

Pomalidomide in lenalidomide-refractory multiple myeloma and carfilzomib in refractory and newly diagnosed multiple myeloma

Pomalidomide and carfilzomib represent active and well-tolerated new options in combination regimens.

Two of the most promising drugs on the horizon for patients with multiple myeloma (MM) are pomalidomide and carfilzomib. Both agents have shown significant single-agent activity in clinical trials. They seem to work in patients whose MM is resistant to other treatments and are being studied in combination regimens.

Pomalidomide

Pomalidomide is a new immunomodulatory drug (IMiD) with high in vitro potency. In initial experience with pomalidomide and low-dose dexamethasone in relapsed MM, Lacy and colleagues found an overall response rate of 63% and observed responses in some patients who were refractory to lenalidomide (Revlimid), suggesting an absence of cross-resistance between pomalidomide and other IMiDs. In a recently reported phase II study,¹ these investigators assessed the combination of pomalidomide and low-dose dexamethasone in patients with lenalidomide-refractory MM, finding the combination to be highly active and well tolerated.

In this study, 34 patients with lenalidomide-refractory MM were treated with oral pomalidomide (2 mg daily) and dexamethasone (40 mg once weekly) in 28-day cycles. Patients had a median age of 61.5 years, 68% were male, 85% had an ECOG (Eastern Cooperative Oncology Group) performance status

What's new, what's important

Treatment of multiple myeloma is evolving rapidly. It is tough to keep up with the rapid pace of new drugs, updates, and changes in the standard of care. In this issue of *Community Oncology* we bring to you two new exciting drugs on the horizon, pomalidomide and carfilzomib. In addition to introducing these two new drugs, we have asked Dr. Noopur Raje to explain how she treats a newly diagnosed patient with multiple myeloma.

Pomalidomide, a thalidomide (Thalomid) analog, is a promising myeloma drug with encouraging responses in relapsed/refractory myeloma patients. Carfilzomib is a novel proteasome inhibitor. When combined with lenalidomide (Revlimid) in the first-line setting, it produced a 100% response rate. Phase III studies are in progress or being completed. It will be exciting to see the final results of these studies.

With this issue we are changing the format of *Community Translations* to incorporate the mechanism of action or pathophysiology of some of these new advances so that a clinician can relate to them in a clinical setting.

— Jame Abraham, MD, Editor

of 0 or 1, and 41% were categorized as high risk. The median time from diagnosis was 62 months. The median number of prior chemotherapy regimens was four. In addition to lenalidomide, 58% of patients had received prior thalidomide (Thalomid), and 59% had received prior bortezomib (Velcade); 68% of patients had undergone prior autologous stem cell transplantation, and 53% had prior radiation therapy. Twenty patients (59%) had peripheral neuropathy at baseline.

Patients received a median of 5 cycles (range, 1–14) of pomalidomide plus low-dose dexamethasone. Prophylaxis for venous thromboembolism was given in 204 of 209 treatment cycles (aspirin in 150 cycles and warfarin in 54 cycles). Treatment responses consisted of a very

good partial response in 9%, a partial response in 23%, and a minimal response in 15%, for an overall clinical benefit rate of 47%; 35% of patients had stable disease, and 18% had disease progression. The median time to response was 2 months. Response was observed in 8 of 14 (57%) high-risk patients, in 8 of 19 (42%) who received previous thalidomide treatment, and in 9 of 20 (45%) who were given previous bortezomib treatment. In eight patients with stable disease, the pomalidomide dose was increased to 4 mg/d, with one patient improving to a partial response. The median duration of response in 11 patients with a partial response or better was 9.1 months. The median progression-free sur-

Summary by Matt Stenger, MS.

vival was 4.8 months, and progression-free survival did not differ between high-risk and standard-risk patients. The median overall survival was 13.9 months. During follow-up, treatment was stopped due to disease progression in 23 patients, 3 withdrew from the study due to patient/physician discretion, and 8 continued to receive treatment. Seven patients died, all due to disease progression. The median follow-up of patients remaining alive was 8.3 months.

