DECEMBER 2014 SPECIAL ISSUE VOL 7, NO 6

#1 WITH ONCOLOGY NURSES

The Oncology Nurse-APN/PA®

The Official Publication for the Hem/Onc Nurse & Advanced Practitioner

Establishing and Managing Expectations for Length of Therapy in Multiple Myeloma

Proceedings from a Multiple Myeloma Nurse Roundtable

an affiliate of the lynx group

The Oncology Nurse-APN/PA®
The Official Publication for the Hem/Onc Nurse & Advanced Practitioner

Green Hill Healthcare Communications, LLC
1249 South River Road - Ste 202A
Cranbury, NJ 08512
phone: 732-656-7935
fax: 732-656-7938

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The Oncology Nurse-APN/PA®, ISSN 1944-9798 (print); ISSN 1944-9801 (online) is published 6 times a year by Green Hill Healthcare Communications, LLC, 1249 South River Road, Suite 202A, Cranbury, NJ 08512. Telephone: 732.656.7935. Fax: 732.656.7938.

EDITORIAL CORRESPONDENCE should be addressed to **EDITORIAL DIRECTOR**, *The Oncology Nurse-APN/PA®*, 1249 South River Road, Suite 202A, Cranbury, NJ 08512. E-mail: editorial@greenhillhc.com. **YEARLY SUBSCRIPTION RATES:** United States and possessions: individuals, $105.00; institutions, $135.00; single issues, $17.00. Orders will be billed at individual rate until proof of status is confirmed. Prices are subject to change without notice. Correspondence regarding permission to reprint all or part of any article published in this journal should be addressed to **REPRINT PERMISSIONS DEPARTMENT**, Green Hill Healthcare Communications, LLC, 1249 South River Road, Suite 202A, Cranbury, NJ 08512.

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This special issue has been co-developed and funded by Takeda.

Establishing and Managing Expectations for Length of Therapy in Multiple Myeloma

Multiple Myeloma Nurse Roundtable
Saturday, October 5, 2013
Boston, Massachusetts

The roundtable was supported by Takeda, and was comprised of oncology nurses, advanced practitioners, and oncology nurse navigators. The purpose of the roundtable was to gain insight on nurse and patient educational needs as well as management of patients during therapy. Participants were asked to provide insight on their experience as it related to managing and navigating patients with multiple myeloma, more specifically their feedback on:

- Managing the length of therapy
- Appropriate treatment options and side effects
- Challenges of staying on therapy
- Best practices to assess and manage side effects.

Participants

Beth Faiman, PhD(c), MSN, APRN-BC, AOCN – Moderator
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

Joseph D. Tariman, PhD, APRN, BC – Faculty
Northwestern University
Myeloma Program
Chicago, Illinois

Jessica Bailey, RN, BSN, OCN
Hematology Oncology Clinic
Baton Rouge, Louisiana

Eileen Bannon, RN, MSN, OCN, CBCN
Hershey Medical Center
Penn State Cancer Institute
Hershey, Pennsylvania

Kristin Barber, APRN
Utah Cancer Specialists
Salt Lake City, Utah

Deborah Christensen, RN, AHNB-BC
Dixie Regional Medical Center
St. George, Utah

Kathleen Clifford, RN, MSN, FNP-BC, AOCNP, ACHPN
St. Luke's Mountain States Tumor Institute
Boise, Idaho

Penny Daugherty, RN, MS, OCN
Northside Hospital
Atlanta, Georgia

Seth Eisenberg, RN, OCN
Seattle Cancer Care Alliance
Seattle, Washington

Paula Falzone, RN, BSN
Mt. Auburn Hospital-Oncology Hematology Clinic
Cambridge, Massachusetts

Gennie Howe, BSRN
North Texas Regional Cancer Center
Plano, Texas

Connie Kinney, RN, BSN, OCN
UPMC Cancer Centers-Hillman Cancer Center
Pittsburgh, Pennsylvania

Margaret Rummel, RN, BSN, OCN, MHA
Abramson Cancer Center
Philadelphia, Pennsylvania

Barbara Watson, RN, MSN, OCN
Community Health Network
Indianapolis, Indiana

Multiple myeloma (MM) is a relatively uncommon type of cancer. It is a malignancy of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure.[1] In the United States, about 24,050 new cases were expected to be diagnosed in 2014, and about 11,090 deaths were expected to occur.[2] MM incidence increases with advancing age.[3] There is a higher incidence of MM in males than in females, and in black Americans than in white Americans.[3] Although MM remains incurable, survival is improving.[4]

Pathophysiology of Multiple Myeloma

Normally, plasma cells produce various types of immunoglobulin (Ig) as part of an immune response.[2,5] In MM, neoplastic plasma cells accumulate in the bone marrow and produce a single clone of an Ig known as M protein, or paraprotein.[2,5,6] MM is characterized by uncontrolled proliferation of these abnormal plasma cells (ie, myeloma cells) and, in most cases, excess M protein, which can be used to diagnose MM.[2,5,6] Myeloma cells can interact with and adhere to bone marrow stromal cells, which leads to adhesion- and

Table 1 Clinical Features of Multiple Myeloma

Symptoms	Common Causes
Bone pain	Pathologic fracture
Easy fatigue	Anemia, high serum IL-6, therapy
Nausea and vomiting	Renal failure, hypercalcemia
Recurrent infections	Low uninvolved Ig, T-cell dysfunction, therapy
Paraplegia	Cord compression
Confusion and CNS symptoms	Hyperviscosity or hypercalcemia
Peripheral neuropathy	Nerve compression, amyloidosis, POEMS, immune-mediated effects, therapy induced

IL, interleukin; Ig, immunoglobulin; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

cytokine-mediated signaling. Cytokines, such as interleukin-6, may mediate tumor cell growth and survival.[5,6]

In addition to M protein, malignant plasma cells produce varying amounts of monoclonal free light chains (components of M protein). Light chains in the urine, referred to as Bence Jones proteins, are sometimes detected in laboratory studies of patients with myeloma. Among patients who have MM, approximately 20% produce only light chains in the serum and urine, and 2% produce neither light chains nor a paraprotein (non-secretors).[2,5,6]

Several types of M protein, most commonly IgG and IgA, are observed in patients with MM[1,2,6]; the subtypes of MM are based on the type of M protein secreted. The most common subtype of MM, with 70% of cases, is IgG; approximately 20% of cases are IgA. Approximately 15% of patients with IgG myeloma have coagulation-related complications, compared with ⩾3% of patients with IgA myeloma. IgA myeloma may be associated with poor prognosis despite higher initial response to therapy, compared with other MM subtypes.[5]

