Cancer Chemotherapy Update

Bortezomib, Melphalan, and Prednisone (VMP) Regimen for Multiple Myeloma

Samantha Bryant, PharmD*; Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP; and
J. Aubrey Waddell, PharmD, FAPhA, BCOP

The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncology Pharmacy Services, Inc., 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net.

Regimen name: VMP

Origin of name: VMP is an acronym for the 3 drugs (bortezomib [*Velcade*], *melphalan*, and *prednisone*) in the regimen.

COMMENTS

Melphalan plus prednisone was the standard therapy for newly diagnosed patients with multiple myeloma who are ineligible for high-dose therapy with autologous hematopoietic stem-cell transplantation (HDT-HSCT). Since the approval of bortezomib, VMP therapy is one of the preferred regimens for patients with untreated multiple myeloma who are ineligible for HDT-HSCT (Table 1).¹

INDICATIONS

The VMP regimen has been studied as initial therapy for multiple myeloma, particularly in elderly patients who are not eligible for HDT-HSCT.²⁻¹⁴ Current guidelines recommend it as a preferred regimen for previously untreated patients who are not eligible for HDT-HSCT.¹

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing and dispensing bortezomib, melphalan, and prednisone.

A. Bortezomib

1. Use bortezomib powder for injection.
2. Reconstitute with 0.9% sodium chloride (NS).
3. The manufacturer recommends using different concentrations for intravenous (IV) and subcutaneous (SQ) injection¹⁵:
 - a. IV: Final concentration – 1 mg/mL.
 - b. SQ: 2.5 mg/mL
4. Some institutions prepare all doses at a concentration of 2.5 mg/mL for either IV or SQ injection.

B. Melphalan

1. Use 2 mg tablets.
2. The tablets should be stored in the refrigerator (2°C to 8°C [35.6°F to 46.4°F]).
3. Protect from light.

C. Prednisone

1. Use:
 - a. 1, 2.5, 5, 10, 20 or 50 mg tablets, or
 - b. Oral solution 1 mg/mL or 5 mg/mL.

*Dr. Bryant is a Pharmacy Practice Resident (PGY1) at Peninsula Regional Medical Center, Salisbury, Maryland. At the time this manuscript was written, Dr. Bryant was a student at the Philadelphia College of Pharmacy, University of the Sciences.

Table 1. VMP regimen²⁻¹¹

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Bortezomib	1.3 mg/m ²	IV or SQ	1, 4, 8, 11, 22, 25, 29, and 32 (cycles 1-4) 1, 8, 22, 29 (cycles 5-9)	10.4 mg/m ² (cycles 1-4) 5.2 mg/m ² (cycles 5-9)
Melphalan	9 mg/m ²	PO	1, 2, 3, 4	36 mg/m ²
Prednisone	60 mg/m ²	PO	1, 2, 3, 4	240 mg/m ²

Cycle repeats: every 6 weeks

Variations

1. Bortezomib 1.3 mg/m² IV days 1,4,8, and 11, melphalan 9 mg/m² and prednisone 60 mg/m² PO on days 1 through 4 every 21 days.¹²
2. Bortezomib 1.3 mg/m² IV twice a week for 6 weeks (cycle 1), then every week for 4 weeks, melphalan 9 mg/m² and prednisone 60 mg/m² PO days 1 through 4 every 4 weeks.¹³
3. Bortezomib 1.3 mg/m² SQ days 1,8, 15, and 22, melphalan 2 mg and prednisone 50 mg PO every other day every 28 days.¹⁴

Note: IV = intravenous; PO = oral; SQ = subcutaneous.

2. Store at room temperature (15°C to 30°C [59°F to 86°F]).

DRUG ADMINISTRATION

A. Bortezomib

1. Bortezomib is given by rapid (3-5 seconds) IV or SQ injection.
2. Most of the studies reviewed did not specify the route of bortezomib administration, although some did mention following the regimen used in the VISA trial, which gave bortezomib IV.^{2,3,5,7,9-12}
3. Several studies reviewed specified that the bortezomib was given IV.^{4,6,8,13}
4. In one study, the bortezomib was given SQ.¹⁴
5. Subcutaneous administration of bortezomib has been reported to significantly decrease the incidence of neurotoxicity.¹⁵⁻¹⁷

B. Melphalan

1. Melphalan is given orally (PO), usually as a single daily dose.
2. Melphalan should be taken on an empty stomach, 1 hour prior to or 2 hours after meals.

