

# Treatment of Patients With Multiple Myeloma: A Relapsed and Refractory Case Study

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Author's disclosures of potential conflicts of interest are found at the end of this article.

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**D**isease relapse is inevitable for the majority of patients with multiple myeloma (MM). Treatment of patients with relapsed and refractory multiple myeloma (RR MM) is complicated by the heterogeneity of the disease as well as the side effects of MM treatments. The majority of patients with RR MM have received all currently available first-line novel agents, including proteasome inhibitors and immunomodulatory drugs (IMiDs). Novel salvage therapies that are efficacious and well tolerated are needed. The following case study features a patient with RR MM entering into treatment with carfilzomib (Kyprolis), which was approved in the United States as a single-agent treatment for RR MM by the US Food and Drug Administration in July 2012.

## DIAGNOSIS

Mr. B., a 45-year-old man, was diagnosed with immunoglobulin G (IgG)  $\kappa$  MM in 2005. He presented with severe arm and neck pain with some right arm weakness. Mr. B. also presented with anemia, with a hemoglobin level of 10.0 g/dL. Laboratory values were IgG 4,100 mg/dL (upper

limit of normal = 1,822 mg/dL),  $\beta_2$  microglobulin 0.9 mg/dL, and albumin 3.7 g/dL. Calcium and creatinine values were within the normal range. Magnetic resonance imaging (MRI) of the neck and skeletal survey showed extensive lytic lesions involving the C6 through T4 vertebrae. In March 2005, Mr. B. underwent corpectomy of C6 through T1, anterior fusion of C5 through T2, and posterior fusion of C4 through T3 as well as a C7 decompressive laminectomy. Biopsy of the vertebral lesion was consistent with an IgG  $\kappa$  plasmacytoma. A bone marrow biopsy showed 10.4% plasma cells with normal cytogenetics.

## TREATMENT HISTORY

Mr. B. was placed on pulse-dose dexamethasone 40 mg daily for 4 days, followed by 4 days a week for 2 weeks while waiting to complete the diagnostic process. He was subsequently treated with lenalidomide (Revlimid) 25 mg daily and dexamethasone 40 mg once weekly for four cycles. Stem cells were then collected. Mr. B. received high-dose chemotherapy (melphalan 200 mg/m<sup>2</sup>) followed by infusion of  $10.7 \times 10^6$  CD34-positive cells (one-half of his collection) in June 2005.

He was also started on monthly zoledronic acid (Zometa) due to documented bone disease.

In April 2008, Mr. B.'s complaint of left hip pain led to a repeat skeletal survey that showed new skeletal lesions. Bone marrow biopsy revealed 18.4% plasma cells and normal cytogenetics. His laboratory values were IgG 2,460 g/dL, a  $\kappa/\lambda$  free light chain ratio of 17.4 (normal = 0.26 to 1.65), and a serum protein electrophoresis M-spike at 2.0 g/dL. Hemoglobin, calcium, and creatinine all remained within normal limits.

From July 2008 through November 2008, Mr. B. was treated with lenalidomide 25 mg and weekly dexamethasone, achieving a complete remission. In January 2009, he had a second autologous hematopoietic stem cell collection (auto-HSCT) using melphalan 200 mg/m<sup>2</sup> as a preparative regimen. Mr. B. then enrolled in a clinical trial and received maintenance therapy with lenalidomide 25 mg daily for a total of 24 months. Due to a gradual increase in the M-protein and  $\kappa$  light chain levels, a bone marrow biopsy and aspirate was performed in August 2011, showing 40% plasma cells consistent with disease progression.

In September 2011, a regimen of bortezomib (Velcade) and dexamethasone with zoledronic acid was initiated. Specifically, Mr. B. was treated with bortezomib 1.3 mg/m<sup>2</sup> subcutaneously on days 1, 4, 8, and 11 for 2 cycles followed by weekly dosing, plus oral dexamethasone 20 mg (days 1, 8, and 15). The treatment resulted in normalization of the bone marrow and serum proteins. Following 11 cycles of bortezomib treatment, levels of IgG and  $\kappa$  light chain increased, and a bone marrow biopsy in August 2012 showed 30% plasma cells.

### CARFILZOMIB TREATMENT

Mr. B. started carfilzomib in September 2012. Prior to initiating treatment, his Ig laboratory values were IgG 2488 mg/dL,  $\kappa$  light chain 3.26 mg/mL,  $\lambda$  light chain 0.20 mg/mL,  $\kappa/\lambda$  ratio 11.30, and M-protein 1.5 g/dL. Blood laboratory values for Mr. B. were as follows: white blood cells  $4.4 \times 10^3/\mu\text{L}$ , hemoglobin 12.6 g/dL, and platelets  $161 \times 10^9/\text{L}$ . Renal and hepatic functions were within normal limits. Due to Mr. B.'s history of two bone marrow transplants, an echocardiogram was performed, showing an ejection fraction of 55%.

Treatment with carfilzomib was started at 20 mg/m<sup>2</sup> administered intravenously (IV) on days 1, 2, 8, 9, 15, and 16 for cycle 1. Prophylaxis included

oral dexamethasone 4 mg, and 250 mL of IV saline was given during the first cycle. The carfilzomib dose was escalated to 27 mg/m<sup>2</sup> for cycle 2 and subsequent cycles. Treatment was tolerated, with mild fatigue as well as mild fluid retention during the first cycle of therapy. The fluid retention resolved following discontinuation of the supplemental fluids in cycle 2. No significant changes in renal or hepatic function were noted. Mr. B. was titrated off dexamethasone with no evidence of hypersensitivity to carfilzomib. He experienced a seasonal upper respiratory infection that resolved readily with standard medical management and continues to work full time. A reduction in Mr. B.'s IgG and  $\kappa$  light chain levels was noted following cycle 2 of therapy.

At the end of May 2013, after 8 months of treatment with carfilzomib, there was continued evidence of response, with normalization of the IgG and  $\kappa$  light chain levels and a continued positive trend in the M-protein. Immunoglobulin lab values were IgG 1,677 mg/dL,  $\kappa$  light chain 1.65 mg/mL,  $\lambda$  light chain 0.43 mg/mL,  $\kappa/\lambda$  ratio 3.84, and M-protein 0.2 g/dL. Mr. B.'s blood laboratory values were: white blood cells  $4.4 \times 10^3/\mu\text{L}$ , hemoglobin 12.7 g/dL, and platelets  $195 \times 10^9/\text{L}$ .

### CONCLUSIONS

This case report illustrates the approved indication and use of carfilzomib in patients with RR MM who have received multiple prior therapies, including IMiDs and bortezomib. Carfilzomib provided durable disease control in this patient with RR MM whose disease progressed following multiple treatment regimens that included two auto-HSCTs as well as lenalidomide and bortezomib regimens. Treatment with carfilzomib was tolerable with manageable side effects. For Mr. B., side effects that were mild to moderate in severity emerged during the first cycle and resolved in subsequent cycles. Mr. B.'s experience is consistent with efficacy and safety data reported in phase II clinical trials.

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### DISCLOSURE

Ms. Kurtin has acted as a consultant for Onyx, Millennium, and Celgene.