Carfilzomib and bortezomib therapy in patients with multiple myeloma

See Commentaries on pages 270 and 272.

In July 2012, carfilzomib was given accelerated approval by the Food and Drug Administration for the treatment of patients with multiple myeloma (MM) who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent and have exhibited disease progression during or within 60 days of completing their last therapy. The approval was based on results of a single-arm, multicenter phase 2 trial of carfilzomib in patients with relapsed and refractory MM. As a condition of the accelerated approval, the manufacturer of the drug has to submit a final analysis of an ongoing phase 3 trial that compares carfilzomib plus lenalidomide plus low-dose dexamethasone with lenalidomide plus low-dose dexamethasone in patients with relapsed and refractory MM after 1 to 3 previous therapies. The primary end point of this trial is progression-free survival (PFS).

In the phase 2 trial,[1] 266 patients with relapsed and refractory MM who had received at least 2 prior therapies, including bortezomib and either thalidomide or lenalidomide, received carfilzomib by IV infusion over 2-10 minutes on 2 consecutive days each week for 3 weeks, followed by a 12-day rest period in each 28-day treatment cycle. The patients received 20 mg/m^2 at each dose in the first cycle and 27 mg/m^2 at each dose in subsequent cycles for a maximum of 12 cycles. All of the patients received premedication with dexamethasone 4 mg orally or intravenously before carfilzomib doses during the first cycle, during the first dose-escalation cycle, and during subsequent cycles if symptoms of infusion reaction occurred. The primary outcome of the trial was overall response rate (ORR) based on assessment by an independent review committee.

The patients had a median age of 63 years, 58% were men, 71% were white, and most of them had an ECOG performance status of 0 (26%) or 1 (61%). They had received a median of 5 lines of therapy for MM (range, 1-20), and 95% of them were refractory to their last therapy. All but 1 patient had received bortezomib; 73% were refractory to any prior line of therapy, and 45% were refractory to their most recent line. All of the patients had received an immunomodulatory agent, including lenalidomide in 94%, thalidomide in 75%, and pomalidomide in 3%; 98% had received high-dose steroid therapy, 92% an alkylating agent, 64% an anthracycline, and 74% at least 1 stem cell transplant. Most patients (80%) were refractory to or intolerant of both bortezomib and lenalidomide. Most had IgG myeloma (73%) and International Staging System (ISS) stage II or III disease (69%). Of 234 patients with cytogenetic or FISH (fluorescence in situ hybridization) data, 32% (25% overall) had poor prognostic markers. In all, 77% of patients had grade 1 or 2 peripheral neuropathy at baseline.

What's new, what's important

Carfilzomib is a next generation proteasome inhibitor approved by the Food and Drug Administration for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and who had disease progression on or within 60 days of the completion of the last therapy. It primarily targets the chymotrypsin-like subunits in both the constitutive proteasome and the immunoproteasome.

Carfilzomib is given intravenously during the course of 2-10 minutes, on 2 consecutive days weekly (for 3 weeks: days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17-28). The recommended dose is 20 mg/m^2 a day for the first cycle, and, if tolerated, the recommended dose for the second and successive cycles is 27 mg/m^2 a day. The incidence of neuropathy is significantly less compared with other proteasome inhibitors, though patients need to be monitored for cardiac adverse side effects, including heart failure and ischemia.

Carfilzomib is a highly promising treatment for patients with multiple myeloma who have progressed on previous therapies. Ongoing clinical trials will evaluate its role in early multiple myeloma, and we will also be able to gain a better understanding of the associated long-term side effects from findings in future studies.

— Jame Abraham, MD

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Commun Oncol 2012;9:278-282
http://dx.doi.org/10.1016/j.cmonc.2012.08.003

The median duration of carfilzomib treatment was 3.0 months (range, 0.03-16.9 months); 31% of patients completed more than 6 cycles, 15% completed 12, and 12% continued on to an extension study. Study discontinuation occurred because of progressive disease in 59% of patients and adverse events in 12%. Discontinuation occurred during the first 2 treatment cycles in 36.5% of patients, with 19% discontinuing during the first cycle; 26% of patients did not receive the carfilzomib dose escalation, primarily because of early discontinuation. The mean and median carfilzomib doses per patient were 23.1 and 23.5 mg/m^2, respectively (median relative dose intensity of 92%). The median cumulative dose of carfilzomib was 470 mg/m^2 (range, 20-2,647 mg/m^2). Dexamethasone doses ranged from 4 to 26 mg per 28-day cycle.

