New Directions in the Treatment of Multiple Myeloma: Reports on Carfilzomib Therapy from ASCO 2013 and EHA 2013
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This publication further provides benefit design decision makers the integrated industry information they require to devise formularies and benefit designs that stand up to today’s special healthcare delivery and business needs.

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Multiple myeloma (MM), the most common type of plasma cell cancer, is characterized by malignant plasma cells in the bone marrow. As these malignant myeloma cells grow and accumulate in the bone marrow, they produce abnormal antibodies and inhibit production of both normal blood cells and normal bone-forming cells (osteoblasts) in the bone marrow. Untreated, MM can result in severe medical consequences, including calcium elevation in the blood, renal insufficiency, anemia, and lytic bone lesions or osteoporosis.

The American Cancer Society determined that approximately 21,700 new cases of MM would be diagnosed in the United States in 2012, with an estimated 10,700 deaths. MM is slightly more common in men than in women, and the incidence of MM is about twice as high in African Americans as it is in Caucasians. While a diagnosis of MM can occur in patients in their 40s, the median age at diagnosis is currently 62 years.

As additional agents have been approved by the US Food and Drug Administration (FDA) for MM, treatment selection has become a multifaceted process for patients and their hematologists. Antimyeloma treatments now available in the United States include bortezomib (intravenous [IV], subcutaneous), carfilzomib (IV), thalidomide (oral), lenalidomide (oral), pomalidomide (oral), pegylated liposomal doxorubicin (IV), melphalan (oral), cyclophosphamide (IV), and dexamethasone (oral). High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is also considered for selected younger patients with MM.

Today, drug regimens are tailored to each patient with MM according to factors such as physical examination and test results, risk status based on disease presentation and cytogenetics, age and general health, and the nature of any treatment- and disease-related complications.

The treatment paradigm for MM continues to evolve in light of the development and introduction of novel agents as well as the growing knowledge of disease biology. Since the introduction of newer therapies in the late 1990s, clinical outcomes for patients with MM, including survival, have improved significantly. One of the newest antimyeloma agents, carfilzomib, was approved in the United States as a single-agent treatment for patients with MM who have received at least 2 prior treatments, including bortezomib and an immunomodulatory drug (ie, lenalidomide or thalidomide), and who have demonstrated disease progression on or within 60 days of completion of the last therapy. This approval was based on response rate data from a single-arm multicenter clinical trial and was not based on survival. Clinical benefit (ie, improvement in survival or symptoms) has not been verified.

**Updates of Carfilzomib Clinical Trials in Multiple Myeloma and Other Tumor Types**

Since its accelerated approval for relapsed or refractory MM in July 2012, carfilzomib has continued to demonstrate efficacy and safety in patients with both relapsed or refractory and newly diagnosed MM. Oral presentations and posters based on ongoing carfilzomib clinical studies in MM and other tumor types were presented at the 2013 American Society of Clinical Oncology (ASCO) meeting, which was held from May 31 to June 4 in Chicago, and the 18th Congress of the European Hematology Association (EHA), which was held June 13-16 in Stockholm, Sweden. A summary of the findings is presented below.

**Carfilzomib Safety in Multiple Myeloma**

**Cardiovascular and Pulmonary Safety**

Shebli Atrash, MD, Assistant Professor of Medicine at the University of Arkansas for Medical Sciences and Myeloma Institute for Research and Therapy, Little Rock, and colleagues reported cardiovascular (CV) events in late-stage, heavily pretreated patients with relapsed and refractory MM who received salvage carfilzomib therapy. Most of the 143 patients had undergone prior ASCT.
Carfilzomib 20 mg/m² to 45 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle was given alone or with weekly dexamethasone 4 mg to 40 mg during the first cycle and with other agents during the second and later cycles. Other agents that were combined with carfilzomib included lenalidomide, thalidomide, cyclophosphamide, doxorubicin, cisplatin, and vorinostat. Any event requiring hospitalization was considered to be a “serious” CV event. B-type natriuretic peptide values were monitored. In this study, carfilzomib was given for a median of 2 cycles.

Of the 27 patients who experienced a serious CV event, 21 had preexisting CV risk factors, 11 developed congestive heart failure (CHF) or experienced worsening of existing CHF, and 3 experienced cardiopulmonary arrest. Left ventricular ejection fraction decreased from a median of 55% to 33% (pretreatment vs posttreatment). Thirteen patients required hospitalization for hypotension (N = 6), arrhythmia (N = 2), hypertension (N = 2), pulmonary edema (N = 1), pulmonary embolism (N = 1), or pulmonary hypertension (N = 1). A significant increase in B-type natriuretic peptide levels was recorded.

The incidence of CV events following carfilzomib administration in heavily pretreated patients with relapsed and refractory MM was occasional. Due to confounding factors and the uncontrolled nature of the data, a direct correlation between carfilzomib and serious CV events cannot be conclusively determined.

### Carfilzomib Combinations in Newly Diagnosed Multiple Myeloma

#### Carfilzomib, Lenalidomide, and Dexamethasone

Neha Korde, MD, Multiple Myeloma Section, National Cancer Institute, National Institutes of Health, Bethesda, MD, and colleagues reported updated results from a single-arm phase 2 trial using carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) followed by lenalidomide extended dosing (CRd-R) in patients newly diagnosed with MM. The study’s primary end point was the occurrence of neuropathy of grade 3 or higher severity.