Pomalidomide/dexamethasone treatment was well tolerated. Toxicity consisted mostly of myelosuppression. Grade 3 or 4 hematologic toxicity at least possibly related to treatment occurred in 38% of patients, including neutropenia in 29%, anemia in 12%, and thrombocytopenia in 9%. The most common grade 3/4 nonhematologic toxicity was fatigue, which occurred in 9% of patients (all grade 3); grade 3 pneumonitis, edema, pneumonia, and folliculitis were each observed in one patient. Nine patients (26%) had neuropathy during treatment (six grade 1, three grade 2); they included six patients with neuropathy at baseline, three of whom had a worsening of grade.

Carfilzomib

Carfilzomib is a highly selective epoxyketone proteasome inhibitor with minimal affinity for nontarget proteases. In a recent phase II trial in patients with relapsed/refractory MM, reported at the 2010 American Society of Hematology (ASH) meeting, carfilzomib produced durable responses and was well tolerated.² An ongoing phase I/II trial assessing carfilzomib, lenalidomide, and dexamethasone in newly diagnosed MM, also reported at the 2010 ASH meeting, has shown good activity and tolerability of the regimen.³ A phase III trial comparing carfilzomib plus lenalidomide and low-dose dexamethasone versus lenalidomide and low-

dose dexamethasone in relapsed MM has been initiated.

Relapsed/refractory MM

In the trial in patients with relapsed/refractory MM, 266 patients with multiply relapsed MM who had disease refractory to their last treatment received carfilzomib (20 mg/m² IV on days 1, 2, 8, 9, 15, and 16) every 28 days for the first cycle, with the dose then being escalated to 27 mg/m² on the same schedule for up to 12 cycles.² Prior therapies included bortezomib, either lenalidomide or thalidomide, and an alkylating agent. Patients had a median duration of MM of 5.4 years and had received a median of 5 prior lines of chemotherapy and a median of 13 antimyeloma treatments; prior treatments included bortezomib in 99.6% of patients (a median of two prior regimens containing bortezomib), lenalidomide in 94%, thalidomide in 74%, corticosteroids in 98%, alkylating agents in 91%, and stem cell transplantation in 74%. Overall, 65% of patients were refractory to bortezomib prior to study entry.

At the time of reporting, 79 patients (30%) had completed at least 6 cycles of study treatment, approximately 11% had completed 12 cycles (with most entering an extension phase of the study), and 15 patients remained on study (all with more than 10 cycles of study treatment). Among 257 patients evaluable for response, 0.4% (one patient) had a complete response, 4.7% had a very good partial response, and 19% had a partial response, for an overall response rate of 24%; an additional 12% of patients had a minimal response, yielding an overall clinical benefit rate of 36%. Stable disease for at least 6 weeks was achieved in 32%. Among patients with a partial response or better, the median duration of response was 7.4 months. Among patients with a minimal response, the median duration of response was 6.3 months, indicating

durable minor responses.

Toxicity consisted mainly of myelosuppression. Grade 3/4 hematologic toxicities consisted of thrombocytopenia in 18% of patients, lymphopenia in 11%, neutropenia in 8%, and anemia in 7%.⁴ Grade 3/4 nonhematologic toxicities included fatigue in 6% of patients; pneumonia and congestive cardiac failure in 3% each; nausea, dyspnea, increased blood creatinine levels, and increased blood uric acid levels in 1% each; and diarrhea in 0.4%. Grade 1/2 peripheral neuropathy was present in 77% of patients at baseline; new-onset neuropathy was infrequent, with grade 3 or lower neuropathy occurring in less than 1% of patients.²

Newly diagnosed MM

In an ongoing phase I/II trial, patients with newly diagnosed MM are receiving carfilzomib, lenalidomide, and dexamethasone.³ Carfilzomib is started at 20 mg/m² (dose level 1) and increased to 27 mg/m² (dose level 2) and 36 mg/m² (dose level 3) given IV on days 1, 2, 8, 9, 15, and 16 in 28-day cycles. Lenalidomide is given at 25 mg/d on days 1–21 in each cycle, and dexamethasone is given weekly at 40 mg during cycles 1–4 and at 20 mg during cycles 5–8. Patients with a partial response or better are eligible to proceed to stem cell collection and autologous stem cell transplantation after at least 4 cycles and can continue study treatment after transplantation. After completion of 8 cycles, patients are to receive maintenance cycles consisting of carfilzomib on days 1, 2, 15, and 16; lenalidomide on days 1–21; and weekly dexamethasone at doses tolerated at the end of 8 cycles. A planned 36 patients are to be treated at the carfilzomib maximum tolerated dose.

