526 patients in the four phase 2 trials reported an incidence of 12.6% grade 1 or 2 PN, with only 1.3% grade 3 PN, and no grade 4 PN. Preclinical data suggest that the difference in the rates of PN between carfilzomib and bortezomib is due to off-target effects. Although the incidence of this toxicity is low with carfilzomib-based therapy, nurses must not neglect to monitor for new-onset PN or worsening of symptoms. Evaluating patients each time they arrive for treatment and follow-up allows for prompt and appropriate interventions that can help minimize severity and complications.

PN can be a dose-limiting toxicity and may frequently affect both the patient’s quality of life and functional status.

Carfilzomib-Based Therapy for Newly Diagnosed Patients with MM

Recently, data were presented regarding carfilzomib in frontline combination regimens. It is important to note that at this time, the use of carfilzomib in newly diagnosed patients or in combination with other agents outside the context of an approved clinical trial is off-label. When treating newly diagnosed patients with MM, determining their transplant eligibility is crucial. Once that decision has been made, many factors determine the choice of therapy. These include performance status, comorbidities, access to care, insurance coverage, patient preference, and adherence. The driving factors for treatment selection are often response rates, including depth and duration of response, and toxicity.
At this time, the most impressive results in the frontline nontransplant setting have been related to the use of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd). All attempted stem cell harvests were successful, and those patients who chose to defer transplant continued to experience an improvement in response with time on therapy. The toxicity profile associated with CRd was managed with only one treatment discontinuation due to AEs.

Early results of the CYCLONE trial, which evaluated a combination of cyclophosphamide, carfilzomib, thalidomide, and dexamethasone are also promising. This regimen may be a good choice for patients presenting with renal impairment; many of the toxicities were manageable and appeared to be thalidomide-related.

Investigators are also studying a combination of carfilzomib, melphalan, and prednisone (CMP) for the treatment of transplant-ineligible patients. Based on data from the phase 3 VISTA trial, we know that a combination of bortezomib, melphalan, and prednisone (VMP) is effective in this population of patients. Although a direct comparison between these trials cannot be made, the overall response rate data for CMP and VMP are similar, but not the depth of response at this early stage. Time will tell with continued treatment, but it is important to recognize that so far, only one case of PN (grade 1) has been reported with CMP. This is an important consideration in the treatment of older, transplant-ineligible patients with MM.

**Conclusion**

Carfilzomib is an exciting new agent that fills an unmet need for individuals with relapsed and/or refractory myeloma. It is important for nurses and other healthcare professionals to stay updated on safety and efficacy results from ongoing clinical trials of this drug and be aware of effective AE management strategies so that patients can receive the optimal benefits of therapy.

**References**

2. Kyprios (carfilzomib) for Injection, for intravenous use [prescribing information]. South San Francisco, CA: Onyx Pharmaceuticals, Inc; 2012.
9. Harvey RD, Lonial S, Patel P, et al. Carfilzomib dose and schedule need not be adjusted for baseline renal dysfunction, including patients on hemodialysis. Poster presented at: 17th Congress of the European Hematology Association (EHA); June 14-17, 2012; Amsterdam, the Netherlands. Poster 0844.
17. Jakubowiak AJ, Griffith KA, Dyrdeld D, et al. Stringent complete response (sCR) in patients (pts) with newly diagnosed multiple myeloma (NDMM) treated with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX). Oral presentation at: 2012 American Society of Clinical Oncology (ASCO) Annual Meeting; June 1-5, 2012; Chicago, IL. Abstract 8011.
What is a QR Code?
A QR Code is a Quick Response Code.

What does a QR Code do?
A QR Code makes print interactive, and it lets you experience educational content in a whole new way.

How does it work?
To use 2D barcodes, download the ScanLife app:
• Text “scan” to 43588
• Go to www.getscanlife.com on your smartphone’s web browser; select “Download”
• Visit the app store for your smartphone

Now that you know how QR Codes work, it’s time to interact with them. We will use them in upcoming publications, so please scan them for a new way to experience educational offerings.