

Bortezomib in multiple myeloma

This novel proteasome inhibitor appears to improve response rates and survival in patients with progressive multiple myeloma

Bortezomib (Velcade) is an inhibitor of the proteasome, a ubiquitous multi-enzyme complex that degrades proteins that regulate cell-cycle progression and induces proteolysis of I κ B, the inhibitor of nuclear factor- κ B. Increased activation of nuclear factor- κ B promotes cell survival, stimulates growth, and inhibits apoptosis, as well as induces drug resistance in myeloma cells. Recent studies have demonstrated the efficacy and safety of bortezomib in patients with relapsed, refractory myeloma.

Efficacy studies

In the phase II SUMMIT study (n = 202), treatment with bortezomib 1.3 mg/m² twice weekly for 2 weeks, followed by 1 week without treatment, for up to 8 cycles (24 weeks) resulted in an overall response rate of 35% (including a complete response in 4% in whom myeloma protein was undetectable and a complete response in 6% in whom myeloma protein was detectable only by immunofixation).¹ In the phase II CREST study, treatment with bortezomib 1.0 mg/m² (n = 28) or 1.3 mg/m² (n = 26) on days 1, 4, 8, and 11 every 3 weeks for up to 8 cycles (6 months) resulted in an overall response rate of 33% (4% complete response) for the 1.0-mg/m² dose and 50% (4% complete response) for the 1.3-mg/m² dose.²

A group of 14 patients from the CREST study and 43 from the SUMMIT study who had a partial or minimal response to bortezomib or stable disease continued receiving the

proteasome inhibitor in an extension study. Most of these patients had already received 8 cycles of bortezomib therapy in the original studies. Preliminary data from the extension study indicated that bortezomib can be administered for up to 13 cycles with a safety profile similar to that observed in the first 8 cycles of treatment.²

Safety demonstrated in renally impaired patients

Renal impairment is a common complication of myeloma and its treatment, and preclinical studies indicate that bortezomib and its metabolites are eliminated by both the renal and hepatic route. An analysis of outcomes in 10 patients with severe renal impairment (creatinine clearance, 10–30 mL/min) in these two studies suggests that bortezomib may be safely given to such patients, with responses and toxicities being comparable to those in patients without severe renal impairment.³ Of the 10 patients, 2 had a partial response and 1 had a minimal response; treatment was well tolerated, with 7 patients receiving at least 30 of the 32 possible study doses.

Pharmacokinetic analysis of eight patients with an initial creatinine clearance rate of 31–169 mL/min in the SUMMIT study indicated that the maximum concentration and distribution half-life of bortezomib were not affected by renal status and that the area under the concentration-time curve was similar to that obtained in the overall population.

Superior to dexamethasone

The APEX Study Group recently reported findings from their international, multicenter phase III

trial comparing bortezomib with dexamethasone in patients with relapsed multiple myeloma.⁴ Patients were randomized to receive intravenous bortezomib 1.3 mg/m² (n = 327) on days 1, 4, 8, and 11 every 3 weeks for 8 cycles, followed by the same dose on days 1, 8, 15, and 22 every 5 weeks for 3 cycles, or oral dexamethasone 40 mg (n = 330) on days 1–4, 9–12, and 17–20 every 5 weeks for 4 cycles, followed by 40 mg on days 1–4 every 4 weeks for 3 cycles.

At the time of the interim analysis, 254 progressive disease events had occurred. Median time to disease progression (using European Group for Blood and Marrow Transplantation criteria) was 5.7 months in the bortezomib-treated group versus 3.6 months in the dexamethasone-treated group ($P < 0.0001$). Overall survival was significantly longer in patients receiving bortezomib than in those taking dexamethasone ($P = 0.038$). At the time of the interim analysis, 13 patients treated with bortezomib and 24 patients given dexamethasone had died; median survival had not yet been reached in either treatment arm.

Significantly fewer patients taking bortezomib than those who were treated with dexamethasone developed grade 3 or worse infections (6.7% vs 10.6%, $P = 0.096$). No other major differences in safety were observed between treatment groups, and no difference was observed between treatment groups with regard to time to skeletal events.

On the basis of the interim analysis, it was recommended that the dexamethasone treatment arm be terminated in the APEX Study, and patients in the dexamethasone treatment group were permitted to receive bortezomib.

The major side effects of bortezomib are gastrointestinal symptoms, transient thrombocytopenia, fatigue, and peripheral neuropathy. Other, less frequent side effects include fever, rash, headache, and dizziness.

Summary by Matt Stenger, MS; reviewed by Vincent Rajkumar, MD, Division of Hematology, Mayo Clinic, Rochester, MN.

Fitting bortezomib into clinical practice

Robert A. Vescio, MD

Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

BORTEZOMIB (VELCADE) WAS RECENTLY approved by the US Food and Drug Administration for use as salvage therapy for patients with relapsed multiple myeloma. Over 200 patients were enrolled in the SUMMIT study, the main randomized clinical trial that established its efficacy and safety, and the response rate was 35%. This response rate does not seem that high, but in this trial all of the patients had been heavily pre-treated, and so a lot of quite treatment-refractory patients were enrolled. The response rate was 50% in a smaller study (CREST) in which patients were treated with bortezomib at first relapse.