Clinical Features

As shown in **Table 1**, MM symptoms and their common causes vary widely depending on the underlying pathophysiology.[5] Anemia, bone fractures, hypercalcemia, and renal impairment are all relatively common in patients with MM.[2] High levels of M protein (or monoclonal gammopathy) can cause symptoms of hyperviscosity (headaches, nosebleed, blurred vision, and confusion),[6] while reduction in the normal immune response can mean recurrent bacterial infections.[2,6] Acute renal failure, cord compression, and hypercalcemia are true medical emergencies. Prompt diagnosis and treatment are vital to minimize long-term organ damage from these complications of MM.[6]

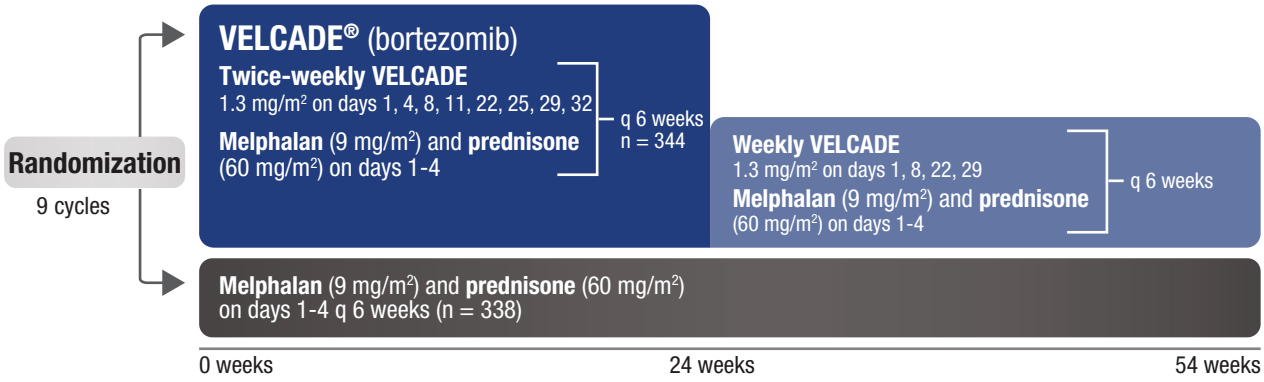
Diagnostic Criteria and Staging

According to the National Comprehensive Cancer Network, patients suspected of having MM should have a history and physical examination as well as blood, serum, urine, and biologic assessments.[1] Laboratory blood assessments include testing for beta-2 microglobulin ($ß_2$M), which is used to measure the tumor burden.[1] Urine analyses include evaluating 24-hour urine for total protein, urine protein electrophoresis, and urine immunofixation electrophoresis.[1] Serum analyses include testing for Ig (IgG, IgA, and IgM) levels, serum protein electrophoresis, and serum immunofixation electrophoresis.[1] Both serum and urine analyses are used to test for M protein and component light chains.[1,5]

In addition to laboratory testing, chromosome analysis is normally conducted to identify cytogenetic abnormalities in MM. Chromosomal deletions, translocations, and amplifications detected by fluorescence in situ hybridization or conventional cytogenetics are common in patients with MM.[1,7,8] High-risk chromosomal aberrations are characterized by 17p deletion, t(14;16) and t(14;20) translocations, and a high-risk gene expression profiling signature. Other abnormalities are typically characterized as standard or intermediate risk.[1,7-10]

In patients with monoclonal gammopathy of undetermined significance, a number of criteria are used to establish a diagnosis of symptomatic MM, including M protein in the serum or urine (required), bone marrow clonal plasma cells ≥10% or documented plasmacytoma

Figure 1 VISTA Trial Design



VISTA indicates VELCADE as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone
Source: San Miguel JF, et al. *N Engl J Med.* 2008;359:906-917.

(required), and related organ and tissue impairment, as measured by "CRAB" criteria (≥1 required)[1,6,11]:

- Hypercalcemia: serum calcium >11.5 mg/dL
- Renal dysfunction: serum creatinine >2 mg/dL
- Anemia: hemoglobin <10 g/dL or 2 g/dL below lower limit of normal
- Bone disease (osteolytic lesions or osteopenia).

Treatment of symptomatic MM may depend on patient age and comorbidities.[1,6] For patients with symptomatic MM, the International Staging System defines 3 risk categories based on serum concentrations of $ß_2$M and albumin.[12]

Stage I is characterized by serum $ß_2$M less than 3.5 mg/L plus serum albumin at least 3.5 g/dL, and stage III by serum $ß_2$M at least 5.5 mg/L (without regard to serum albumin level). Stage II is identified in either of 2 ways: serum $ß_2$M less than 3.5 mg/L plus serum albumin less than 3.5 g/dL or serum $ß_2$M greater than 3.5 mg/L but less than 5.5 mg/L (without regard to serum albumin level).[12]

Treatment of Multiple Myeloma with Velcade

Velcade (bortezomib) is indicated for the treatment of patients with MM. Bortezomib is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.[13]

Bortezomib is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol. Reactions have included anaphylactic reactions. Bortezomib is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of bortezomib.[13]

Efficacy Data

Bortezomib was studied in the Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone (VISTA) trial, a randomized, open-label, international trial evaluating the efficacy and safety of bortezomib plus melphalan/prednisone (Bortezomib + MP) versus melphalan/prednisone (MP) in previously untreated patients with MM who were ineligible for high-dose therapy plus autologous stem cell transplantation. The primary end point for the study was time to progression and secondary end points included complete response, overall response rate, progression-free survival, and overall survival.[14]

In the VISTA trial, 682 patients were randomized to bortezomib + MP (n=344) or MP (338). In the bortezomib + MP arm, bortezomib was administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles. In cycles 1 through 4 (total of 24 weeks), bortezomib (1.3 mg/m^2) was administered by intravenous (IV) bolus twice weekly on days 1, 4, 8, 11, 22, 25, 29, and 32, and melphalan (9 mg/m^2) and prednisone (60 mg/m^2) were administered on days 1 to 4 of each cycle. In cycles 5 through 9 (total of 30 weeks), bortezomib (1.3 mg/m^2) was administered once weekly on days 1, 8, 22, and 29, and melphalan (9 mg/m^2) and prednisone (60 mg/m^2) were administered on days 1 to 4 of each cycle. In the MP arm of the study, melphalan (9 mg/m^2) and prednisone (60 mg/m^2) were administered on days 1 to 4, every 6 weeks, for a total of 54 weeks (**Figure 1**).[14]

The MP arm crossed the median at the 36.7 months median follow-up analysis and it was not until the 60.1 months median follow-up analysis that overall survival was defined for both arms. Likewise, bortezomib combination therapy delivered significantly higher complete response and overall response rate in the bortezomib + MP arm versus the MP arm, as measured by the European Group for Blood and Marrow Transplantation criteria[13-15]—a standard for complete response.[16] Further

enrollment was halted, and patients receiving MP alone were offered bortezomib in addition.[13,14] Response rates are shown in **Figure 2**.