Patients with newly diagnosed MM who had undergone prior ASCT and those who had not undergone prior ASCT were included in the study. Carfilzomib (20-36 mg/m²) was given on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Lenalidomide (25 mg) was given on days 1 to 21. Dexamethasone (IV 20 mg/oral 10 mg) was given on days 1, 2, 8, 15, 16, 22, and 23. Extended therapy with lenalidomide (10 mg) was administered after 8 cycles of CRd to patients who achieved a clinical outcome of stable disease (SD) or better.

As of June 2013, 36 patients were evaluable for toxicity and response after a median of 8.5 cycles of therapy. The mean baseline M-protein (N = 31) was 3.0 g/dL (range, 1.0-7.1 g/dL). Isotypes included 7 immunoglobulin (Ig)A, 24 IgG, 4 kappa, and 1 lambda.

No grade 3 or higher neuropathy was reported in this study, such that it met the primary end point. The percentage of patients with at least a very good partial response (VGPR) increased with subsequent CRd cycles. The median time to stringent complete response (sCR) was 5 cycles. After 8 cycles of CRd, 76% obtained a near complete response (nCR), complete response (CR), or sCR. After a median of 8.5 cycles, the overall response rate (ORR) was 97%. Among patients who had achieved sCR or nCR, all who underwent assessment for minimal residual disease were negative. After a median follow-up of 9 months, progression-free survival (PFS) was 83.3%. Mean M-protein levels (N = 31) declined by 85% after 2 cycles of CRd.

Toxicities with CRd were similar to those previously reported. The most common grade 3 or 4 toxicities included nonhematologic rash, electrolyte disturbance, and liver function test elevation. Hematologic grade 3 or 4 toxicities included lymphopenia, anemia, and neutropenia.

CRd-R in newly diagnosed patients with MM was well tolerated and demonstrated deep response rates.

#### Prolonged Carfilzomib, Lenalidomide, and Dexamethasone

In June 2012, Andrzej Jakubowiak, MD, PhD, Professor of Medicine and Director of the Myeloma Program of The University of Chicago, IL, and colleagues reported updated results of an investigator-initiated phase 1/2 trial conducted under the auspices of...
the Multiple Myeloma Research Consortium. This trial evaluated the CRd combination—carfilzomib (20-36 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle), lenalidomide (25 mg on days 1-21), and low-dose dexamethasone (weekly at 40 mg for cycles 1-4, then weekly at 20 mg for cycles 5-8)—in patients newly diagnosed with MM. At that time, safety and efficacy data were reported after patients had received a median of 12 cycles of CRd treatment and had been followed for a median of 13 months.11

In May 2013, Jakubowiak and colleagues presented newly updated results after extended CRd treatment. Fifty-three patients with newly diagnosed MM in the CRd trial were followed for a median of 25 months. Seven of these patients opted for ASCT after cycle 4 of CRd. Twenty-four patients received lenalidomide maintenance for a median of 8 cycles. Outcome measures included response, PFS, and overall survival (OS). Table 1 shows response to CRd after a median follow-up of 25 months.12

The median times to achieve ≥VGPR, ≥nCR, and sCR were 3.7, 6.7, and 13.1 cycles, respectively.12

Extended use of CRd was effective and well tolerated in patients with newly diagnosed MM. Depth of response improved over the course of CRd treatment.12

**Carfilzomib, Melphalan, and Prednisone in Elderly Patients**

Cyrielle Touzeau, MD, from the Service d’Hématologie, Hôpital Hôtel-Dieu, Centre Hospitalier Universitaire de Nantes, France, and colleagues reported findings from a phase 1/2 study evaluating the safety of the combination of carfilzomib, melphalan, and prednisone (CMP) in elderly (>65 years) newly diagnosed patients with MM. Carfilzomib was initiated at 20 mg/m² and escalated to 27, 36, and 45 mg/m² on days 1, 2, 8, 9, 22, 23, 29, and 30 of a 42-day cycle. Melphalan (9 mg/m²) and prednisone (60 mg/m²) were given on days 1 to 4 of every 42-day cycle.13

A total of 24 patients were enrolled in the phase 1 portion of the trial. Two dose-limiting toxicities, fever and hypotension, resulted in a maximum tolerated dose of 36 mg/m² for carfilzomib. This maximum tolerated dose is being administered to an additional 44 patients in the ongoing phase 2 portion of the trial. After a median of 12 months of follow-up, grade 3 peripheral neuropathy (PN) was noted in 1 patient (1.5%); no grade 4 PN was seen. Three patients (4.5%) experienced grade 3 or 4 CHF during the trial.13

To date, efficacy results with the CMP combination are at least comparable to those seen in previous studies conducted in elderly newly diagnosed patients with MM. In this study, the ORR among 66 patients receiving CMP for a median of 12 months was 91%, and ≥VGPR was 56%. Among patients taking all doses of carfilzomib for a median of 12 months, median PFS is 22.0 months. The projected 2-year OS is 87%.13