Among the 257 who were patients evaluable for response, the ORR on independent review committee assessment was 23.7%. Complete response occurred in 1 patient (0.4%), very good partial response in 13 (5.1%), and partial response (PR) in 47 (18.3%). An additional 34 patients (13.2%) had minimal response (MR), yielding an overall clinical benefit rate of 37.0%. ORRs were 20.1% in patients refractory to or intolerant of both bortezomib and lenalidomide at baseline, 15.4% in those refractory to both at baseline, 23.8% in patients with grade 1 or 2 peripheral neuropathy at baseline, 17.9% in patients with ISS stage III disease, and 22.0% in those who were aged 65 years or older (46% of evaluable population). ORRs were lower in patients with 2 or more prior lines of bortezomib, compared with those with fewer than 2 lines (18.5% vs 29.5, respectively) and in patients refractory to bortezomib during their last line of therapy, compared with those whose last line did not include bortezomib (18.6% vs 28.3%). Multivariate analysis showed that ORR was not generally influenced by most baseline factors, including unfavorable cytogenetics or FISH markers and renal impairment.

Median durations of response were 7.8 months in patients with PR or better, 8.3 months in those with MR or better, 7.4 months in those refractory to or intolerant of both bortezomib and lenalidomide, and 7.8 months in those refractory to both. Median PFS for all evaluable patients was 3.7 months. Median overall survival (OS) durations were 15.4 months for all patients, 15.6 months for evaluable patients, 13.2 months in patients refractory to or intolerant of both bortezomib and lenalidomide, and 11.9 months in those refractory to both. There was a trend toward improved PFS and OS with deeper response, and a landmark analysis at 2 months after the start of treatment showed significantly prolonged OS ($P < .0001$) in patients with MR or better compared with patients with no response.

TABLE 1 Summary of adverse events in patients receiving carfilzomib

Adverse event	Percentage of patients (N = 266)		
	All grades	Grade 3 or 4	Carfilzomib-related (any grade)
Hematologic			
Anemia	46	24	22
Thrombocytopenia	39	29	29
Lymphopenia	23	20	17
Neutropenia	18	11	15
Leukopenia	14	6.8	12
Nonhematologic			
Fatigue	49	7.5	37
Nausea	45	1.9	34
Dyspnea	34	3.4	17
Diarrhea	32	0.8	24
Pyrexia	31	1.5	15
Headache	28	1.9	17
Upper respiratory tract infection	27	4.5	5.6
Increased serum creatinine	25	2.6	17
Other events of interest			
Vomiting	22	0.8	16.5
Peripheral neuropathy	12	1.1	8.3
Hypophosphatemia	12	6.0	7.1
Pneumonia	12	9.4	4.9
Hyponatremia	12	8.3	4.9
Acute renal failure	4.9	3.4	1.5
Febrile neutropenia	0.8	0.8	0.8
Tumor lysis syndrome	0.4	0	0

Adapted from Siegel et al.[1]

The most common nonhematologic adverse events were fatigue, nausea, dyspnea, diarrhea, and fever (see Table 1). Dyspnea tended to be transient and not associated with progressive lung injury. Cardiac adverse events included congestive heart failure in 3.8% of patients, cardiac arrest in 1.5%, and myocardial infarction in 0.8%. Acute renal failure occurred in 4.9% of patients and chronic renal failure occurred in 3.8%. Grade 3 or 4 hematologic adverse events included thrombocytopenia in 29% of patients, anemia in 24%, and lymphopenia in 20%. As noted, 77% of patients started the study with peripheral neuropathy of grade 1 or 2; new onset or worsening of peripheral neuropathy occurred in 12.4%. Adverse events most frequently associated with discontin-

uation of treatment were hypercalcemia (6 patients), congestive heart failure, cardiac arrest, dyspnea, pneumonia, spinal cord compression (4 patients each), and increased serum creatinine (3 patients). Adverse events led to at least 1 dose level reduction in 17.7% of patients and dose delay in 21.4%.

Death occurred in 24 patients (9.0%) on study or within 30 days of their last carfilzomib dose. In 12 patients (4.5%), death was related to progressive disease. In 11 patients (4.1%), death was associated with adverse events, consisting of cardiac arrest in 3 patients, hepatic failure in 2, and acute coronary syndrome secondary to progressive disease, dyspnea, intracranial hemorrhage, pneumonia, sepsis, and sepsis secondary to progressive disease in 1 each. Death was considered potentially related to carfilzomib treatment in 5 patients (1.9%), with causes consisting of cardiac arrest in 2 patients and dyspnea, hepatic failure, and unknown cause in 1 patient each.

Reference

1. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma [published online ahead of print July 25, 2012]. *Blood*. http://dx.doi.org/10.1182/blood-2012-05-425934.