At a later pre-specified analysis with a 3-year median follow-up, bortezomib + MP provided an overall survival advantage over MP that was not regained with subsequent therapies.[13] Of the 69% of MP patients who received subsequent therapies, 50% received bortezomib or a bortezomib-containing regimen.[17]

After median follow up of 60.1 months, there was a 31% reduced risk of death following treatment with VELCADE MP versus MP (HR 0.695; *P* <.001).[18] Bortezomib-based therapy delivered a statistically significant 13.3-month overall survival advantage over MP (*P* <.05); median overall survival was 56.4 months for bortezomib + MP versus 43.1 months for MP alone (**Figure 3**). These were achieved with a median of 50 weeks of treatment.[13]

With bortezomib + MP, responses deepened with continued treatment through 54 weeks and beyond completion of therapy, and 28% of complete responses were achieved after 24 weeks of therapy. Furthermore, at the end of the planned duration of therapy (54 weeks), 102 patients (30% of the evaluable population) had achieved a complete response and 136 patients (40% of the evaluable population) had achieved a partial response (refer to **Figure 4**, on page 8).[19]

Bortezomib dosing schedule for previously untreated patients with MM

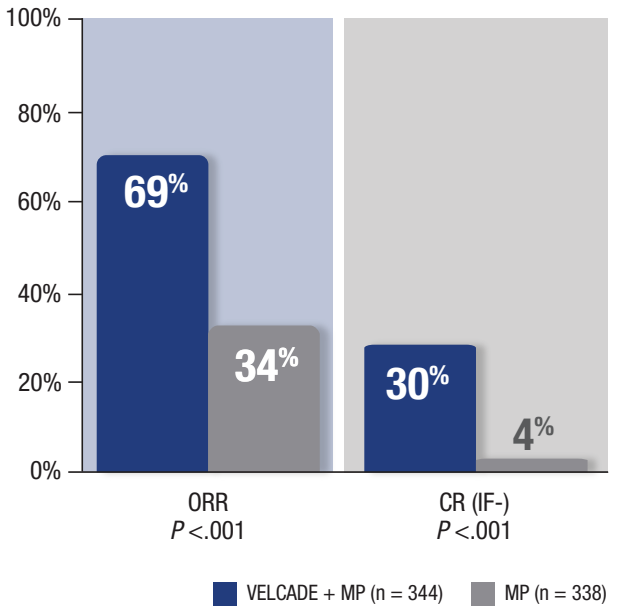
The recommended dose of bortezomib is 1.3 mg/m^2 administered in combination with melphalan (9 mg/m^2) plus prednisone (60 mg/m^2).[13]

- Twice weekly (cycles 1-4): Bortezomib should be administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of a 6-week cycle, and MP should be administered on days 1 through 4 every cycle for a total of 24 weeks
- Weekly (cycles 5-9): Bortezomib should be administered on days 1, 8, 22, and 29 of a 6-week cycle, and MP on days 1 through 4 every cycle for a total of 30 weeks

Bortezomib can be administered subcutaneously or as a 3- to 5-second bolus IV injection. At least 72 hours should elapse between consecutive doses of bortezomib.[13] There are treatment calendars available to help patients stay on track with their bortezomib therapy.

In the VISTA trial, rates of discontinuation as a result of treatment-related adverse reactions

Figure 2 Response Rates[a]: Initial VISTA Analysis (16.3-Month Median Follow-Up)

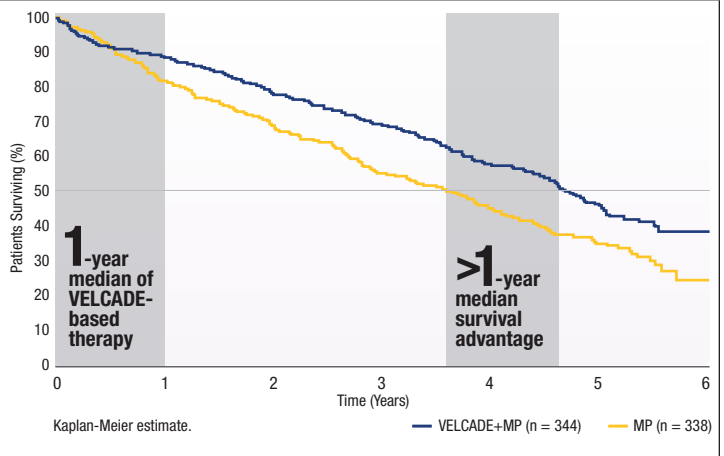


CR indicates complete response; IF --, immunofixation negative; MP, melphalan/prednisone; ORR, overall response rate; VISTA, VELCADE as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone.

[a]Response rates were based on criteria established by the European Group for Blood and Marrow Transplantation.

Sources: VELCADE [prescribing information]. Millennium Pharmaceuticals, Inc; 2014. Data on file 42, Millennium Pharmaceuticals, Inc.

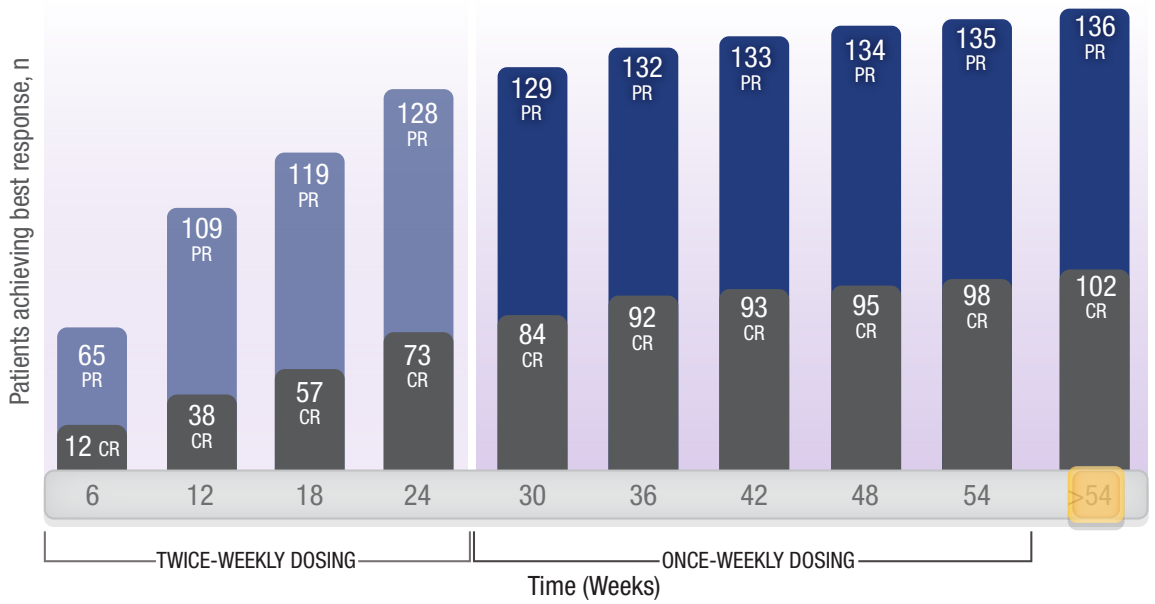
Figure 3 Updated VISTA Analysis: 60.1-Month Median Follow-Up



MP indicates melphalan/prednisone; VISTA, VELCADE as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone.

Source: VELCADE [prescribing information]. Millennium Pharmaceuticals, Inc; 2014.

Figure 4 Achievement of Best Response[a-c] to VELCADE + MP Over Time



CR indicates complete response; MP, melphalan/prednisone; PR, partial response; VISTA, VELCADE as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone.

[a]Responses were based on criteria established by the European Group for Blood and Marrow Transplantation.[19]

[b]Intent-to-treat population for the VELCADE + MP arm in the VISTA trial was 344; number of patients responding was 238.[19]

[c]Response evaluated every 3 weeks during the 54-week treatment phase and then every 8 weeks until disease progression.[14]

Table 2 Incidence of New-Onset ARs with VELCADE over the Course of Treatment

Most commonly reported (>20%) ARs	MP (n = 337) TOTAL	VELCADE+MP (n = 340) TOTAL	VELCADE+MP weeks 1-24* (n = 340) Twice-weekly dosing	VELCADE+MP weeks 25-54* (n = 249) Once-weekly dosing
Thrombocytopenia	42% (140)	48% (164)	44% (148)	31% (78)
Neutropenia	42% (143)	47% (160)	43% (145)	26% (64)
Anemia	46% (156)	32% (109)	26% (87)	18% (45)
Leukopenia	28% (93)	32% (108)	29% (97)	19% (47)
Lymphopenia	15% (51)	23% (78)	21% (70)	13% (33)
Nausea	21% (70)	39% (134)	39% (131)	9% (22)
Diarrhea	6% (20)	35% (119)	34% (114)	8% (19)
Vomiting	12% (41)	26% (87)	24% (81)	6% (15)
Constipation	4% (14)	23% (77)	21% (73)	5% (13)
Peripheral neuropathy	1% (4)	46% (156)	41% (141)	11% (27)
Neuralgia	<1% (1)	34% (117)	31% (107)	6% (15)
Fatigue	14% (48)	25% (85)	24% (81)	6% (16)

*Based on a total plan of nine 6-week cycles.

ARs indicates adverse reactions; MP, melphalan/prednisone.

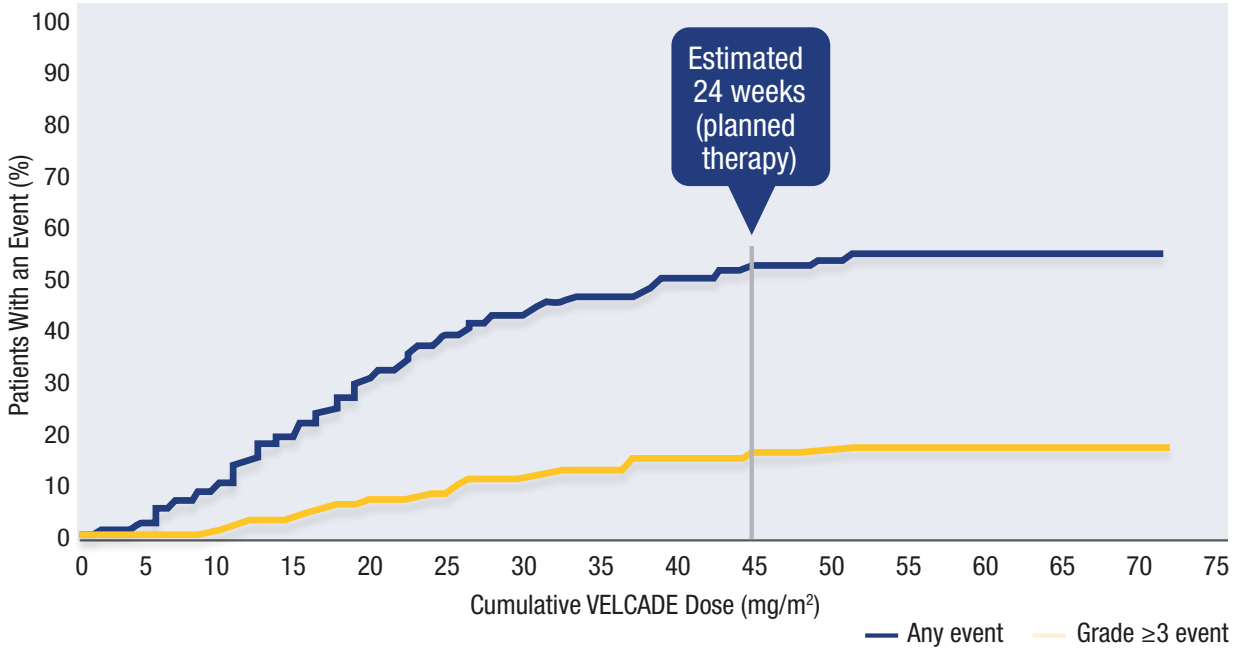
Sources: VELCADE [prescribing information]. Millennium Pharmaceuticals, Inc; 2014. Data on file, Millennium Pharmaceuticals, Inc.

(ARs) were 11% for bortezomib combination and 10% for MP alone.[14] Prior to initiating any cycle of therapy with bortezomib in combination with MP, platelet count should be at least 70 × 10^9/L and absolute neutrophil count should be at least 1.0 × 10^9/L.[13] Dosing adjustments of bortezomib are not necessary for patients with renal insufficiency. In patients undergoing dialysis, bortezomib should be administered after the dialysis procedure.[13] Dose modifications may be necessary for hematologic toxicities, nonhematologic toxicities, peripheral neuropathy (PN), and moderate to severe hepatic impairment.[13]

Safety Data

Patients participating in the VISTA trial experienced hematologic and nonhematologic ARs. With bortezomib + MP, the most commonly reported (≥20%) treatment-related ARs included thrombocytopenia (48% vs 42% with MP), neutropenia (47% vs 42% with MP), anemia (32% vs 46% with MP), leukopenia (32% vs 28% with MP), lymphopenia (23% vs 15% with MP), nausea (39% vs 21% with MP), diarrhea (35% vs 6% with MP), vomiting (26% vs 12% with MP), constipation (23% vs 4% with MP), peripheral neuropathy

Figure 5 Cumulative VELCADE Dose to First Onset of PN in the VISTA Trial



PN indicates peripheral neuropathy, VISTA, VELCADE as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone.