C. Prednisone

1. Prednisone is given PO, usually as a single daily dose.
2. To avoid gastric irritation, the medication should be taken with food or after a meal.

SUPPORTIVE CARE

- ### A. Acute and Delayed Emesis Prophylaxis: The VMP regimen is predicted to cause acute emesis in 10%

to 30% of patients.¹⁸⁻²¹ The studies reviewed reported nausea in 48% to 55% of patients²⁻⁴ and vomiting in 30% to 33% of patients,²⁻⁴ respectively. Severe nausea or vomiting was reported in 2% to 4% of patients.^{2-4,8} For most patients, prophylactic antiemetic therapy with a single agent is recommended.¹⁹⁻²¹ One of the following regimens is recommended:

1. Prochlorperazine 10 mg PO, ±diphenhydramine 25 to 50 mg PO if needed, given 30 minutes before VMP.
2. Metoclopramide 0.5 to 2 mg/kg PO, ±diphenhydramine 25 to 50 mg PO if needed, given 30 minutes before VMP.
3. Promethazine 25 to 50 mg PO, ±diphenhydramine 25 to 50 mg PO if needed, given 30 minutes before VMP.

Because prednisone is one of the components of the VMP regimen, additional corticosteroids as part of the antiemetic regimen generally are not necessary. In some patients, no additional antiemetic may be necessary.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category added to the previous prophylactic antiemetic regimen.¹⁸⁻²¹ One of the following regimens is recommended:

1. Patients who received a steroid only, add a dopamine antagonist.
2. Patients who received a dopamine antagonist only, add a steroid.

3. Patients who received a steroid and dopamine antagonist, substitute a serotonin antagonist for the dopamine antagonist.

If a steroid and dopamine antagonist combination is not effective, a serotonin antagonist and steroid combination may be required. One of the following regimens is recommended:

1. Ondansetron 8 mg to 16 mg and dexamethasone 12 mg given PO 30 minutes before bortezomib.
2. Granisetron 1 mg to 2 mg and dexamethasone 12 mg given PO 30 minutes before bortezomib.
3. Dolasetron 100 mg and dexamethasone 12 mg given PO 30 minutes before bortezomib.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg given PO 30 minutes before bortezomib on days 1, 8, 22, and 29.

Patients who do not respond to a 2-drug combination may benefit from a steroid, dopamine antagonist, and serotonin antagonist regimen or the addition of a neurokinin (NK₁) antagonist to their previous regimen.

Because prednisone is one of the components of the VMP regimen, additional corticosteroids as part of the antiemetic regimen generally are not necessary. One of the following regimens is suggested:

1. Ondansetron 8 mg to 16 mg given PO 30 minutes before bortezomib.
2. Granisetron 1 mg to 2 mg given PO 30 minutes before bortezomib.
3. Dolasetron 100 mg given PO 30 minutes before bortezomib.
4. Palonosetron 0.25 mg IV 30 minutes before bortezomib on day 1 only.

- B. Breakthrough Nausea and Vomiting¹⁸⁻²¹:** Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is recommended:

1. Metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
2. Prochlorperazine 10 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
3. Prochlorperazine 25 mg rectally every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.
4. Promethazine 25 to 50 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.

Patients who do experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category. There is no evidence that substituting granisetron for ondansetron in subsequent treatment cycles, or increasing the dose, even to very high doses, is effective. This approach is not recommended.¹⁶⁻²⁰

- C. Hematopoietic Growth Factors:** Accepted practice guidelines and pharmacoeconomic analysis suggest that an antineoplastic regimen have a greater than 20% incidence of febrile neutropenia before prophylactic use of colony stimulating factors (CSFs) is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of CSFs should be considered. For regimens with an incidence of febrile neutropenia less than 10%, routine prophylactic use of CSFs is not recommended.^{22,23}

Febrile neutropenia was not reported in the trials reviewed. Severe (grade 3 or 4) neutropenia was reported in 10% to 77% of patients.²⁻⁸ Prophylactic use of CSFs is not recommended.^{22,23} CSFs may be appropriate in some patients and should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of VMP.

MAJOR TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (<http://ctep.info.nih.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities, but make, or consider making, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

- A. Cardiovascular:** Deep venous thrombosis (DVT) 2%,⁹ (grade 3) 1%,⁴ (grade 3 or 4) 1%⁶; edema (grade 1 or 2) 19%⁸; edema, peripheral 20%,⁴ (grade 3) 1%⁴; unspecified cardiac events (grade 3 or 4) 5%⁷; unspecified vascular events (grade 3 or 4) 2%.⁷
- B. Central Nervous System:** Dizziness 16%,⁴ (grade 3) 2%^{4,15}; insomnia 20%,⁴ (grade 1 or 2) 23%,⁸ (grade 3) <1%.⁴

- C. Constitutional:** Asthenia 21% to 63%,^{2,4} (grade 3) 6%,⁴ (grade 3 or 4) 5%,^{2,3} (grade 4) <1%⁴; back pain 17%,⁴ (grade 3) 3%,⁴ (grade 4) <1%⁴; fatigue 29%,⁴ (grade 1 or 2) 21%,⁸ (grade 3) 7%,⁴ (grade 3 or 4) 2% to 10%,^{8,9} (grade 4) 1%⁴; malaise (grade 1 or 2) 36%,⁸ (grade 3 or 4) 1%⁸; pyrexia 29%,⁴ (grade 1 or 2) 30%,⁸ (grade 3) 2%,⁴ (grade 4) 1%⁴; unspecified systemic events (grade 3 or 4) 3%⁷; decreased weight (grade 1 or 2) 45%,⁸ (grade 3 or 4) 4%⁸; increased weight (grade 1 or 2) 20%.⁸
- D. Dermatologic:** Rash 19%,⁴ (grade 1 or 2) 53%,⁸ (grade 3) 1%,⁴ (grade 3 or 4) 5%⁸; unspecified dermatologic events (grade 3 or 4) 3%.⁷
- E. Gastrointestinal:** Anorexia 23% to 38%,^{2,4} (grade 1 or 2) 49%,⁸ (grade 3) 3%,⁴ (grade 3 or 4) 2% to 8%,^{2,3,8} (grade 4) <1%⁴; constipation 37% to 52%,^{2,4} (grade 1 or 2) 44%,⁸ (grade 3) 1%,⁴ (grade 3 or 4) 2% to 8%,^{2,3,8}; diarrhea 46% to 55%,^{2,4} (grade 1 or 2) 47%,⁸ (grade 3) 7%,⁴ (grade 3 or 4) 9% to 16%,^{2,3,8,9}; (grade 4) 1%,⁴ nausea 48% to 55%,^{2,4} (grade 1 or 2) 46%,⁸ (grade 3) 4%,⁴ (grade 3 or 4) 2% to 3%,^{2,3,8}; stomatitis (grade 1 or 2) 18%⁸; unspecified gastrointestinal toxicity (grade 3 or 4) 7% to 8%^{6,7}; vomiting 30% to 33%,^{2,4} (grade 1 or 2) 34%,⁸ (grade 3) 4%,⁴ (grade 3 or 4) 2%.^{2,3,8}
- F. Hematologic:** Anemia 43% to 86%,^{2,4} (grade 1 or 2) 30%,⁸ (grade 3) 16%,⁴ (grade 3 or 4) 10% to 40%,^{2,3,5-8} (grade 4) 3%⁴; leukocytosis (grade 1 or 2) 51%,⁸ leukopenia 33%,⁴ (grade 1 or 2) 24%,⁸ (grade 3) 20%,⁴ (grade 3 or 4) 75%,⁸ (grade 4) 3%⁴; lymphopenia (24%),⁴ (grade 1 or 2) 5%,⁸ (grade 3) 14%,⁴ (grade 3 or 4) 94%,⁸ (grade 4) 5%⁴; neutropenia 40% to 85%,^{2,4} (grade 1 or 2) 20%,⁸ (grade 3) 30%,⁴ (grade 3 or 4) 27% to 77%,^{2,3,5-8} (grade 4) 10%⁴; thrombocytopenia 52% to 93%,^{2,4} (grade 1 or 2) 43%,⁸ (grade 3) 20%,⁴ (grade 3 or 4) 20% to 56%,^{2,3,5-8} (grade 4) 17%.⁴
- G. Hepatic:** Abnormal hepatic function (grade 1 or 2) 43%,⁸ abnormal hepatic function (grade 3 or 4) 6%⁸; increased alanine aminotransferase (ALT) (grade 1 or 2) 27%⁸; increased alkaline phosphatase (grade 1 or 2) 37%,⁸ (grade 3 or 4) 3%⁸; increased aspartate aminotransferase (AST) (grade 1 or 2) 21%,⁸ (grade 3 or 4) 1%⁸; increased lactate dehydrogenase (LDH) (grade 1 or 2) 49%,⁸ (grade 3 or 4) 1%⁸.
- H. Infection:** Herpes zoster 13%,⁴ (grade 3) 3%⁴; pneumonia 16%,⁴ (grade 3) 5%,⁴ (grade 3 or 4) 6% to 9%,^{5,9} (grade 4) 2%⁴; unspecified 75%,^{2,3} (grade 3 or 4) 5% to 16%.^{2,3,6,7}
- I. Metabolic:** Increased C-reactive protein (grade 1 or 2) 56%,⁸ (grade 3 or 4) 1%⁸; hyperglycemia (grades 1 or 2) 45%,⁸ (grade 3 or 4) 5%⁸; hyperkalemia (grade 1 or 2) 32%,⁸ (grade 3 or 4) 7%⁸; hypoalbuminemia (grade 1 or 2), 36%⁸; hypocalcemia (grade 1 or 2) 33%,⁸ (grade 3 or 4) 2%⁸; hypochloremia (grade 1 or 2) 21%⁸; hypokalemia 13%,⁴ (grade 1 or 2) 38%,⁸ (grade 3) 6%,⁴ (grade 3 or 4) 10%,⁸ (grade 4) 1%⁴; hyponatremia (grade 1 or 2) 34%,⁸ (grade 3 or 4) 17%⁸; hypophosphatemia (grade 1 or 2) 25%,⁸ (grade 3 or 4) 21%.⁸
- J. Musculoskeletal:** Arthralgia 11%,⁴ (grade 3) 1%.⁴
- K. Neurologic:** Neuralgia 36%,⁴ (grade 3) 8%,⁴ (grade 3 or 4) 7% to 9%,^{5,11} (grade 4) 1%⁴; peripheral neuropathy 55% to 59%,^{2,3,11} (grade 1 or 2) 50%,⁸ (grade 3 or 4) 7% to 23%,^{2,3,6,8,9}; peripheral sensory neuropathy 44%,⁴ (grade 3) 13%,⁴ (grade 3 or 4) 13%,⁵ (grade 4) <1%⁴; sensory neuropathy/neuralgia (grade 3) 8%,¹⁵ (grade 3 or 4) 12%,⁷ neuralgia (grade 4) 1%.¹⁵
- L. Pulmonary:** Cough 21%⁴; dyspnea 15%,⁴ (grade 3) 3%,⁴ (grade 4) 1%.⁴