Bortezomib

A recent randomized, open-label phase 3 noninferiority study showed that subcutaneous (SC) bortezomib produced a response rate that was noninferior to that observed with intravenous (IV) bortezomib in patients with relapsed multiple myeloma (MM), while potentially improving the safety profile of bortezomib therapy.[1,2] Bortezomib can be given SC or IV in patients with previously untreated or relapsed MM, as well as in patients with mantle cell lymphoma who have received at least 1 prior treatment.

In the trial that compared SC and IV bortezomib, 222 patients aged 18 years or older with relapsed MM after 1 to 3 previous lines of chemotherapy were randomized (2:1) to SC (148 patients) or IV (74 patients) bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 every 21 days for 8 cycles.[1] SC injections were administered at 2.5 mg/mL (3.5 mg bortezomib reconstituted with 1.4 mL normal saline) to limit the volume of injection. Patients with less than complete response (CR) after cycle 4 could receive dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 from cycle 5 onward. Patients with stable disease or partial response (PR) as best response at the end of cycle 8 who were evolving to late PR or CR could receive 2 additional cycles of treatment. Patients had to have Karnofsky performance status of ≥ 70% and adequate hematologic, hepatic, and renal function. Patients with prior bortezomib treatment, grade 2 or higher peripheral neuropathy or neuropathic pain, or treatment with antineoplastic or investigational agents or prednisone >10 mg a day (or equivalent) within the previous 3 weeks were excluded from the study. The primary objective of the

How I treat multiple myeloma

The current approach to treatment of multiple myeloma has undergone a dramatic transformation in the past decade with advent of several new drugs and a better understanding of the disease biology. While the tools have changed, the overall approach and the goals have remained same. A stepwise approach to myeloma management significantly reduces the complexity of the treatment approach, which has become increasingly confusing with a wide array of options and opinions.

The first step is the determination that a particular patient with a monoclonal gammopathy has symptomatic myeloma requiring therapy rather than a monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma, conditions that are currently observed rather than treated. The next step is to risk stratify these patients and presence of various genetic abnormalities detected by FISH appear to be key in determining survival. The initial therapy should take into account the risk stratification, the complications at presentation and patient age and performance status, as detailed at www.msmart.org.

Patients with high risk disease should receive bortezomib-based initial therapy. The goal of the initial therapy is to rapidly control the disease and reverse the complications while limiting toxicity and allowing stem cell collection in those considered eligible for transplant. After the initial 3-4 cycles of therapy, the response requires further consolidation, which can either use autologous stem cell transplantation or continued therapy with the initial regimen modified to minimize toxicity.

Post transplant, maintenance therapy using bortezomib, lenalidomide, or thalidomide may be employed in selected patients with high risk myeloma. In the non-transplant situation, the duration of therapy is not well defined, but is reasonable to continue treatment to a plateau, often 18-24 months. Once in a plateau, use of continued maintenance therapy till progression remains a matter of debate and needs to be decided on based on the tolerability, cost and other quality of life aspects. All patients should receive maximal supportive care including bisphosphonates, calcium and vitamin D supplementation, prompt treatment of infectious complications, and the required vaccinations.

— Shaji K. Kumar, MD

study was to demonstrate that SC bortezomib was not inferior to IV bortezomib in overall response rate after 4 cycles of single-agent treatment. To be considered noninferior, SC treatment had to be associated with a treatment effect at least 60% of that of IV treatment over the first 4 cycles of single-agent treatment.

Patients in both groups had a median age of 64.5 years, with 50% in both groups being 65 years of age or older. The SC and IV groups were well matched for most baseline characteristics, including ethnic origin (97% vs 96% white, respectively), proportion of patients with > 1 line of prior therapy (38% vs 35%), and proportion with >10 lytic bone lesions (47% and 46%). The SC group had a smaller percentage of men (50% vs 64%), a greater percentage of patients from Eastern Europe (66% vs 45%), a greater percentage of patients with Karnofsky performance scores of 70% or 80% (60% vs 48%), a smaller percentage of patients with high-risk cytogenetics (14% vs 19%), and a greater percentage with creatinine clearance ≤ 60 mL/min (41% vs 32%). Melanoma type was IgG and IgA in 65% and 26% of SC patients, respectively, and 72% and 19% of IV patients. The median time since the last line of therapy was 3.4 months in the SC group and 5.8 months in the IV group, with 43% and 49% of patients, respectively, receiving the last line of therapy at more than 6 months before the start of the study.