**Carfilzomib, Cyclophosphamide, and Dexamethasone in Elderly Patients**

Sara Bringhen, MD, Myeloma Unit, University of Torino, Italy, and colleagues reported on the efficacy and safety of carfilzomib, cyclophosphamide, and dexamethasone (CCd) in elderly patients with newly diagnosed MM. Patients were given cyclophosphamide (300 mg/m² on days 1, 8, and 15 of a 28-day cycle), dexamethasone (40 mg on days 1, 8, 15, and 22), and carfilzomib (20 mg/m² on days 1 and 2 and 36 mg/m² on days 8, 9, 15, and 16 of cycle 1; 36 mg/m² on days 1, 2, 8, 9, 15, and 16 of the following cycles) for cycles 1 to 9. Beginning with cycle 10, patients received maintenance therapy of carfilzomib (36 mg/m² on days 1, 2, 15, and 16 every 28 days) until progression or intolerance.14

Forty-one patients were evaluated for response to CCd after at least 4 cycles, with a median follow-up of 8 months. The 1-year PFS was 85%, and the 1-year OS was 86%. As shown in Table 2, responses to CCd improved over time.14

Fifty-six patients were evaluated for safety after at least 1 cycle of CCd. Hematologic adverse events (AEs) included grade 4 neutropenia in 2 patients (4%). Nonhematologic grade 3 or 4 AEs included infections (4 patients, 7%), cardiac (2 patients, 4%), constitutional (2 patients, 4%), renal (2 patients, 4%), and gastrointestinal (1 patient, 2%) complications.14

At least 1 grade 3 or 4 event was reported in 11 (20%) of 56 patients. Six patients (11%) discontinued treatment because of AEs. Nine patients (16%) required carfilzomib dose reductions secondary to AEs.14

Combination therapy with CCd was well tolerated.
and showed beneficial activity in elderly patients with newly diagnosed MM.\textsuperscript{14}

**Carfilzomib Combinations in Relapsed and/or Refractory Multiple Myeloma**

**Carfilzomib, Lenalidomide, and Dexamethasone**

In 2011, Michael Wang, MD, Tenured Associate Professor, Department of Lymphoma/Myeloma, Division of Cancer Medicine of The University of Texas MD Anderson Cancer Center, Houston, and colleagues reported interim data from a phase 1b/2 study of CRd therapy in 84 patients with relapsed or progressive MM.\textsuperscript{15} Final results of this study were presented by Dr Wang at the 2013 ASCO meeting, and by Ruben Niesvizky, MD, Associate Professor of Medicine, Weill Cornell Medical College and Director of the Multiple Myeloma Service at the Center of Excellence for Lymphoma and Myeloma at New York Presbyterian Hospital-Cornell Medical Center, NY, and colleagues, at EHA.\textsuperscript{16,17}

Carfilzomib 15 mg/m\textsuperscript{2} to 27 mg/m\textsuperscript{2} was administered on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle, while lenalidomide 10 mg to 25 mg was given daily on days 1 to 21, and dexamethasone 40 mg was given weekly. The maximum planned doses were 20 mg/m\textsuperscript{2} on days 1 and 2 of cycle 1 and 27 mg/m\textsuperscript{2} thereafter for carfilzomib, 25 mg daily for lenalidomide, and 40 mg weekly for dexamethasone, given no maximum tolerated dose.\textsuperscript{16}

Fifty-two patients with relapsed or progressive MM were followed for a median of 24.4 months at the maximum planned dose. Most of these patients had received prior bortezomib or lenalidomide. Primary outcome measures included ORR and PFS as shown in Table 3.\textsuperscript{16}

AEs associated with CRd in these patients with relapsed or progressive MM were similar to those seen in earlier studies using single-agent carfilzomib. A median of 8.5 carfilzomib cycles were initiated, and 4% of patients required carfilzomib dose reductions. Fifteen percent of patients discontinued carfilzomib due to AEs.\textsuperscript{16}

CRd therapy produced responses and was well tolerated in patients with relapsed or progressive MM. The CRd combination is currently undergoing further evaluation in phase 2 and phase 3 trials in patients with relapsed or progressive MM as well as newly diagnosed MM.\textsuperscript{16}

**Carfilzomib as a Replacement for Bortezomib**

James Berenson, MD, Institute for Myeloma & Bone Cancer Research in Los Angeles, California, and colleagues conducted a phase 1/2 trial to investigate the safety and efficacy of replacing bortezomib with carfilzomib in 14 unique bortezomib-containing regimens for bortezomib-treated patients with relapsed and refractory MM. Carfilzomib, with doses escalated to 45 mg/m\textsuperscript{2} or to the maximum tolerated dose for each regimen, was given on days 1, 2, 8, 9, 15, and 16 of each cycle.\textsuperscript{18}

Thirty-seven patients were evaluated for safety and efficacy after a median of 4 cycles of various carfilzomib-based combinations. Combinations included bendamustine, clarithromycin, cyclophosphamide, dexamethasone, melphalan, methylprednisolone, pegylated liposomal doxorubicin, thalidomide, lenalidomide, and ascorbic acid. Twelve patients continued to maintain therapy.\textsuperscript{18}

Primary outcome measures for the 37 patients with relapsed and refractory MM showed clinical benefit in 63% of patients: CR, 8%; VGPR, 16%; partial response (PR), 19%; and minimal response (MR), 19%. SD was seen in another 16%. The median time to progression was 9.2 months. Lymphopenia (35%), thrombocytopenia (19%), neutropenia (11%), and anemia (8%) were the most common grade 3 AEs.\textsuperscript{18}