At this point, I tend to use bortezomib as my third-line agent for patients with multiple myeloma or as second-line therapy if they were initially treated with thalidomide (Thalomid) and dexamethasone. I also use the drug early on if patients cannot tolerate corticosteroids for various reasons, such as diabetes.

I believe the response rates with bortezomib alone are as good, if not better, than those achieved with thalidomide, but thalidomide remains a more easily administered medication.

Bortezomib is 'extremely well tolerated'

For many patients, bortezomib is extremely well tolerated, with about half of the patients treated with this drug having few, if any, side effects. Many patients experience some fatigue related to treatment with bortezomib, and it often causes a low-grade fever the first few times it is given. Some patients will develop diarrhea, which can usually be controlled with loperamide or diphenox-

ylate and atropine. Bortezomib does not cause much nausea, and, typically, premedication with prochlorperazine is sufficient. Many of my patients can take this drug without any antiemetics.

Bortezomib causes a reproducible fall in the platelet count, but the thrombocytopenia seems to be more transient than that seen with typical chemotherapy agents. The platelet count typically recovers quickly during the week patients are off drug, and I tend to be relatively aggressive with treatment, not withholding the drug because of thrombocytopenia unless the platelet count falls below 30,000/mm³.

The main long-term toxicity is neuropathy. Patients describe a feeling of discomfort in their feet and then legs, which is often described as "frostbite." It is important to ask patients about any symptoms of peripheral neuropathy they might be having and adjust the drug dose downward if symptoms occur. Most patients will experience an improvement in neuropathic symptoms, or at least stabilization, at a lower drug dosage (1.0 mg/m² or lower, if necessary). If one waits too long to adjust the medication, however, the neuropathy may become more severe and adversely affect the patient's quality of life, limiting one's ability to use the drug.

Tailoring therapy to different stages

If a patient has multiple myeloma but is asymptomatic, I wait before starting treatment until repeated lab tests show that the patient is becoming progressively more anemic or is developing other complications. Once treatment is needed, I treat most new patients with either

liposomal encapsulated doxorubicin (Doxil), vincristine, and dexamethasone (DVD) or thalidomide and dexamethasone. I tend to use DVD or vincristine, doxorubicin, and dexamethasone (VAD) for patients with more aggressive disease because I think the regimen has a faster onset of action, which is especially important for patients presenting with renal insufficiency.

If I am anticipating a future stem-cell transplant as consolidation therapy for the patient (which I do for most patients under 70 years of age), I again tend to favor DVD or VAD. I do this because the patients will likely need a catheter anyway for their stem-cell transplant, making this less of a negative issue for the patient.

I also like to save thalidomide and dexamethasone as a salvage regimen because it can be given long-term (at a reduced monthly dexamethasone dose) with relatively little toxicity. Patients who relapse after transplant often feel well at the time, and this regimen does not seem to interfere with their routine or well being as much as chemotherapy does.

For patients who progress beyond this stage, I use bortezomib alone or in combination with liposomal doxorubicin, the latter for patients with a particularly aggressive relapse of their disease. After this, I tend to use chemotherapy with cyclophosphamide- or melphalan (Alkeran)-based regimens. Arsenic trioxide (Trisenox) is another good choice for patients with poor bone marrow reserve, as it is well tolerated but doesn't cause much pancytopenia. For older patients with other comorbid illnesses, melphalan and prednisone (MP) remains a good option. It is well tolerated and has a reasonable response rate (50%). However, I avoid MP in younger patients, who could at any point be considered for stem-cell transplan-

tation, and in all patients with what appears to be less-aggressive disease. The only three multiple myeloma patients I have had who died from leukemia all had significant exposure to melphalan 7–10 years prior to the development of leukemia. Melphalan also tends to burn out the bone marrow, making future treatment more difficult.

Prognosis for myeloma patients is brightening

Bortezomib is a very active drug. We are now conducting a clinical trial using bortezomib as initial therapy for patients with multiple myeloma. The response rate in the first 30 patients is greater than 80%, and the drug appears to be very well tolerated.

I suspect that in the near future a regimen combining bortezomib with other agents, such as dexamethasone

and either liposomal doxorubicin or thalidomide, will become the standard upfront regimen for multiple myeloma. As stem-cell transplantation becomes increasingly better tolerated, I think more patients will undergo transplantation as a part of their standard treatment. While cures are rare, most patients have a period following transplantation where they feel normal, are able to return to work, and have a more prolonged disease-free and overall survival. Maximizing the percentage of patients attaining complete responses seems to be a good surrogate measure of long-term outcome and may avoid the need for randomized trials to document regimen benefits. This concept should speed development of more effective regimens.

Finally, the new thalidomide-like drug CC-5013 (to be marketed under the trade name Revlimid) will like-

ly be approved for use in multiple myeloma next year. Current studies look very promising for this oral immunomodulatory agent, which is better tolerated overall than thalidomide. The majority of patients I have had a chance to treat with this drug have responded to it, with the main side effect being pancytopenia. In the more distant future, I think multiple myeloma will become a more chronic condition, with many patients living with their disease for 5–10 years. These new treatments finally seem to be prolonging survival times, and with many other investigational drugs in development, it is likely that this trend will continue.

Dr. Robert A. Vescio is Director of the Myeloma Program at the Outpatient Cancer Center of the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA. He can be reached at RVescio@esccc.com.

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