(PN) (46% vs 1% with MP), neuralgia (34% vs <1% with MP), and fatigue (25% vs 14% with MP).[13]

With regard to hematologic toxicities, complete blood count should be monitored regularly throughout treatment. Prior to initiating any cycle of therapy with bortezomib + MP, platelet count should be at least 70 × 10^9/L and the absolute neutrophil count should be at least 1.0 × 10^9/L.[13]

Likewise, patients should be monitored for nonhematologic toxicities, including hepatic impairment. Cases of acute liver failure have been reported, in addition to other hepatic events such as elevated liver enzymes, hyperbilirubinemia, and hepatitis. Prior to initiating any cycle of therapy with bortezomib + MP, nonhematologic toxicities (except PN) should have resolved to grade 1 or baseline.[13]

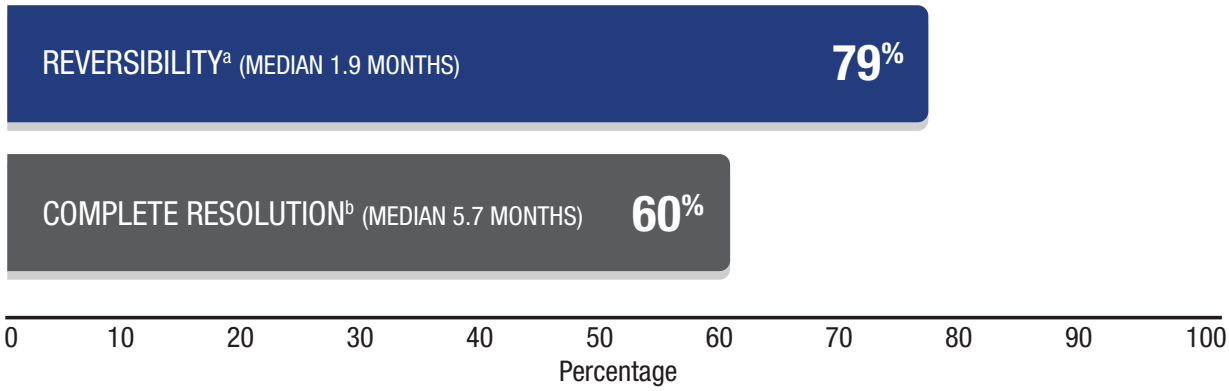
Refer to Section 2 of the full bortezomib Prescribing Information for specific dose modification guidelines for hematologic and nonhematologic toxicities.

As shown in **Table 2**, in the VISTA trial, the incidence of new-onset ARs was lower after week 24 of bortezomib-based therapy. Results were achieved with bortezomib + MP twice weekly followed by once-weekly administration. The incidence of new-onset ARs was defined as the number of patients having a new onset of an event within weeks 1 to 24 and weeks 25 to 54.[15] Rates of discontinuation because of ARs were 11% with bortezomib + MP and 10% with MP alone.[15] Among patients in the VISTA trial treated with bortezomib + MP, 36% had 1 dose reduction during the study and 18% required 2 dose reductions.[15]

A total of 25% of patients in the treatment group receiving bortezomib + MP experienced serious ARs versus 18% of patients in the treatment group receiving MP. The most commonly reported serious ARs with bortezomib + MP versus MP alone included pneumonia (5% vs 4%), diarrhea (4% vs 0%), thrombocytopenia (3% vs 1%), vomiting (3% vs <1%), nausea (2% vs <1%), anemia (2% vs 2%), herpes zoster (2% vs <1%), and dehydration (2% vs <1%).[15]

In patients treated with bortezomib + MP, 47% experienced treatment-emergent PN, including 13% with grade ≥3. Eleven percent of patients discontinued treatment with bortezomib because of PN and continued MP; 3% of patients discontinued treatment with bortezomib + MP because of PN.[20] However, onset of PN plateaued after approximately 24 weeks of planned therapy (as measured by cumulative bortezomib dose to first onset of PN)—**Figure 5**.[20]

Figure 6 Reversibility of PN with Appropriate Dose Modification in the VISTA Trial



PN indicates peripheral neuropathy; VISTA indicates VELCADE as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone.

[a]Improvement by at least 1 National Cancer Institute Common Terminology Criteria for Adverse Events grade.

[b]Return to PN baseline in those patients with preexisting grade 1 PN and a complete absence of PN in all other patients.

Source: Dimopoulos MA, et al. *Eur J Haematol.* 2011;86:23-31.

Table 3 Guidelines for Dose Modification for PN

Severity of PN Signs/ Symptoms[a]	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or grade 2 (moderate symptoms; limiting instrumental ADL[b])	Reduce VELCADE to 1 mg/m^2
Grade 2 with pain or grade 3 (severe symptoms; limiting self-care ADL[c])	Withhold VELCADE until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of 0.7 mg/m^2 once per week
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue VELCADE

ADL indicates activities of daily living; PN, peripheral neuropathy.

[a]Grading based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

[b]Instrumental ADL include preparing meals, shopping for groceries or clothes, using the telephone, and managing money.

[c]Self-care ADL include bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

Source: VELCADE [prescribing information]. Millennium Pharmaceuticals, Inc; 2014.