Replacing bortezomib with carfilzomib is an effective and well-tolerated general treatment strategy for patients with MM who have progressed while receiving their most recent bortezomib-containing combination regimen.\textsuperscript{18}

**Carfilzomib, Lenalidomide, Vorinostat, and Dexamethasone**

Elizabeth Bilotti, MSN, BSN, APN-C, Hackensack University Medical Center, NJ, and colleagues presented results from a phase 1/2 study that investigated the synergistic effects and tolerability of a 4-drug regimen—carfilzomib, lenalidomide, vorinostat, and dexamethasone (QUAD)—in patients with relapsed and/or refractory MM.\textsuperscript{19} Vorinostat, a histone deacetylase inhibitor, is currently approved by the FDA for use in cutaneous

| Table 3 | Efficacy Outcomes with CRd in Patients with Relapsed or Progressive Multiple Myeloma |
|---|---|---|
| Efficacy parameter | Overall (N = 84) | Maximum planned dose (N = 52) |
| ORR, % | 69.0 | 76.9 |
| VGPR, % | 36.9 | 38.5 |
| sCR, % | 3.6 | 3.8 |
| Median duration of response, months | 18.8 | 22.1 |
| Median PFS, months | 11.8 | 15.4 |

CRd indicates carfilzomib, lenalidomide, and low-dose dexamethasone; ORR, overall response rate; PFS, progression-free survival; sCR, stringent complete response; VGPR, very good partial response.

Source: Reference 16.
T-cell lymphoma and has demonstrated activity in MM when combined with lenalidomide and dexamethasone.\textsuperscript{20} Objectives of the QUAD study included determining the maximum tolerated dose of the 4-drug combination and assessing responses, time to progression, and time to next therapy.\textsuperscript{19}

All patients had relapsed and/or refractory MM following at least 1 line of therapy. Lenalidomide was administered on days 1 to 21 of a 28-day cycle. Vorinostat was given on days 1 to 7 and 15 to 21. Carfilzomib was given on days 1, 2, 8, 9, 15, and 16. Dexamethasone was given on days 1, 8, 15, and 22. Dose escalation followed a standard 3+3 schedule (3 patients in each cohort, first cohort at starting dose and subsequent cohorts at increasing doses in planned increments) during the first cycle, presuming no dose-limiting toxicities occurred.\textsuperscript{19}

As of May 30, 2013, 17 patients were enrolled. All patients had prior ASCT and prior medical treatment. In this trial, all patients experienced drug-related AEs. These included anemia (N = 11), fatigue (N = 9), thrombocytopenia (N = 9), neutropenia (N = 7), muscle cramping (N = 7), and diarrhea (N = 6). Grade 3 or 4 AEs occurred in 9 patients, including neutropenia (N = 6), anemia (N = 4), thrombocytopenia (N = 3), infection (N = 3), electrolyte imbalances (N = 2), hyperglycemia (N = 1), fatigue (N = 1), and constipation (N = 1). No grade 5 AEs were reported. The majority of serious AEs that occurred on study were infection related. One AE was possibly due to study drug(s). Cohort 4 had not reached the maximum tolerated dose, and no dose-limiting toxicities had been observed.\textsuperscript{19}

Among the 13 patients with relapsed and/or refractory MM who were evaluable for response to QUAD, the ORR was 46%. Six patients had a PR, 1 had an MR, 2 achieved SD, and 4 had progressive disease (PD) as their best response. Six of the 9 patients in cohorts 2 and later had a PR. No patients discontinued the study due to toxicity. Six patients discontinued the study either due to PD (N = 5) or patient choice (N = 1).\textsuperscript{19}

The QUAD combination appeared to be well tolerated with a favorable response rate in patients with relapsed and/or refractory MM.\textsuperscript{19}

### Carfilzomib Combinations in Other Tumor Types

#### Chronic Lymphocytic Leukemia

Jennifer Woyach, MD, Assistant Professor of Internal Medicine, Division of Hematology, The Ohio State University, Columbus, and colleagues reported the results from a single-institution phase 1 trial of single-agent carfilzomib in patients with heavily pretreated, relapsed or refractory chronic lymphocytic leukemia (CLL). Nineteen patients received at least 1 dose of carfilzomib, which was administered using the standard myeloma schedule, starting with 20 mg/m² and escalating to 56 mg/m². No maximum tolerated dose was identified.\textsuperscript{21}

Most AEs in this trial were grade 1 or 2, and included anemia, hypocalcemia, thrombocytopenia, and hypokalemia. Grade 3 or 4 AEs, primarily neutropenia and thrombocytopenia, were reversible.\textsuperscript{21}

After 8 weeks of carfilzomib therapy, 12 patients with CLL were eligible for response evaluation. The median number of carfilzomib cycles completed was 2 (range, 1-10+). All 12 evaluable patients achieved SD at 8 weeks. After 7 months of therapy, 1 patient achieved PR by International Workshop on Chronic Lymphocytic Leukemia 1996 criteria after 7 months of therapy. The efficacy of carfilzomib was deemed limited but improved at higher doses.\textsuperscript{21}

Toxicities associated with carfilzomib were acceptable in patients with CLL. Further study of carfilzomib in patients with CLL was suggested using different dosing schedules and using carfilzomib in combination with other active agents.\textsuperscript{21}

### Oprozomib in Hematologic Malignancies

Oprozomib is an oral proteasome inhibitor in clinical development for MM and other hematologic malignancies. Jonathan Kaufman, MD, Assistant Professor, Emory School of Medicine, Atlanta, GA, and colleagues presented updated results of a phase 1b/2 trial of once-daily, modified-release oprozomib tablets in patients with hematologic malignancies. The primary goals were to determine the maximum tolerated dose, safety, and tolerability of oprozomib; secondary end points included response and pharmacodynamics.\textsuperscript{22}

Dose escalation of oprozomib was implemented using 2 dosing schedules: oprozomib once-daily, modified-release tablets (150 mg daily starting dose), either on days 1, 2, 8, and 9 or on days 1 to 5, each on a 14-day cycle.
For each schedule, the oprozomib dose was increased in increments of 30 mg, using the 3+3 study design (3 patients in each cohort, first cohort at starting dose and subsequent cohorts at increasing doses in the planned 30-mg increments), with no maximum planned dose.22

As of April 2013, 24 patients were enrolled in the study (16 with MM; 8 with Waldenström’s macroglobulinemia) in 7 cohorts. In patients who received the days 1, 2, 8, and 9 schedule of oprozomib, no dose-limiting toxicities were observed. On the days 1 to 5 schedule, 1 dose-limiting toxicity (renal failure) was noted at 180 mg daily. The maximum tolerated dose of oprozomib had not been reached for either schedule at the time of the EHA 2013 presentation.22

Kaufman and colleagues reported response rate data for patients with MM or Waldenström’s macroglobulinemia, as summarized in Table 4.22

AEs included grade 1 or 2 gastrointestinal disorders. Although gastrointestinal disorders occurred with moderate frequency, they were described as transient and mild.22

On the basis of these preliminary data, oprozomib modified-release tablets given once daily showed an acceptable safety and tolerability profile. The modified tablet formulation appeared to have lower grades of gastrointestinal AEs and required decreased use of antiemetic medications compared with the original formulation. Dose escalation will continue in this study until the maximum tolerated dose of oprozomib is reached.22

References
The treatment paradigm for multiple myeloma (MM) continues to evolve with the development and introduction of novel agents as well as the growing knowledge of disease biology. Since the introduction of newer therapies in the late 1990s, clinical outcomes for patients with MM, including survival, have improved significantly.1

One of the newest antimyeloma agents, carfilzomib, was approved by the US Food and Drug Administration (FDA) as a single-agent treatment for patients with MM who have received at least 2 prior treatments, including bortezomib and an immunomodulatory drug (ie, lenalidomide or thalidomide), and who have demonstrated disease progression on or within 60 days of completion of the last therapy.2 This approval was based on response rate data from a single-arm multicenter clinical trial, which included 266 patients with relapsed and/or refractory MM who had received at least 2 prior therapies (including bortezomib and thalidomide and/or lenalidomide). The primary end point of overall response rate (ORR)—stringent complete response + complete response + very good partial response + partial response—was 23.7%. The median duration of response was 7.8 months.3

With the availability of carfilzomib and many newer agents that may soon be approved, including oral agents such as oprozomib, pharmacists need to understand the differences in these agents. In particular, they need to be able to counsel patients on adverse event (AE) profiles and to provide good insight on strategies to prevent many AEs. Studies presented at the 2013 American Society of Clinical Oncology meeting in Chicago, IL (May 31-June 4) and the 18th Congress of the European Hematology Association in Stockholm, Sweden (June 13-16) provided some of the latest data on the efficacy and safety of carfilzomib in the treatment of MM and other hematologic cancers.

Safety Considerations with Carfilzomib

The first proteasome inhibitor, bortezomib, was approved in 2003 and rapidly became a mainstay in the treatment of relapsed/refractory and, subsequently, of previously untreated MM. Carfilzomib is different from bortezomib in that it provides benefit after patients relapse or become refractory to bortezomib, and carfilzomib also has a different AE profile. For example, one of the most common reasons for dose reduction or discontinuation of bortezomib is peripheral neuropathy (PN), whereas carfilzomib rarely causes PN. Carfilzomib, like bortezomib, is associated with hematologic AEs that include thrombocytopenia and both agents can also cause congestive heart failure (CHF). Common adverse reactions associated with carfilzomib infusion are fatigue, nausea, dyspnea, and diarrhea. The most common serious AEs are pneumonia, acute renal failure, fever, and CHF.2

The FDA-approved dose of carfilzomib is 20 mg/m² for cycle 1 and 27 mg/m² for cycle 2 and beyond on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Of the 526 patients studied at this dose, cardiac failure events (eg, cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients.2 Atrash and colleagues reported cardiovascular (CV) events in 143 late-stage, heavily pretreated patients with relapsed and refractory MM who received salvage carfilzomib therapy. Carfilzomib 20 to 45 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle was given alone or with weekly dexamethasone 4 to 40 mg (during the first cycle) along with other agents during the second and later cycles. Of the 27 patients who experienced a serious CV event, 21 had preexisting CV risk factors, 11 developed CHF or experienced worsening of existing CHF, and 3 had cardiopulmonary arrest. Among the 10 patients with CHF who had a baseline echocardiogram, left ventricular ejection fraction decreased from a median of 55% to 33% (pretreatment vs posttreatment). The incidence of CV events following carfilzomib administration in heavily pretreated patients with relapsed and refractory MM was occasional. Due to confounding factors and the uncontrolled nature of the data, direct correlation between carfilzomib and serious CV events cannot be conclusively determined.4
Carfilzomib Use in Patients with Newly Diagnosed Multiple Myeloma

Many studies are looking into combination therapies with carfilzomib in patients with newly diagnosed MM. There were 2 studies presented that evaluated the combination of carfilzomib, lenalidomide, and dexamethasone. In both studies, carfilzomib was given at a dose higher than the FDA-approved dose—36 mg/m² after cycle 1 instead of 27 mg/m². The ORR was 97% after a median of 8.5 cycles in the study by Korde and colleagues, which evaluated 36 patients. In the other study, Jakubowiak and colleagues evaluated 53 patients with newly diagnosed MM and they found an ORR of 98%. Both studies found that this regimen was well tolerated.5,7

Other carfilzomib-containing regimens may hold promise in elderly patients with newly diagnosed MM, including combinations with the oral alkylating agents melphalan or cyclophosphamide. Touzeau and colleagues studied 66 patients who received carfilzomib, melphalan, and prednisone. The ORR at a median of 12 months was 91%. In this trial, 3 patients experienced grade 3 or 4 CHF.8 Another trial by Bringhen and colleagues evaluated 41 patients for the combination of carfilzomib, cyclophosphamide, and dexamethasone. The ORR after 9 cycles of therapy was 100%. In this trial, at least one grade 3 or 4 event was reported in 11 (20%) of 56 patients. Nonhematologic grade 3 or 4 AEs included infections and cardiac, renal, constitutional, and gastrointestinal complications.9

Research continues to evaluate the optimal dose of carfilzomib in new combination therapies to improve efficacy. When comparing these regimens, it is important to be aware of these differences as well as the characteristics of any agents administered concurrently.

Carfilzomib Use in Patients with Relapsed and/or Refractory Multiple Myeloma and Chronic Lymphocytic Leukemia

Since patients with relapsed and/or refractory MM are generally heavily pretreated, the doses of chemotherapy used are lower than in patients with newly diagnosed MM. Carfilzomib given at 15 mg/m² to 27 mg/m² in combination with lenalidomide 10 mg to 25 mg and dexamethasone was studied in 84 patients with relapsed or progressive MM, as reported by Niesvizky and colleagues. Among the 52 patients at maximum planned dose, the ORR was 76.9% with a median follow-up of 24.4 months. Grade 3 or 4 hematologic AEs were similar to those in earlier studies using similar doses of single-agent carfilzomib.10

The 4-drug phase 1/2 combination of carfilzomib, lenalidomide, vorinostar, and dexamethasone (QUAD) study results were presented by Bilotti and colleagues. Among the 13 patients with relapsed and/or refractory MM who were evaluable for response, the ORR was 46%. All of the patients in the QUAD study experienced drug-related AEs, and the most common were anemia, fatigue, thrombocytopenia, neutropenia, and muscle cramping.11

Carfilzomib has been shown to induce apoptosis in the cells of patients with chronic lymphocytic leukemia (CLL) in the presence of human serum. These data, published by Gupta and colleagues, provide new mechanistic insights into the activity of carfilzomib in CLL.12 Woyach and colleagues presented a phase 1 trial on heavily pretreated patients with relapsed and/or refractory CLL who received carfilzomib on the standard melphalan schedule, with escalated dosing at 20 mg/m² to 56 mg/m². There were 19 patients who received at least 1 dose of carfilzomib; 12 were eligible to be evaluated for response after 8 weeks of therapy—all 12 achieved stable disease. The efficacy of carfilzomib was deemed limited and the toxicities associated with carfilzomib were acceptable in patients with CLL. Further study of carfilzomib in patients with CLL will evaluate different dosing schedules and combinations with other active agents.13

Future of Multiple Myeloma

A great deal of interest in MM is focusing on the use of oral agents (ixazomib, oprozomib, and the new immunomodulatory drug pomalidomide). The ease of administering these agents provides great convenience to patients. Oprozomib, an oral proteasome inhibitor, is in clinical development for MM and other hematologic malignancies. Kaufman and colleagues updated results of a phase 1b/2 trial of once-daily, modified-release oprozomib tablets in patients with hematologic malignancies. Dose escalation of oprozomib was implemented using 2 dosing schedules: oprozomib once-daily, modified-release tablets (150 mg/day starting dose), on either days 1, 2, 8, and 9 or on days 1 to 5, both on a 14-day cycle.14

As of April 2013, 24 patients were enrolled in the study (16 with MM; 8 with Waldenström’s macroglobulinemia [WM]) in 7 cohorts. Patients with MM and WM on the days 1, 2, 8, and 9 schedule have shown no response with the doses studied. Patients with MM and WM on the days 1 to 5 schedule have shown 25% and 80% ORR, respectively. The maximum tolerated dose of oprozomib had not been reached for either schedule. The most common AEs seen were gastrointestinal and associated with the use of the original formulation. The modified tablet formulation appears to have lower grades of gastrointestinal AEs, and requires decreased use of antiemetic medications compared with the original formulation.14
New Directions in the Treatment of Multiple Myeloma

Conclusion

The role of carfilzomib continues to evolve in relapsed and/or refractory MM, newly diagnosed MM, and other hematologic malignancies. Ongoing clinical trials are exploring the drug’s single-agent activity, safety, and optimal dose and schedule, as well as its feasibility in various drug combinations. With the constantly changing therapeutic environment in MM, pharmacists need to know about newer treatments to help patients achieve maximum benefit with the most favorable AE profile.

