Multiple myeloma (MM), a clonal malignancy of plasma cells, is responsible for 10% to 15% of all hematologic malignancies and for 20% of deaths resulting from hematologic cancers. In most patients, MM evolves from monoclonal gammopathy of undetermined significance (MGUS), an asymptomatic plasma-cell disorder. In some patients, MGUS progresses through an intermediate, asymptomatic, premalignant stage, smoldering MM, before the disease is diagnosed. Although the cause of MM is not known, it is more common in older individuals aged >65 years than in younger persons, is more common in blacks than in whites, and is slightly more common in men than in women. Other factors associated with MM include exposure to certain chemicals, being overweight or obese, having been exposed to radiation, or having another plasma-cell disorder.

The Burden and Impact of Multiple Myeloma

In 2012, the American Cancer Society estimated that there would be 21,700 patients diagnosed with MM and 10,710 deaths would occur from MM. Patients with MM frequently experience fatigue, bone pain, osteolytic bone lesions, and/or compression fractures. End-organ damage, including hypercalcemia, anemia, renal dysfunction, or bone lesions caused by proliferation of myeloma cells, is considered diagnostic of symptomatic MM. Patients with MM experience leukopenia and thrombocytopenia in addition to anemia, and they are at risk for recurrent infections. Also, peripheral neuropathy (PN) can be present at diagnosis. This is important, because cytopenias and PN are significant toxicities associated with some antimyeloma therapies.

The median survival for patients with MM was less than 1 year before the introduction of alkylating agents in the 1960s. Median survival increased with the introduction of high-dose chemotherapy and autologous stem-cell transplant (ASCT) in the 1980s. Supportive therapies, such as growth factors, bisphosphonates, and improved modalities to treat fractures, have also played a role in increasing survival.

Much of the increased survival for patients with MM since approximately 2000 can be attributed to the development of novel, targeted therapies, including the immunomodulatory agents thalidomide and lenalidomide, and the proteasome inhibitor bortezomib.

Current treatment approaches for newly diagnosed or relapsed MM are based on patient-specific factors, such as eligibility for ASCT and the presence of comorbidities, and disease-related factors, such as high-risk characteristics. Almost all patients with MM will eventually experience a relapse. The duration of remission in patients with relapsed MM is shorter with each successive treatment regimen. Once MM relapses, it tends to become more resistant to chemotherapy over time, and patients are likely to require continuous treatment with one regimen after another as their disease progresses. Therefore, despite the progress in developing novel, targeted therapies, MM remains incurable.

FDA Approves Carfilzomib for Myeloma

On July 20, 2012, the US Food and Drug Administration (FDA) granted accelerated approval for carfilzomib for injection (Kyprolis; Onyx Pharmaceuticals), which is indicated for the treatment of patients with MM who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent (thalidomide or lenalidomide), and have demonstrated disease progression on or within 60 days of the completion of the last therapy.

The approval of carfilzomib was based on the response rate determined in a single-arm clinical trial and is not based on survival. Furthermore, a clinical benefit (eg, increased survival or improved symptoms) has not been confirmed.

Carfilzomib Fills an Unmet Need

Currently, the median survival for patients with MM that is refractory to bortezomib is 9 months; for those with MM refractory to lenalidomide, the median survival is only 5 months. As the second-in-class—approved proteasome inhibitor, carfilzomib should provide a new option...
for patients whose MM has become resistant to bortezo-
mib, the first approved proteasome inhibitor for MM.10

As a condition of the accelerated approval, Onyx
Pharmaceuticals will submit the results of an ongoing
phase 3 randomized trial comparing lenalidomide plus
low-dose dexamethasone with lenalidomide plus low-
dose dexamethasone plus carfilzomib in patients with
MM that has relapsed or is refractory after 1 to 3 prior
therapies. The primary end point of this phase 3 trial is
progression-free survival.9 Carfilzomib is not currently
indicated for the treatment of newly diagnosed MM.

According to Jamie Shapiro, PharmD, BCOP, Clini-
cal Coordinator at H. Lee Moffitt Cancer Center,
Tampa, FL, “Carfilzomib is an exciting new option for
our patients with progressive disease after receiving treat-
ment with bortezomib and lenalidomide. Carfilzomib is
an important addition to our antimyeloma therapies and
meets an unmet need in our patients with progressive
multiple myeloma.”

Page Bertolotti, RN, BSN, OCN, of Cedars-Sinai
Outpatient Cancer Center at the Samuel Oschin Com-
prehensive Cancer Institute, Los Angeles, CA, com-
mented that, “Carfilzomib is an important treatment
option for our patients with refractory multiple myelo-
ma. We had several patients who missed the clinical trial
enrollment and waited anxiously for the approval.”