Oncology nurses and other clinicians should be aware that PN may be manageable and reversible with appropriate dose modification, including discontinuation. In a subanalysis of the phase 3 VISTA trial data, 79% of patients experienced improvement by at least 1 grade, using the National Cancer Institute Common Terminology Criteria for Adverse Events, within a median of 1.9 months. Furthermore, 60% of patients experienced complete resolution within a median of 5.7 months (**Figure 6**).[20]

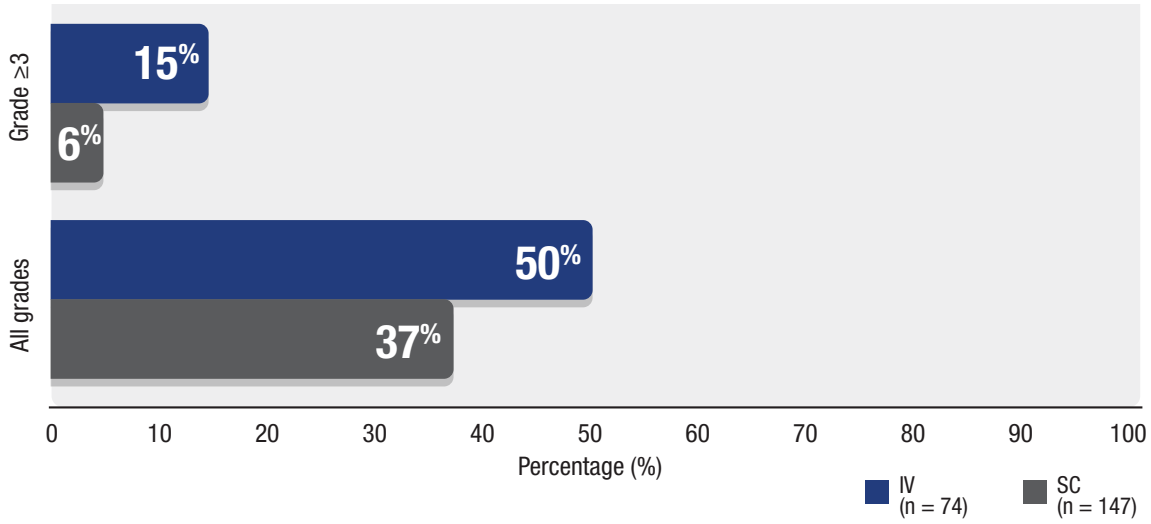
Complete resolution was defined as a return to PN baseline in those patients with preexisting grade 1 PN and a complete absence of PN in all other patients.[20] As shown in **Table 3**, guidelines for dose modification for PN vary by the severity of PN signs/symptoms.

No drugs are specifically approved for the treatment of PN seen with MM, but recommendations across the grades may include healthy habits to maintain optimal weight and nutritional status, correcting any vitamin deficiencies, physical therapy, and pain management.[21,22]

Efficacy and Safety of Subcutaneous Bortezomib

In 2012, bortezomib received US Food and Drug Administration approval for subcutaneous (SC) administration.[13] A randomized, phase 3, noninferiority study was conducted to evaluate SC versus IV administration of bortezomib in patients with relapsed MM. A total of 222 patients were randomly assigned to receive up to eight 21-day cycles of bortezomib 1.3 mg/m^2 via SC (n=148) or IV (n=74) routes of administration. Patients received a median of 8 cycles (range

Figure 7 Incidence of PN in Relapsed MM: SC and IV



SC vs IV Trial: a noninferiority, phase 3, randomized (2:1), open-label trial that compared the efficacy and safety of VELCADE administered subcutaneously (n = 148) with VELCADE administered intravenously (n = 74) in patients with relapsed MM. Patients who did not obtain a CR after 4 cycles were allowed oral dexamethasone. The primary end point was ORR at 4 cycles. Secondary end points included response rate at 8 cycles, median TTP and PFS (months), 1-year overall survival, and safety.

CR indicates complete response; IV, intravenous; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; PN, peripheral neuropathy; SC, subcutaneous; TTP, time to progression.

Source: VELCADE [prescribing information]. Millennium Pharmaceuticals, Inc; 2014.

1 - 10) in both groups.[23]

In the study, overall response rate at 12 weeks was 43% with SC bortezomib versus 42% with IV bortezomib. The study met its primary noninferiority objective that single-agent SC bortezomib retained at least 60% of the overall response rate after 4 cycles relative to single-agent IV bortezomib.[13]

With bortezomib, PN incidence varies by route of administration (**Figure 7**). In relapsed MM, a total of 37% of patients receiving SC bortezomib experienced PN (6% grade ≥3), compared with 50% of patients receiving IV bortezomib (15% grade ≥3). Starting patients subcutaneously may be considered for patients with preexisting PN or patients at high risk for PN. The dosing schedule of bortezomib is the same for IV and SC routes of administration; however, the reconstitution volumes and final concentrations for administration differ.[13]

Subcutaneous Administration of Bortezomib

SC bortezomib should be administered in a manner consistent with best practices and good nursing principles, which include the following:[24]

- For all SC injections, maintain aseptic procedures
- Nurses should wash their hands before giving the injection and following the administration of bortezomib
- Gloves should be worn; however, they may not protect from needlestick injuries
- Sharps should be carefully and immediately disposed of at the point of administration.

The abdomen or thighs are the recommended sites for SC administration of bortezomib (**Figure 8**). Injection sites should be rotated. New injections should be administered at least 1 inch from an old site

Figure 8 Recommended Subcutaneous VELCADE Administration Sites

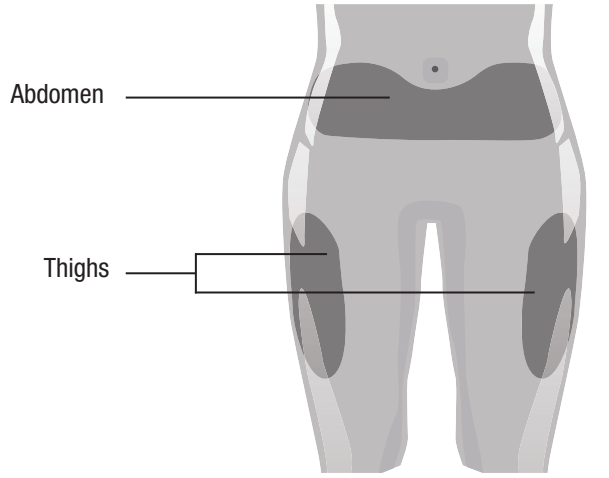
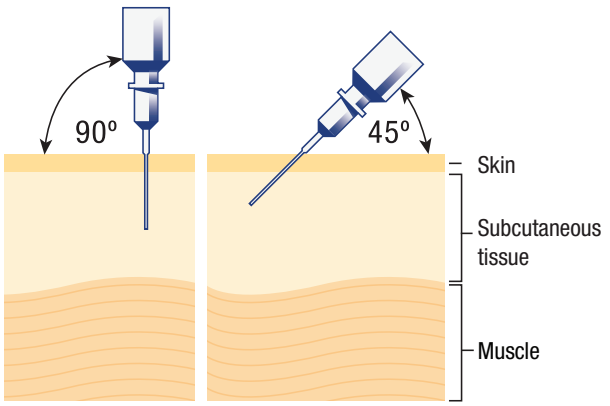


Figure 9 Administration Technique for Subcutaneous VELCADE



and never into areas where the skin is tender, bruised, erythematous, or indurated.[13]