References


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

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Survival has improved for patients with multiple myeloma (MM), primarily as a result of improved risk stratification and the use of novel agents in the initial treatment of the disease. Yet, MM remains an incurable disease with multiple relapses over the course of the illness, each relapse generally characterized by a diminished depth of response and shorter time to progression. Relapsed and/or refractory MM presents a particular challenge because patients with relapsed and/or refractory MM have typically failed all frontline novel agents and many have failed autologous stem cell transplantation (ASCT). Life expectancy for these patients is generally less than 9 months.

On July 20, 2012, the US Food and Drug Administration granted accelerated approval to carfilzomib injection, which is indicated for the treatment of patients with MM who have received at least 2 previous therapies, including bortezomib and an immunomodulatory agent (ie, 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, multicenter clinical trial, and was not based on survival. The approval of carfilzomib, together with the approval of pomalidomide on February 8, 2013, also for relapsed and/or refractory MM, provided an important unmet...
need, and both agents received accelerated approval. Both agents were evaluated in combination with dexamethasone; however, carfilzomib was approved as a single agent whereas pomalidomide was approved in combination with dexamethasone.

The challenge now is to effectively integrate these new therapies into the treatment paradigm for MM, including use in combination regimens and use earlier in the disease trajectory, with consideration of efficacy and safety. Dr Raedler provides an update of studies relative to carfilzomib use in the treatment of MM presented at the 2013 American Society of Clinical Oncology meeting and the 2013 (18th) Congress of the European Hematology Association.

Continued development of new agents for the treatment of MM allows for therapies tailored by consideration of disease-related risk factors, personal attributes, and patient preferences. Understanding the risk profile for newly approved agents and the populations studied, including inclusion and exclusion criteria, is necessary to appropriately introduce these agents into the postmarketing populations.

A study presented by Atrash and colleagues using carfilzomib in a compassionate use setting demonstrates the importance of evaluating each patient for preexisting comorbidities. In this case, cardiopulmonary disease or risk factors including multiple lines of therapy and prior ASCT were the focus.

Cardiopulmonary adverse events (AEs) reported in the prescribing information for single-agent carfilzomib used in the relapsed and/or refractory MM setting include dyspnea (all grades, 34.6%; grade ≥3, 4.9%), hypertension (all grades, 14.3%; grade ≥3, 3.2%), peripheral edema (all grades, 24%; grade ≥3, 0.6%), and pneumonia (all grades, 12.7%; grade ≥3, 10.5%). Patients at high risk for these cardiopulmonary AEs should be evaluated by a cardiologist prior to receiving carfilzomib-containing regimens. Effective screening for underlying cardiopulmonary disease and management with cardiology colleagues will allow the safe administration of carfilzomib-containing regimens to many patients with relapsed and/or refractory MM. Ongoing randomized clinical trials using carfilzomib in patients with previously untreated MM will help to clarify any correlation of carfilzomib-based therapies with cardiopulmonary AEs.

The gold standard for the treatment of MM is to achieve an early and deep response with preserved or improved quality of life and an acceptable level of toxicity. The ability to maintain that response over time is paramount to efficacy. The median age of patients newly diagnosed with MM is 62 years, and most patients will receive multiple therapies over the course of their disease. Therefore, therapies that have established safety and efficacy in the older adult and preserve future treatment options, including clinical trials, are essential. Dr Raedler highlights reports on several trials using carfilzomib in combination regimens that demonstrate these principles.

Korde and colleagues evaluated the combination of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in patients with newly diagnosed MM; the primary end point was the occurrence of grade 3 or higher peripheral neuropathy (PN). In this update of the single-arm phase 2 trial, there were no cases of grade 3 or higher PN in the 36 evaluable patients.

Dose-limiting PN is a well-established AE for bortezomib-containing regimens as highlighted in the analysis reported by Martin and colleagues. Trials using alternative dosing and subcutaneous administration of bortezomib have demonstrated reduced rates of PN, with overall response rates (ORRs) of 97% and 98%, respectively; a rapid decline in M-protein levels; the ability to bridge to ASCT; and the absence of minimal residual disease in patients achieving a stringent complete response (sCR), complete response (CR), or near complete response (nCR). With a median follow-up of 25 months, Jakubowiak reported that responses of a very good partial remission or greater (≥VGPR) in patients who had not had ASCT exceeded 90% (≥VGPR, 91%; ≥nCR, 78%; CR, 70%; sCR, 59%).