The overall response rate after 4 cycles of single-agent treatment was 42% in both groups, including CR or near CR in 12% of SC patients and 14% of IV patients. SC treatment thus met the response criterion for noninferiority (P = .002). In both groups, patients received a median of 8 cycles of treatment, and bortezomib dose intensities in the SC group and the IV group were similar during the first 4 cycles (5.13 vs 4.89 mg/m^2 per cycle) and from cycle 5 onward (4.88 vs 4.91 mg/m^2 per cycle). Overall, 56% of SC patients and 52% of IV patients received dexamethasone beginning at cycle 5, with an identical dose intensity of 160 mg per cycle in both groups. Treatment was continued through 10 cycles in 12% of patients in each group.

After 8 cycles, overall response rates were 52% in both groups, with 20% of SC patients and 22% of IV patients achieving CR or near CR and 25% in both groups achieving at least very good PR. Median time to first response was 3.5 months in all patients who were evaluable for response in both groups and 1.4 months in patients in both groups who had response. Median duration of response was 9.7 months in SC patients and 8.7 months in IV patients. After median follow up of 11.8 months in the SC group and 12.0 months in the IV group, there were no significant differences in time to progression (median, 10.4 vs 9.4 months; hazard ratio [HR], 0.84; 95% CI, 0.56-1.25), progression-free survival (median, 10.2 vs 8.0 months; HR, 0.82;, 95% CI, 0.57-1.18) or overall survival (1 year survival, 72.6% vs 76.7%).

TABLE 2 Adverse events of any grade in ≥ 15% of patients, or grade 3 or higher in ≥5% of patients and hematologic abnormalities

	Percentage of Patients			
	SC Bortezomib (n = 147)		IV Bortezomib (n = 74)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
Adverse Event				
Anemia	36	12	35	8
Thrombocytopenia	35	13	36	19
Peripheral sensory neuropathy	35	5	49	15
Neutropenia	29	18	27	18
Diarrhea	24	2	36	5
Neuralgia	24	3	23	9
Leukopenia	20	6	22	7
Pyrexia	19	0	16	0
Nausea	18	0	19	0
Asthenia	16	2	19	5
Weight decreased	15	0	3	1
Constipation	14	1	15	1
Fatigue	12	2	20	4
Vomiting	12	2	16	1
Pneumonia	8	5	9	8
Hematologic laboratory data				
Hemoglobin	98	14	97	12
WBC count	80	8	88	18
Absolute neutrophil count	67	22	77	28
Platelets	88	18	93	23

Abbreviations: IV, intravenous; SC, subcutaneous. From Moreau et al.[1]

Overall, adverse events of any grade occurred in 95% of SC patients and 99% of IV patients, with adverse events of grade 3 or higher occurring in 57% and 70%, respectively. Rates of adverse events of any grade occurred in ≥ 15% of all patients, adverse events of grade 3 or higher occurred in ≥ 5% of patients, and hematologic adverse events (see Table 2). By system organ class, rates of gastrointestinal disorders, respiratory, thoracic, and mediastinal disorders, and nervous system disorders were ≥ 10% lower in SC patients, as were rates of diarrhea and peripheral sensory neuropathy. Treatment was discontinued because of adverse events in 22% of SC patients and 27% of IV patients; 31% and 43%, respec-

tively, required bortezomib dose reductions because of adverse events. Serious adverse events occurred in 35% of SC patients and 36% of IV patients. Death occurred within 30 days of the last dose of study treatment in 5% of SC patients and 7% of IV patients.

Rates of peripheral neuropathy adverse events of any grade were 38% in the SC group and 53% in the IV group ($P = .04$), including events of grade 3 or higher in 6% and 16% ($P = .03$), respectively. Risk factors for peripheral neuropathy (grade 1 peripheral neuropathy at baseline, diabetes, previous exposure to neurotoxic agents) were balanced between the 2 groups. Among 34 SC patients and 21 IV patients with grade 1 peripheral neuropathy at baseline, 29% and 43%, respectively, developed grade 2 peripheral neuropathy and 9% and 24%, respectively, developed grade 3 peripheral neuropathy. At the time of reporting, 62% of peripheral neuropathy events in the SC group and 67% in the IV group had resolved or improved over a median of 2.8 months and 1.5 months, respectively.

Subcutaneous injection-site reactions occurred in 6% of the SC group, requiring discontinuation or dose withholding in 1%. All reactions resolved in a median of 6 days.

References

1. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study [published correction appears in *Lancet Oncol*. 2011;12(6):522]. *Lancet Oncol*. 2011; 12(5):431-440.

2. Velcade [package insert]. Cambridge, MA: Millenium Pharmaceuticals Inc; 2012. http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf.