Velcade (Bortezomib) Receives 2 New FDA Indications: For Retreatment of Patients with Multiple Myeloma and for First-Line Treatment of Patients with Mantle-Cell Lymphoma

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Multiple myeloma, also referred to as myeloma, is a malignant neoplasm of plasma cells in the bone marrow that leads to bone destruction and bone marrow failure.[1,2] According to the American Cancer Society, an estimated 26,850 new cases of myeloma will be diagnosed in 2015, and 11,240 deaths will be attributed to myeloma.[3]

Relatively uncommon, myeloma represents approximately 1% of all cancers. Nevertheless, myeloma is the second most common hematologic malignancy after non-Hodgkin lymphoma (NHL).[4] Although the overall incidence of myeloma has increased nearly 1% annually since 1975, the mortality rates associated with myeloma have declined during the past 2 decades.[1]

Myeloma is more common in men than in women. Middle-aged or older individuals, those with a family history of myeloma, or with a personal history of monoclonal gammopathy of undetermined significance are at an increased risk for myeloma.[1]

The complications associated with myeloma include back pain, kidney dysfunction, bone loss, impaired immunity, and anemia.[5] Based on one study, the annual US costs attributed to metastatic bone disease, including myeloma, were an estimated $12.6 billion.[6] The median cost for patients with metastatic bone disease was $75,329 annually compared with $31,382 annually for cancers that are not associated with metastatic bone disease. The regression-adjusted incremental costs were highest for patients with myeloma; that is, $63,455 for myeloma versus $44,442 across all cancer types (P <.001).[6]

The treatment of patients with myeloma has evolved substantially in recent years. The introduction of novel drugs, including thalidomide, lenalidomide, and bortezomib, as well as a better understanding of the bone marrow microenvironment, have led to new combination therapies and new anticancer drugs.[7] In fact, the use of novel agents for first-line treatment of myeloma has improved outcomes, including overall responses, for patients with relapsed or refractory myeloma.[7] Nevertheless, despite strides in the treatment of myeloma, there remains a marked need for additional therapeutic options and approaches for this patient population.[8]

Current therapies for myeloma include chemotherapy, corticosteroids, angiogenesis inhibitors, targeted therapies, biologic therapies, radiation therapy, stem-cell transplantation, and supportive care.[1]

Because patients with myeloma will experience disease relapse after initial treatment, multiple lines of therapy may be required. The therapeutic considerations for patients with relapsed myeloma include the duration of response to previous treatment, as well as the toxicity profile of a specific treatment and patient-specific factors.[7]

Mantle-Cell Lymphoma

Mantle-cell lymphoma (MCL) is a rare malignancy, comprising approximately 5% of all NHL cases.[9] MCL, which can be an aggressive cancer, most often affects men aged >60 years.[9,10] The median overall survival is approximately 5 to 7 years, making MCL one of the poorest prognosis B-cell lymphomas.[11]

The survival outcomes are poor in part because MCL is typically diagnosed in later stages, such that the gastrointestinal tract and bone marrow are involved.[9] Although data suggest a possible increase in the incidence of MCL during the past 20 years, this may be the result of improved diagnostic methods.[11]

In clinical practice, combinations of chemotherapy agents with anti-CD20 monoclonal antibody therapy, high-dose chemotherapy followed by autologous stem-cell transplantation, and radioimmunotherapy are relevant options for treatment-naïve patients with MCL.[9] MCL typically responds to initial treatment, but the disease relapses within a few years or becomes refractory to therapy, requiring subsequent lines of therapy.[10]

There is no consensus regarding the management of patients with relapsed or refractory MCL. Treatment

decisions are based on several factors, including timing of disease relapse, disease extent, patient age, overall health, and previous therapies.[10]

Currently, bortezomib, lenalidomide, and ibrutinib are approved by the US Food and Drug Administration (FDA) for the treatment of patients with MCL. Bortezomib was initially indicated for use in patients with MCL who have received at least 1 previous therapy.[12] Lenalidomide is approved for use in patients with MCL whose disease had relapsed or progressed after 2 previous therapies, 1 of which included bortezomib.[13] Most recently, ibrutinib was granted accelerated approval by the FDA for the treatment of patients with MCL who have received at least 1 previous therapy.[14] Other novel options under investigation for MCL include phosphoinositide 3-kinase inhibitors, cell-cycle inhibitors, monoclonal antibodies, and mTOR inhibitors.[15]

There are few assessments of the cost burden associated with MCL. A 2012 cost-effectiveness study based on US payer data showed that the total per-patient costs for patients with MCL exceeded $100,000.[16] In this study, which compared the combination of bendamustine plus rituximab with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in treatment-naïve patients with MCL, the calculated average per-patient costs exceeded $115,000 and $100,200 for bendamustine plus rituximab and R-CHOP, respectively.[16]

Bortezomib Receives 2 New Indications in 2014

In 2014, the FDA approved bortezomib (Velcade; Millennium Pharmaceuticals [Takeda]) for 2 new indications. On August 8, 2014, bortezomib was approved for the retreatment of adult patients with myeloma whose disease had previously responded to bortezomib therapy and relapsed at least 6 months after the completion of that therapy with bortezomib.[17,18] (The initial FDA approval of bortezomib was in 2003 for the treatment of patients with myeloma.[19])

The new indication for retreatment with bortezomib was based on findings from the phase 2 clinical trial known as RETRIEVE, as well as other supportive data.[17,18] The revised drug labeling now includes dosing guidelines and safety and efficacy data on bortezomib therapy as a single agent or in combination with dexamethasone in patients who had previously received treatment with bortezomib.[19]

According to Michael Vasconcelles, MD, Global Head, Oncology Therapeutic Area Unit, Takeda Pharmaceuticals, "For the past 11 years, Velcade has played an important role as the only therapy proven to extend overall survival for patients with newly diagnosed and relapsed multiple myeloma." Dr Vasconcelles added, "With these newly approved dosing guidelines, physicians will be able to provide their patients, who have previously received Velcade, with an effective treatment extending Velcade use across the continuum of care of multiple myeloma."[18]

On October 9, 2014, the FDA approved bortezomib for the treatment of treatment-naïve patients with MCL, making it the first US treatment to receive FDA approval for this setting.[20] This approval extends the use of bortezomib beyond relapsed or refractory MCL, for which it has been indicated since 2006. The approval for treatment-naïve patients with MCL was based on the results of a phase 3 clinical trial comparing the regimen of bortezomib plus rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) with the R-CHOP regimen.[19,20]

According to Andrew Evens, DO, MSc, Director, Tufts Cancer Center; Chief, Division of Hematology/Oncology; and Director, Lymphoma Program, Tufts School of Medicine, "There are several new targeted drugs approved by the FDA for patients with relapsed or refractory, but up to this point, there had been none approved for the treatment of patients with previously untreated disease. Velcade, when used in the VcR-CAP regimen, has demonstrated improved outcomes for patients, making it an important advance for the treatment of newly diagnosed patients with MCL."[20]

Mechanism of Action

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. The disruption of the normal homeostatic mechanisms on the cellular level can lead to cell death.[19] In vitro experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types. In nonclinical tumor models, bortezomib therapy causes a delay in tumor growth in vivo.[19]

Dosing and Administration

Bortezomib is available as a single-use vial containing 3.5 mg of bortezomib as lyophilized powder. The recommended starting dose is 1.3 mg/m^2. Bortezomib may also be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL.[19]

Retreatment with bortezomib may be considered for patients with myeloma whose disease had previously responded to treatment with bortezomib and had relapsed at least 6 months after completing previous bortezomib

therapy. Retreatment with bortezomib may be started at the last tolerated dose.[19]

The updated labeling for bortezomib is consistent with the National Comprehensive Cancer Network Clinical Practice Guidelines for the treatment of patients with relapsed myeloma, which state that if disease relapse occurs more than 6 months after the completion of the initial primary therapy, patients may be retreated with the same primary regimen.[2]

In patients with MCL, bortezomib 1.3 mg/m^2 is administered intravenously in combination with VcR-CAP.[19] Bortezomib should be administered first, followed by rituximab. Bortezomib is administered twice weekly for 2 weeks on days 1, 4, 8, and 11, followed by a 10-day rest period. At least 72 hours should elapse between consecutive bortezomib doses.[19]

Six 3-week treatment cycles of VcR-CAP are recommended for patients with MCL.[19] Two additional VcR-CAP cycles should be administered to patients whose first documented response occurs at the end of 6 cycles.[19]

When administered intravenously, bortezomib is given as a 3- to 5-second bolus injection. Bortezomib is indicated for intravenous or subcutaneous administration only; it should not be administered by any other route. Because each route of administration has a different reconstituted concentration, caution should be used when calculating the required administration volume.[19]

Clinical Trials

Pivotal Phase 2 Clinical Trial: Bortezomib Retreatment in Relapsed Myeloma

The efficacy and safety of bortezomib retreatment of patients with relapsed myeloma were evaluated in the RETRIEVE study, an international, single-arm, open-label, phase 2 clinical trial.[7] In this study, 130 patients (aged ≥18 years) with myeloma who previously had at least a partial response after receiving a bortezomib-based regimen (median of 2 previous lines of therapy) were retreated with intravenous bortezomib at disease progression.[7] Patients were excluded from this trial if they had peripheral neuropathy or neuropathic pain of grade ≥2.[7]

At least 6 months after the completion of previous bortezomib therapy, patients restarted bortezomib therapy at the last tolerated dose of 1.3 mg/m^2 (N = 93) or ≤1.0 mg/m^2 (N = 37), which was administered on days 1, 4, 8, and 11 every 3 weeks for a maximum of 8 cycles, as a single agent or in combination with dexamethasone in accordance with the standard of care. Dexamethasone was administered in combination with bortezomib to 83 patients during cycle 1; 11 additional patients received dexamethasone during subsequent bortezomib retreatment cycles.[7,19]

Table 1 Patients Receiving Previous Therapies in the RETRIEVE Study

Type of previous nonbortezomib therapy	Patients receiving this therapy,[a] N
Steroids	115
Alkylating agents	100
Anthracyclines	75
Thalidomide	40
Other	
Previous high-dose therapy/stem-cell transplant	39
Previous bortezomib treatment	
Bortezomib single-agent	48
Bortezomib plus other agents	82

[a]Among the 130 patients with relapsed myeloma in the study.
Source: Petrucci MT, et al. *Br J Haematol.* 2013;160:649-659.

Table 2 Response to Bortezomib Retreatment in Patients with Relapsed Myeloma

Best confirmed response[a]	Patients achieving response, N (N = 130)
Partial response or better	50[b]
• Complete response	1
• Partial response	49
Overall response rate, %	38.5 (95% CI, 30.1-47.4)

[a]As assessed by the European Group for Blood and Marrow Transplantation criteria.
[b]In the 50 patients who responded, the median duration of response was 6.5 months (range, 0.6-19.3 months).
CI indicates confidence interval.
Source: Velcade (bortezomib) for injection prescribing information; October 2014.

The patients' median age was 67 years (range, 38-86 years), and the median time from myeloma diagnosis was 4.5 years (range, 0.8-13.9 years).[7,19] **Table 1** lists the various previous therapies used by the 130 patients in the RETRIEVE trial.

The primary end point of this clinical trial was the best confirmed response to bortezomib retreatment as assessed by the European Group for Blood and Marrow Transplantation criteria. Retreatment with bortezomib demonstrated a 38.5% overall response rate (**Table 2**), with a median duration of response of 6.5 months (range, 0.6-19.3 months).[19]

Open-Label Phase 3 Clinical Trial: Bortezomib Therapy in Untreated Mantle-Cell Lymphoma

The approval of bortezomib in patients with previous-

ly untreated MCL was based on an open-label phase 3 clinical trial.[19,20] In this trial, 487 adults with stage II to IV MCL who were ineligible or not considered for bone marrow transplantation received VcR-CAP (N = 243) or R-CHOP (N = 244).[19]

The VcR-CAP regimen consisted of bortezomib at 1.3 mg/m^2 administered intravenously on days 1, 4, 8, and 11 (rest period, days 12-21), rituximab at 375 mg/m^2 on day 1, cyclophosphamide at 750 mg/m^2 on day 1, doxorubicin at 50 mg/m^2 on day 1, and prednisone at 100 mg/m^2 on days 1 to 5 every 21 days for 6 cycles. In both groups, patients whose response was first documented at cycle 6 could receive 2 additional cycles of therapy.[19]

The patients' median age was 66 years; 74% were male, 66% were white, and 32% were Asian.[19] The majority of these patients had stage IV disease (76%), positive bone marrow aspirate and/or biopsy (69%), and an International Prognostic Index score ≥3 (54%).[19]

The primary end point of this trial was median progression-free survival, which was based on independent radiographic assessment. The progression-free survival results demonstrated a significant advantage of the VcR-CAP regimen over the R-CHOP regimen—25 months with the VcR-CAP regimen versus 14 months with the R-CHOP regimen (**Table 3**).[19]

The overall response rate was 88% in the VcR-CAP group versus 85% in the R-CHOP group, with complete response of 44% in the VcR-CAP group versus 34% in the R-CHOP group.[19]

Adverse Events

Bortezomib Retreatment in Relapsed Myeloma

The most frequently reported adverse reactions (incidence ≥20%) associated with bortezomib therapy in clinical studies included nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.[19]

In the RETRIEVE trial, the safety profile was consistent with the known safety profile of patients with relapsed myeloma who received bortezomib therapy. No cumulative toxicities were observed upon retreatment.[19] The most common adverse reaction was thrombocytopenia, which occurred in 52% of the patients (grade ≥3, 24% of the patients). Peripheral neuropathy occurred in 28% of the patients (grade ≥3, 6% of the patients).[19]

The incidence of serious adverse reactions was 12.3%; the most common serious adverse reactions were thrombocytopenia (3.8%), diarrhea (2.3%), herpes zoster (1.5%), and pneumonia (1.5%).[19]

Adverse reactions leading to discontinuation of bortezomib therapy occurred in 13% of patients.[19] The reasons for treatment discontinuation included peripheral neuropathy (5%) and diarrhea (3%).[19] Overall, 2 deaths were attributed to bortezomib therapy and occurred within 30 days of the last bortezomib dose; 1 death occurred in a patient with a cerebrovascular accident, and the other in a patient with sepsis.[7,19]

Bortezomib in Patients with Untreated Mantle-Cell Lymphoma

The safety of the VcR-CAP regimen was assessed in 240 patients with previously untreated MCL.[19] Adverse reactions led to the discontinuation of VcR-CAP in 8% of these patients and in 6% of patients who received R-CHOP in this phase 3 clinical trial.[19] Among patients receiving VcR-CAP, the most common adverse reaction that led to treatment discontinuation was peripheral neuropathy (1%).[19] The most common adverse reaction that led to the discontinuation of R-CHOP was febrile neutropenia (<1%).[19]

The rates of peripheral neuropathy (all severity grades) were higher among patients receiving VcR-CAP (30%) than in patients receiving R-CHOP (27%). In addition, the incidence of grade 3 peripheral neuropathy was higher in the VcR-CAP group (7%) compared with the R-CHOP group (4%).[19]

The rate of thrombocytopenia (all grades) was substantially higher among patients who received the VcR-CAP regimen (72%) compared with those receiving R-CHOP (17%). Overall, 3 patients who received VcR-CAP and 1 patient who received R-CHOP had a bleeding event of grade ≥3.[19]

Neutropenia (all grades) was more common in the VcR-CAP group (87%) compared with the R-CHOP group (71%).[19] Grade ≥3 febrile neutropenia occurred in 15% of patients in the VcR-CAP group and in 13% of patients in the R-CHOP group.[19]

Table 3 VcR-CAP versus R-CHOP: Progression-Free Survival in Previously Untreated Mantle-Cell Lymphoma

Efficacy end point	VcR-CAP (N = 243)	R-CHOP (N = 244)
Progression-free survival[a]		
Events, N (%)	133 (55)	165 (68)
Median, mo	25 (95% CI, 20-32)	14 (95% CI, 12-17)
Hazard ratio	0.63 (95% CI, 0.50-0.79)	
	P <.001	

[a]By independent radiographic assessment.
CI indicates confidence interval; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.
Source: Velcade (bortezomib) for injection prescribing information; October 2014.