### Clinical Pharmacology

#### Mechanism of Action

Carfilzomib is in the epoxyketone class of proteasome
inhibitors and irreversibly binds to the proteolytic core
particle within the 26S proteasome. Carfilzomib has se-
lectivity for the chymotrypsin-like activity of protea-
some, and in preclinical studies it has induced cell-cycle
arrest and programmed cell death and activated stress
response pathways.10,11

### Dosing and Administration

Carfilzomib is administered intravenously over 2 to 10
minutes on 2 consecutive days each week for 3 weeks on
days 1, 2, 8, 9, 15, and 16, followed by a 12-day rest peri-
don from days 17 to 28. These 28 days constitute 1 treat-
mence cycle.11 This dosing regimen is shown in Table 1.

The dose for cycle 1 is 20 mg/m² using the baseline
patient’s body surface area. If this dose is tolerated, the
dose is increased to 27 mg/m² beginning at cycle 2, and the
dose is maintained at this level for subsequent cycles.11

### Hydration and Premedication

Patients should be hydrated with intravenous (IV)
normal saline or with another appropriate IV fluid before
each dose of carfilzomib in cycle 1 and after administra-
tion, as needed, to reduce the risk of renal toxicity and
tumor lysis syndrome. Maintaining adequate hydration
and monitoring blood chemistries is recommended. Hy-
dration can be continued for subsequent cycles if needed.11

To reduce the incidence and severity of infusion reac-
tions, patients should receive premedication with 4-mg
oral or IV dexamethasone before all doses in cycle 1 and
the first cycle of escalation to the higher dose. Pre-
medication with this dose of dexamethasone may be
administered if infusion reactions occur or recur during
treatment.11

### Dose Modifications Based on Toxicity

The dose of carfilzomib may be modified if hematolog-
ic or nonhematologic toxicities occur, including grade 3
or grade 4 cytopenias; cardiac, hepatic, or renal toxici-
ties; pulmonary complications; PN; or other toxicities.
In general, carfilzomib is withheld until resolution, fol-
lowed by restarting therapy at the same or at a reduced
dose, depending on the type of toxicity and whether it
was attributable to carfilzomib.11
Pivotal Phase 2 Clinical Trial

Carfilzomib was approved by the FDA based on the results of a single-arm, multicenter phase 2 clinical trial enrolling 266 patients with relapsed MM who had received at least 2 previous therapies that included bortezomib and either thalidomide or lenalidomide. The results of this trial have recently been published.

Trial Design

The trial included patients with MM who had a response rate of ≤25% to the most recent therapy or had disease progression during or within 60 days of the most recent therapy they received before enrolling in the trial. Patients received carfilzomib by IV infusion over 2 to 10 minutes on 2 consecutive days weekly for 3 weeks followed by a 12-day rest period (one 28-day cycle) until disease progression, unacceptable toxicity, or for a maximum of 12 cycles. The carfilzomib dose was 20 mg/m^2 for the first cycle and was escalated to 27 mg/m^2 for subsequent cycles.

Premedication with 4 mg of dexamethasone was administered before each dose during cycle 1 and during the first dose escalation cycle and subsequently, when needed, to reduce the incidence and severity of infusion reactions.

Patient Population

Key baseline patient demographic and disease characteristics are listed in Table 2.

Safety Profile

The most common adverse reactions experienced by ≥30% of patients in clinical trials included fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia.

The safety of carfilzomib as monotherapy or with premedication with dexamethasone has been assessed in 526 patients with relapsed and/or refractory myeloma. This patient population includes the 266 patients treated in the phase 2 approval trial. Patients received a median of 4 treatment cycles of carfilzomib.

Of the total population, there were 37 deaths (7%) within 30 days of the last carfilzomib dose, including 21 from disease progression; 5 from cardiac issues (eg, acute coronary syndrome, cardiac arrest, and cardiac disorder); 4 from end-organ failure (ie, multiorgan, hepatic, and renal); 4 from infection; and 1 each from dyspnea, intracranial hemorrhage, and unknown causes.

Serious adverse reactions were reported in 45% of patients receiving carfilzomib—the most common being pneumonia (10%), acute renal failure (4%), pyrexia (3%), and congestive heart failure (3%). In addition, 15% of the patients had serious adverse reactions that led to the discontinuation of carfilzomib monotherapy.