Before administration, ensure that the needle used during preparation has been changed to a new, clean, sharp, dry needle.[25] This practice may reduce the chance of topical contact of medication with the skin, which may cause injection-site reactions. In addition, make sure there is adequate adipose tissue at the site of injection.[25,26]

Ensure medication is deposited in the SC tissue, as shown in **Figure 9**.[26] Generally, when using a 25-gauge needle that is 5/8 inch in length, insert the needle at a 45-degree angle.[26,27] When using a 26- to 30-gauge needle that is 1/2 inch in length, insert the needle at a 90-degree angle.[26,27] Inject slowly and steadily, over several seconds,[25] to allow absorption into SC tissue; pause briefly before withdrawing the needle to avoid backtracking of the fluid and absorption into the skin.[24]

As with IV injections, it is important to educate patients and their families about the ARs that patients may experience with SC injections.[24] If local injection-site reactions occur following administration of bortezomib subcutaneously, a less concentrated bortezomib solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, consider the IV route of administration.[13]

For more information, please see Administration Precautions, section 2.7, in the full Prescribing Information.

Patient Management Considerations with Bortezomib

The Oncology Nurse Roundtable was convened to bring together oncology nurses, advanced practitioners, and oncology nurse navigators to discuss the use of bortezomib in the treatment of MM, describe the challenges of keeping patients on bortezomib therapy, and allow participants to share best practices in managing ARs and ensuring that appropriate length of therapy is reached. This highly interactive program included several case studies to stimulate dialogue and exchange of ideas among the participants. The following section highlights the key discussion points and insights from the meeting.

Addressing Patient Needs

Nurses, advanced practitioners, and nurse navigators play a critical role in the care of patients with MM. Similar to many other cancers, the number of treatment options for MM has grown in recent years.[4]

Roundtable participants identified a number of considerations to help guide interaction with new patients and foster good communication throughout the treatment process, including[28]:

- Establishing rapport as quickly as possible
- Being a good listener and allowing patients to ask as many questions as possible
- If appropriate, bringing family members and/or caregivers into treatment discussions early in the process
- Recognizing that each patient is different; therefore, education should be individualized as much as possible
- Understanding that patients are often overwhelmed by their diagnosis; therefore, ongoing education and reinforcement of key educational messages is crucial to ensuring that patients understand their treatment plan.

"Our practice has an education program where new patients meet with the nurse navigator. We try to create a supportive environment, where patients feel comfortable asking as many questions as they need to, and we spend as much time with them as we can."

- Deborah Christensen, RN, AHNB-BC

Oncology nurses and other clinicians should be aware that their patients may face nonclinical barriers to treatment such as cost of treatment and access to therapy. In particular, travel restrictions were singled out by a number of participants as a limiting factor for patients requiring frequent appointments. Travel issues may sometimes affect dosing schedules for anticancer agents. To address this issue, some practices have made an effort to "bundle" chemotherapy treatment and ancillary care appointments. It was also noted that some institutions offer free or subsidized transportation services for patients in need.

In addition to recognizing and addressing nonclinical barriers to treatment, it is critical to begin educating patients about MM and their treatment regimen as soon as possible, preferably before therapy is initiated. According to several participants, education is best accomplished using a holistic, coordinated approach,

involving both clinical and nonclinical aspects of treatment. These efforts may include nurses, advanced practitioners, physicians, pharmacists, dietitians, nurse navigators, and financial counselors.

Setting Expectations Regarding Treatment

As with other anticancer agents, it is important for oncology nurses and other clinicians to appropriately manage patients receiving bortezomib-containing regimens. Management considerations may include (but not be limited to) dosing, administration, management of toxicities, and adherence to treatment.

As part of the treatment education process, participants voiced the need to set patient expectations about length of therapy. In the VISTA trial, responses deepened over time with longer bortezomib combination (bortezomib + MP) therapy, and after 16.3 months, 69% of evaluable patients in the intent-to-treat group had achieved either a complete or a partial response.[19] This information resonated with the roundtable panel, and many participants indicated that they strongly encourage their patients with previously untreated MM to remain on bortezomib therapy as long as possible (up to 54 weeks as seen in the VISTA trial). Nevertheless, practices may encounter challenges if patients want a "break" from bortezomib treatment. In this case, it is important to remind patients that uninterrupted treatment (in accordance with labeled dosing) provides patients with the best opportunity to achieve the therapeutic benefit seen in the clinical trial.

"We tell patients that they're going to be on (Bortezomib) therapy for quite a while. Our physicians will usually administer 8 cycles and then reevaluate. For patients responding to treatment, we'll continue therapy with the goal of one year of therapy."

- Paula Falzone, RN, BSN

Participants indicated that frequent patient follow-up, practice accessibility during nonbusiness hours, and ongoing patient education were all helpful in supporting treatment adherence. When appointments are missed, participating practices typically call the patient the same day to check on them and try to schedule another appointment.

"Patient education is an ongoing process. It's very important to build that rapport with the patient and then keep them engaged throughout the treatment process."

- Eileen Bannon, RN, MSN, OCN, CBCN

Management of Treatment-Related ARs with Bortezomib

Some patients on bortezomib-containing regimens may experience treatment-related ARs. Prior to treatment initiation, participants indicated that they try to educate their patients about the possibility of ARs. According to the participants, informing patients in advance often serves to reduce anxiety, especially in the early stages of treatment.[28]

When treatment-related ARs occur, they should be identified, assessed, and reported as soon as possible. Patients may experience fatigue, gastrointestinal issues, and other symptoms, but oncology nurses, advanced practitioners, and nurse navigators are often the first to identify these symptoms as ARs during their interactions with patients. Other ARs, such as myelosuppression, may be identified through laboratory work.

PN is a common AR of bortezomib.[13] Starting bortezomib subcutaneously may be considered for patients with preexisting PN or at high risk for PN.

When monitoring for PN, several participants noted that it is important to recognize that symptoms may vary.

"Sometimes nurses focus on the tingling and numbness, but there may be other symptoms such as pain, weakness, or difficulty walking.[29] Those are suggestive of neuropathy as well, and we make sure that we ask questions about those symptoms.

- Seth Eisenberg, RN, OCN

PN may be identified through the use of validated assessment tools, such as the 11-item Neurotoxicity Assessment Tool adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events.[29] However, many participants indicated that they use less formal techniques to detect loss of sensation, such as asking the patient to pick up a paper clip or button a shirt in their presence. Sometimes patients may not be aware that they are experiencing PN (or other ARs). Therefore, it may be helpful for the nurse to investigate whether patients may be altering their normal habits because of treatment-related symptoms. In some cases, family members and caregivers may be instrumental in helping nurses and other clinicians to identify PN and other treatment-related ARs.