It is important to note that the depth of response appeared to improve with continued treatment. The median time to achieve ≥VGPR was 4 cycles, 4.5 cycles for ≥nCR, and 10 cycles for sCR. Wang and colleagues reported final results on the use of the CRd regimen in the relapsed or progressive MM setting using a dose-finding model with the maximum planned dose being carfilzomib 20 mg/m² on days 1 and 2 of the first cycle, 27 mg/m² on days 8, 9, 15, and 16, and thereafter; lenalidomide 25 mg on days 1 to 21; and dexamethasone 40 mg weekly. With a median follow-up of 24.4 months at the maximum planned dose, an ORR of 76.9% was reached, with a median duration of response of 22.1 months and a median progression-free survival of 15.4 months.

Bringhen and colleagues presented updated results...
from carfilzomib, cyclophosphamide, and dexamethasone (CCd) in elderly patients newly diagnosed with MM. The depth of response improved over time for these patients. After 9 cycles of CCd therapy, 100% of the patients (N = 41) treated with the maximum planned dose achieved ≥ partial response, compared with 93% of the patients after at least 4 cycles. Other response rates were: ≥ VGPR, 77%; ≥ CR/nCR, 53%; and sCR, 23%—all exceeding those after at least 4 cycles of therapy.16

These data support the common approach of treating patients with MM until disease progression or unacceptable toxicity, taking into consideration any known long-term effects. Patients over the age of 70 years were included in each of these trials, with similar efficacy and safety demonstrated in all trials.

Based on the trials presented in this update, carfilzomib provides a good option for patients with MM in the relapsed and/or refractory setting, in earlier lines of therapy in combination with lenalidomide and low-dose dexamethasone (CRd), and in older patients—demonstrating both efficacy and safety. Ongoing clinical trials, including long-term follow-up, are necessary to further characterize both early- and late-onset treatment-emergent AEs and confirm long-term efficacy. Preserving future treatment options by considering the risk profile of each agent or combination of agents, effectively managing comorbidities while managing the MM, in essence, treating the whole patient, will allow continued treatment over time.

References

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

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The evolving treatment of patients with multiple myeloma (MM) epitomizes the multiple current issues experienced by managed care organizations (MCOs) related to cancer management today. The challenge of increasing health outcomes with the incremental benefit received from new therapies conflicts with the ongoing efforts to bend the cost curve of care downward in an effort to improve the affordability of healthcare. More tolerable treatment options provide real-world opportunities for improved survival, but the studies undertaken by pharmaceutical manufacturers promote incremental benefit in order to gain US Food and Drug
Administration (FDA) approval, generally based on end points that are of limited real-world applicability. Shifting healthcare demographics result in shifting management priorities. For MCOs, cancer management has, in many ways, become a chess match with pharmaceutical manufacturers designed to try to remain one step ahead of the cost curve in relation to the dramatically escalating costs of new medications.

As noted in this publication, MM has been a management challenge for many years because of shortened survival and the availability of few effective nontoxic therapies. Recent next-generation novel therapies have begun to change the survival curve of MM but at significant cost to health plans and, more importantly, to the many members and/or patients insured by these health plans. Newer therapies, such as carfilzomib, offer the hope of improved outcomes in terms of improved tolerability and reduced side effects, but the lack of survival data makes management difficult at this point in time. Carfilzomib was approved in the United States as a single-agent treatment for patients with MM who have received at least 2 prior treatments, including bortezomib and an immunomodulatory drug (ie, lenalidomide or thalidomide), and who have demonstrated disease progression on or within 60 days of completion of the last therapy. FDA approval was based on response rates in a single-arm clinical trial and was not based on survival.\(^1\)

The clinical trial data presented at the 2013 American Society of Clinical Oncology meeting and the 2013 (18th) Congress of the European Hematology Association illustrate another current issue related to cancer management in general and, specifically, to management of MM. New therapies continue to emerge but they lack head-to-head comparisons to current standards of care when they are launched in the relapsed and/or refractory setting. Although the clinical trials demonstrate significant potential for improved outcomes, none of the trials have an active comparator. This lack of an active comparator makes it difficult for MCOs to comfortably advance the place for newer, potentially better tolerated therapies in the treatment algorithm—despite the positive findings of these many trials. This issue presents potential conflicts with members and physicians treating those members who consider these therapies an improvement over therapies established for an earlier line of therapy. With ongoing research such as the ENDEAVOR trial, which compares carfilzomib plus dexamethasone versus bortezomib plus dexamethasome in the relapsed setting,\(^2\) there is a bright future for the data needed to make reliable decisions in MM.

The data highlighted in this publication suggest that carfilzomib offers the hope of improved health outcomes. For example, the trial data reported by Berenson and colleagues suggest efficacy of carfilzomib in place of bortezomib in 14 combination regimens and demonstrates efficacy of these regimens in earlier lines of therapy,\(^3\) providing the type of data MCOs need. However, the lack of a direct comparison to bortezomib makes any formulary decisions challenging. While the goal of incorporating new treatments into disease management paradigms is to improve patient outcomes rather than to merely extend the lines of therapy, without real advances in survival or other important health end points, improvement is still to be determined.

Whether these new therapies bring improved value to healthcare is not yet established as we await forthcoming head-to-head data. The determination of medical cost offsets is challenging to assess at this point because more time and data need to accrue. MCOs are searching for value in new cancer therapies and not just incremental benefit. The hope is that, as additional studies are completed, this value will be demonstrated.

References