At the time of reporting, 24 patients had been enrolled, 4 at dose level 1, 14 at dose level 2, and 6 at dose level 3. Toxicity data were available for 21 patients, including 19 who completed

at least 1 cycle of treatment. A single dose-limiting toxicity event was observed, consisting of nonfebrile neutropenia in a patient at dose level 2. The maximum tolerated dose had not yet been reached. Grade 3/4 hematologic toxicities consisted of neutropenia in three patients, thrombocytopenia in three patients, and anemia in one patient. Grade 3 nonhematologic toxicities included five cases of elevated blood glucose levels, deep vein thrombosis during aspirin prophylaxis in one patient, and fatigue in one patient. Emergent peripheral neuropathy was observed in two patients, who developed grade 1 neuropathy.

At the time of reporting, 23 patients continued on treatment, with

20 having no need for dose modifications. After a median of 4 months of treatment (range, 1–8 months), the preliminary response rate in 19 evaluable patients completing at least 1 cycle was 100% with at least a partial response, including 63% with a very good partial response and 37% with a complete response or near-complete response. Partial responses were observed in 17 of 19 patients after 1 cycle, with responses improving in all patients with continuing treatment. Seven patients had proceeded to stem cell collection using growth factors only after a median of 4 cycles, and all resumed study treatment after stem cell collection. No disease progression had been observed in any of the eval-

uable patients, and all remained alive.

References

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From the Oncologist's Perspective

Evolving therapies for multiple myeloma

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Although multiple myeloma (MM) remains an incurable bone marrow cancer, survival rates have improved markedly over the past decade. An understanding of MM pathobiology (Figure 1) and improvement in stem cell transplantation, better supportive care, and novel therapies with higher efficacy and lower toxicity are all responsible for this improvement. The availability of a rich pipeline of novel agents undergoing early-phase clinical trials in MM is an exciting and active area of research.¹

Current treatment

Over the past several years, five therapeutic strategies have received US Food and Drug Administration (FDA) approval either as monotherapy or in combination for treating MM,

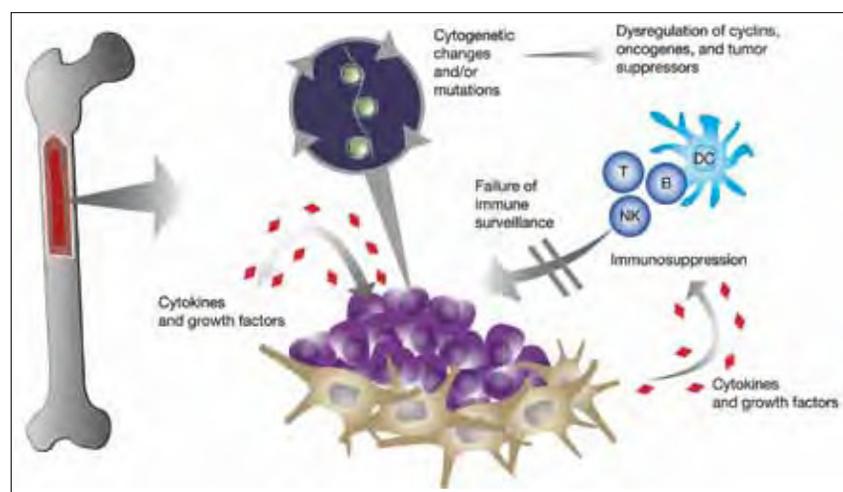


FIGURE 1 Development of multiple myeloma: cellular/cytokine pathways. DC = dendritic cell; NK = natural killer cell; T, B = T and B cells. © Celgene Corporation.

with thalidomide (Thalomid), lenalidomide (Revlimid), and bortezomib (Velcade) as important backbone drugs in these approaches. In the upfront

setting, thalidomide with dexamethasone² and bortezomib in combination with melphalan and prednisone³ increased the overall response rate and