PRETREATMENT LABORATORY STUDIES NEEDED^{1,6}

- A. Baseline**
1. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT)
 2. Total bilirubin
 3. Serum creatinine
 4. Complete blood count (CBC) with differential
- B. Prior to Each Treatment**
1. CBC with differential
 2. Serum creatinine
 3. Bilirubin
 4. ALT/AST
- C. Recommended Pretreatment Values:** The minimally acceptable pretreatment CBC values required to begin a cycle with full-dose therapy in the trials reviewed were:
1. Absolute neutrophil count (ANC) greater than or equal to 1,000 cells/mcL.^{2,6,8}
 2. Platelet count greater than or equal to:
 - a. 100,000 cells/mcL.²
 - b. 75,000 cells/mcL.⁸
 - c. 50,000 cells/mcL.⁶
 3. Hemoglobin greater than or equal to 8 g/dL.^{2,6}
 4. Serum creatinine less than or equal to 2 mg/dL.^{2,6,8}
 5. Serum calcium (corrected) less than or equal to 14 mg/dL.²

6. Serum bilirubin less than or equal to 1.5 times the upper limit of normal (ULN).⁸
7. ALT/AST less than or equal to 2.5 times the ULN.⁸

In clinical practice, a pretreatment ANC of 1,000 cells/mcL and platelets of 75,000 cells/mcL are usually considered acceptable.