Drug Interactions

Coadministration of bortezomib with strong cytochrome (CY) P3A4 inhibitors (eg, ketoconazole) can increase the exposure of bortezomib. Patients receiving bortezomib in combination with strong CYP3A4 inhibitors should be closely monitored.[19] The coadministration of strong CYP3A4 inducers (eg, rifampin) can decrease the exposure of bortezomib. The use of strong CYP3A4 inducers should be avoided.[19]

Contraindications

Bortezomib is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. Bortezomib therapy is also contraindicated for intrathecal administration.[19]

Warnings and Precautions

Peripheral neuropathy. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy during bortezomib therapy may require a decrease in dose and/or a less dose-intense schedule, or a discontinuation of bortezomib. Patients with preexisting severe neuropathy should receive bortezomib only after a careful risk–benefit assessment.[19]

Hypotension. Caution should be exercised when treating patients with a history of syncope, patients receiving antihypertensive agents, or patients experiencing dehydration.[19]

Cardiac toxicity. The worsening and development of cardiac failure have occurred during bortezomib therapy. Patients with existing heart disease or with risk factors for heart disease should be closely monitored.[19]

Pulmonary toxicity. Acute respiratory syndromes have occurred during bortezomib therapy. Patients should be closely monitored for new or worsening symptoms of pulmonary toxicity.[19]

Posterior reversible encephalopathy. Magnetic resonance imaging should be considered for an onset of visual or neurologic symptoms; bortezomib therapy should be discontinued if posterior reversible encephalopathy syndrome is suspected.[19]

Gastrointestinal toxicity. Nausea, diarrhea, constipation, and vomiting may require the use of antiemetic and antidiarrheal medications or fluid replacement.[19]

Thrombocytopenia or neutropenia. The cyclical pattern of platelet and neutrophil decreases and recovery that is associated with bortezomib use were also observed in studies of retreatment for myeloma and in untreated MCL, with no evidence of cumulative thrombocytopenia or neutropenia. Complete blood counts should be monitored regularly during treatment with bortezomib.[19]

Tumor lysis syndrome. Patients with a high tumor burden should be monitored closely for tumor lysis syndrome.[19]

Hepatic toxicity. Hepatic enzymes should be monitored in patients receiving bortezomib therapy.[19]

Embryofetal risk. Women of reproductive potential should avoid becoming pregnant while receiving bortezomib therapy. Pregnant women should be advised of the potential for embryofetal harm.[19]

Use in Specific Populations

Pregnancy. No adequate studies were conducted with bortezomib in pregnant women. Women who are pregnant while receiving bortezomib should be informed of the potential hazards to the fetus.[19]

Nursing mothers. It is not known whether bortezomib is excreted in human milk. A decision whether to discontinue nursing or to discontinue bortezomib therapy should be based on the importance of this drug to the mother.[19]

Pediatric use. The safety and efficacy of bortezomib in children have not been established.[19]

Geriatric use. No overall differences in the safety or efficacy of bortezomib were observed between patients aged ≥65 years and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.[19]

Renal impairment. Dosing adjustments are not necessary for patients with renal insufficiency. Because dialysis may reduce bortezomib concentrations, bortezomib should be administered after the dialysis procedure.[19]

Hepatic impairment. The exposure of bortezomib is increased in patients with moderate (ie, bilirubin ≥1.5-3 times the upper limit of normal [ULN]) or severe (ie, bilirubin >3 times ULN) hepatic impairment. The starting dose of bortezomib should be reduced in patients with moderate or severe hepatic impairment.[19]

Patients with diabetes. In clinical studies, hypoglycemia and hyperglycemia were reported in patients with diabetes who were receiving oral hypoglycemic therapy. Patients with diabetes who receive bortezomib therapy may require close monitoring of their blood glucose levels and dose adjustment of antidiabetic medications.[19]

Conclusions

Retreatment with bortezomib is now an FDA-approved option for patients with myeloma whose disease had previously responded to bortezomib therapy and relapsed at least 6 months after the completion of previous bortezomib therapy. The safety profile of bortezomib retreatment was consistent with the known safety profile of bortezomib in patients with relapsed myeloma, with no cumulative toxicities.

Bortezomib is the first treatment to be approved in the

United States for use in patients with previously untreated MCL. A large randomized clinical trial demonstrated improved progression-free survival and superior response rates with the VcR-CAP regimen compared with the R-CHOP regimen, a frequently used first-line regimen in this setting. Clinical studies are under way to evaluate the use of bortezomib in combination with other regimens that are used in previously untreated and relapsed MCL.[21] ■

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