Peripheral neuropathy. PN is often associated with MM therapies. Any-grade PN occurred in 14% of patients enrolled in carfilzomib clinical trials, but only 1% of patients experienced grade 3 PN. Serious PN events resulting in dose reductions or treatment discontinuations occurred in <1% of patients.

The incidence of PN associated with carfilzomib is lower than that associated with thalidomide or with bortezomib, and the low rate of new-onset or worsening PN suggests that patients with PN associated with other therapies may be able to tolerate treatment with carfilzomib.

Commenting on carfilzomib, Dr Shapiro noted that, “One of the most beneficial aspects with carfilzomib is the low incidence of peripheral neuropathy.”

Renal events. The most common renal adverse reactions of any grade were increased blood creatinine (24%) and renal failure (9%). Grade 3 renal events occurred in 6% of patients and grade 4 in 1%. Discontinuations resulting from increased blood creatinine and acute renal failure, each, occurred in 1% of patients. Furthermore, 1 patient died from concurrent sepsis and worsening renal function.

Response

Response rates for the phase 2 approval trial population were determined by an independent review committee. The overall response rate was 22.9% (n = 61); of these, 17.6% of patients (n = 47) achieved a partial response (PR); 4.9% (n = 13) achieved a very good PR; and 0.4% (n = 1) achieved a complete response. The median duration of response was 7.8 months.
Overall survival (OS) was 15.6 months in this group of patients with heavily pretreated MM refractory to or intolerant of bortezomib and lenalidomide, and compares favorably to an OS of 9 months in similar settings. Response and survival may have been affected by treatment discontinuation resulting from progressive disease in almost 23% of patients in the first 2 treatment cycles.12

Warnings and Precautions

A number of adverse reactions associated with carfilzomib are discussed in the “Warnings and Precautions” section of the prescribing information (Table 3).11 These reactions, which may require dose modification, include cardiac arrest, congestive heart failure, myocardial ischemia, pulmonary hypertension and other complications, infusion reactions, tumor lysis syndrome, thrombocytopenia, and hepatic toxicity and failure.11

Women of child-bearing potential are advised to avoid becoming pregnant during treatment with carfilzomib, because it has been shown to cause fetal harm in animal studies.11

References


<table>
<thead>
<tr>
<th>Table 3 Carfilzomib Warnings and Precautions</th>
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<tbody>
<tr>
<td>Potential adverse reactions</td>
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<tr>
<td>Description</td>
</tr>
<tr>
<td>Cardiac events</td>
</tr>
<tr>
<td>• Cardiac failure in 7% of patients</td>
</tr>
<tr>
<td>• Death resulting from cardiac arrest within 1 day of administration reported</td>
</tr>
<tr>
<td>• Patients with heart failure, myocardial infarction within preceding 6 months, and uncontrolled conduction abnormalities may be at increased risk</td>
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<tr>
<td>Pulmonary arterial hypertension</td>
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<tr>
<td>• Reported in 2% of patients</td>
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<tr>
<td>• ≥Grade 3 in &lt;1%</td>
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<tr>
<td>Pulmonary complications</td>
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<tr>
<td>• Dyspnea in 35% of patients in clinical trials</td>
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<tr>
<td>• Grade 3 in 5%</td>
</tr>
<tr>
<td>• 1 death reported</td>
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<tr>
<td>Infusion reactions</td>
</tr>
<tr>
<td>• Characterized by fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina</td>
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<tr>
<td>• Can occur immediately or up to 24 hours after administration</td>
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<tr>
<td>• Premedication with dexamethasone reduces incidence and severity</td>
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<tr>
<td>Tumor lysis syndrome</td>
</tr>
<tr>
<td>• Occurred in &lt;1% of patients</td>
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<tr>
<td>• High tumor burden may increase risk</td>
</tr>
<tr>
<td>• Ensure patients are well hydrated before administration</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>• Occurred in 36% of patients</td>
</tr>
<tr>
<td>• Grade 4 in 10%</td>
</tr>
<tr>
<td>• Platelet nadirs around day 8 of each cycle, recover to baseline by start of next cycle</td>
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<tr>
<td>• Monitor platelet counts frequently</td>
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<tr>
<td>Hepatic toxicity and hepatic failure</td>
</tr>
<tr>
<td>• Hepatic failure including deaths in &lt;1% of patients</td>
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<tr>
<td>• Carfilzomib can cause elevated serum transaminases and bilirubin</td>
</tr>
<tr>
<td>• Monitor liver enzymes frequently</td>
</tr>
</tbody>
</table>

Source: Kyprolis (carfilzomib) for Injection [prescribing information]. South San Francisco, CA: Onyx Pharmaceuticals, Inc; July 2012.