In a clinical trial with bortezomib-based therapy, the incidence of new-onset ARs was highest in the first 24 weeks of treatment.[15] Participants indicated that patients are typically monitored very closely early in the course of therapy, especially for the first few cycles of treatment. Patients experiencing new or worsening PN during therapy with bortezomib may require a decrease in the dose, a less dose-intense schedule, or discontinuation. For these patients, there are specific guidelines that depend on the severity of signs and symptoms (refer to Table 3, page 10). In general, participants indicated that they were aware of these guide-

lines and used them when appropriate.

Bortezomib can be administered through SC and IV routes of administration. Because there is a difference in the incidence of PN by route of administration in patients with MM, practices may consider starting bortezomib subcutaneously for patients with preexisting PN or patients at high risk for PN.

When treatment-related ARs develop, they are assessed by the clinical team and, in consultation with the patient and/or family/caregiver, a path of action is agreed upon. Depending on severity, some ARs may necessitate dose modification or discontinuation. Please see full prescribing information at **http://www.velcade.com/Files/PDFs/VELCADE_PRESCRIBING_INFORMATION.pdf** for dosing modification information with hematologic toxicities, nonhematologic toxicities, peripheral neuropathy, and moderate to severe hepatic impairment.

Supportive and Prophylactic Care

In randomized studies in previously untreated and relapsed MM, herpes zoster reactivation was more common in subjects treated with bortezomib (range, 6%-11%) than in the control groups (3%-4%). Therefore, antiviral prophylaxis should be considered in patients being treated with bortezomib.[13]

Conclusion

In summary, the roundtable panel was comprised of a knowledgeable, experienced group of oncology nurses, advanced practitioners, and oncology nurse navigators who were well versed in managing anticancer therapies in general and bortezomib in particular. Participants emphasized a number of key points for helping patients through treatment:

- Begin speaking with patients about their anticancer treatment regimen as soon as possible. Build rapport to foster good communication throughout the treatment period
- Encourage patients to include family members and/or caregivers in the process early and maintain open dialogue throughout the treatment process
- Identify and seek to address any nonclinical impediments to treatment such as cost, travel issues, or cultural barriers. Be aware that these issues may impact adherence to therapy if they are not addressed
- Set treatment expectations early. Let patients know that treatment of MM is typically long term. Patients receiving bortezomib for previously untreated MM should expect treatment for up to 54 weeks
- Be realistic about potential ARs such as PN and fatigue. Reinforce the importance of reporting ARs when they occur.

Roundtable participants agreed that following these general guidelines could contribute to a positive treatment experience for patients with MM, including those receiving bortezomib.

Support services, including financial, treatment, and personal assistance and resources, are available to patients with MM who are receiving bortezomib.

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Indications and Important Safety Information for VELCADE® (bortezomib)

INDICATIONS

VELCADE (bortezomib) is indicated for the treatment of patients with multiple myeloma. VELCADE is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

WARNINGS AND PRECAUTIONS

VELCADE (bortezomib) is for subcutaneous or IV administration only. Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

- **Peripheral neuropathy,** including severe cases, may occur. Patients should be monitored for symptoms and managed with dose modification or discontinuation. Patients with preexisting symptoms may experience worsening peripheral neuropathy (including ≥grade 3). Starting with VELCADE subcutaneously may be considered for patients who either have preexisting or are at high risk for peripheral neuropathy.
- **Hypotension:** Caution should be used when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated.
- **Cardiac toxicity,** including acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction, has occurred. Isolated cases of QT-interval prolongation have been reported. Patients with risk factors for, or existing, heart disease should be closely monitored.
- **Pulmonary toxicity:** Acute respiratory distress syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology have occurred (sometimes fatal). Pulmonary hypertension, in the absence of left heart failure or significant pulmonary disease, has been reported. In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt and comprehensive diagnostic evaluation is conducted.
- **Posterior reversible encephalopathy syndrome** has occurred. Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.
- **Gastrointestinal toxicity,** including nausea, diarrhea, constipation, and vomiting, has occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement. Interrupt VELCADE (bortezomib) for severe symptoms.
- **Thrombocytopenia/Neutropenia:** Manage with dose and/or schedule modifications. Complete blood counts should be monitored frequently during treatment. There have been reports of gastrointestinal and intracerebral hemorrhage. Transfusions may be considered.
- **Tumor lysis syndrome:** Closely monitor patients with high tumor burden and take appropriate precautions.
- **Hepatic toxicity:** Monitor hepatic enzymes during treatment. Upon occurrence, interrupt therapy with VELCADE to assess reversibility.
- **Embryo-fetal risk:** Women should avoid breast-feeding or becoming pregnant while on VELCADE.
- **Patients with diabetes** may require close monitoring and adjustment of the antidiabetic medications.

DRUG INTERACTIONS

Closely monitor patients receiving VELCADE (bortezomib) in combination with strong CYP3A4 inhibitors. Avoid concomitant use of strong CYP3A4 inducers.

ADVERSE REACTIONS

- **Previously untreated multiple myeloma (MM):** In the phase 3 study of VELCADE administered intravenously with melphalan and prednisone (MP) vs MP alone, the most commonly reported adverse reactions (ARs) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), and leukopenia (32% vs 28%).
- **Relapsed MM and mantle cell lymphoma:** In the integrated analysis of 1163 patients in phase 2 and 3 studies of VELCADE (bortezomib) administered intravenously, the most commonly reported ARs were nausea (49%), diarrhea NOS (46%), fatigue (41%), peripheral neuropathy NEC (38%), and thrombocytopenia (32%). A total of 26% of patients experienced serious ARs. The most commonly reported serious ARs included diarrhea, vomiting, and pyrexia (each 3%); nausea, dehydration, and thrombocytopenia (each 2%); and pneumonia, dyspnea, peripheral neuropathies NEC, and herpes zoster (each 1%).
- **Relapsed MM subcutaneous vs IV:** In the phase 3 study of VELCADE administered subcutaneously vs intravenously in relapsed MM, safety data were similar between the two treatment groups. The most commonly reported ARs in the subcutaneous vs IV treatment groups were peripheral neuropathy (37% vs 50%) and thrombocytopenia (30% vs 34%). The incidence of serious ARs was similar in the subcutaneous treatment group (20%) and the IV treatment group (19%). The most commonly reported serious ARs were pneumonia and pyrexia (each 2%) in the subcutaneous treatment group and pneumonia, diarrhea, and peripheral sensory neuropathy (each 3%) in the IV treatment group.

Please click here for full Prescribing Information, also available at www.VELCADEHCP.com