DOSAGE MODIFICATIONS

A. Renal Function

1. Bortezomib: No dosage adjustment is needed.^{15,24}
2. Melphalan:
 - a. Creatinine
 - (1) Greater than 2 mg/dL, reduce dose 50%.^{2,5}
 - (2) Greater than 4 mg/dL, discontinue therapy.²
 - b. Creatinine clearance greater than 50 mL/min, no adjustment needed.²⁵
 - c. Creatinine clearance less than or equal to 50 mL/min and greater than or equal to 10 mL/min, reduce dose 25%.²⁵
 - d. Creatinine clearance less than 10 mL/min, reduce dose 50%.²⁵
 - e. The manufacturer provides no information concerning dose adjustment.²⁶
3. Prednisone:
 - a. No information available.²⁷
 - b. No adjustment required.²⁵

B. Hepatic Function

1. Bortezomib:
 - a. Bilirubin^{15,28}:
 - (1) Greater than 1.5 times the ULN and less than or equal to 3 times the ULN, decrease the dose to 0.7 mg/m².
 - (2) Greater than 3 times the ULN, decrease the dose to 0.7 mg/m².
2. Melphalan: No information is available.²⁶
3. Prednisone: No information is available.²⁷

C. Myelosuppression

1. ANC²:
 - a. Less than 1,000 cells/mcL and greater than or equal to 500 cells/mcL, delay therapy until resolution.
 - b. Less than 500 cells/mcL
 - (1) on day 43 (6 week cycle) or day 36 (5 week cycle), delay therapy until resolution (maximum 2 week delay).
 - (2) during week 3 or 6 of the cycle, reduce melphalan dose 25% in subsequent cycles.

2. Platelets²:

- a. Less than 25,000 cells/mcL and greater than or equal to 50,000 cells/mcL, delay therapy until resolution.
- b. Less than 25,000 cells/mcL
 - (1) on day 43 (6 week cycle) or day 36 (5 week cycle), delay therapy until resolution (maximum 2 week delay).
 - (2) during week 3 or 6 of the cycle, reduce melphalan dose 25% in subsequent cycles.

D. Neuropathy: Peripheral neuropathy or neuropathic pain²:

1. Grade 1, no reduction required.
2. Grade 1 with pain/Grade 2, reduce bortezomib dose to 1 mg/m².
3. Grade 2 with pain/Grade 3
 - a. delay therapy until resolution.
 - b. may reinitiate at 0.7 mg/m² once weekly.
4. Grade 4, discontinue therapy.

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines Multiple Myeloma. V.1.2015. http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed September 8, 2014.
2. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Results of a multicenter phase 1/2 study. *Blood*. 2006;108(7):2165-2172.
3. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Updated time-to-events results and prognostic factors for time to progression. *Haematologica*. 2008;93(4):560-565.
4. San Miguel JF, Schlag R, Khuageva NK et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med*. 2008;359(9):906-917.
5. Dimopoulos MA, Richardson PG, Schlag R, et al. VMP (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: Cohort analysis of the phase III VISTA Study. *J Clin Oncol*. 2009;27(36):6086-6093.
6. Mateos MV, Oriol A, Martinez-Lopez J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomized trial. *Lancet Oncol*. 2010;11(10):934-941.
7. Morabito F, Gentile M, Mazzone C, et al. Safety and efficacy of bortezomib-melphalan-prednisone-thalidomide

followed by bortezomib-thalidomide maintenance (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in untreated multiple myeloma patients with renal impairment. *Blood*. 2011;118(22):5759-5766.

8. Ogawa Y, Suzuki K, Sakai A et al. Phase1/11 study of bortezomib-melphalan-prednisolone for previously untreated Japanese patients with multiple myeloma. *Cancer Sci*. 2013;104(7): 912-919.

9. Niesvizky R, Flinn IW, Rifkin R, et al. Efficacy and safety of three bortezomib-based combinations in elderly, newly diagnosed multiple myeloma patients: Results from all randomized patients in the community-based, phase 3b UPFRONT study [abstract 478]. *Blood*. 2011. <http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/478>. Accessed November 14, 2014.

10. Mateos MV, Richardson PG, Shi H, et al. Higher cumulative bortezomib dose results in better overall survival (OS) in patients with previously untreated multiple myeloma (MM) receiving bortezomib-melphalan-prednisone (VMP) in the phase 3 VISTA study [abstract 1968]. *Proc Am Soc Hematol*. 2013. <http://www.bloodjournal.org/content/122/21/1968>. Accessed September 8, 2014.

11. Kim K, Lee M, Kim HJ, et al. Observational study of VMP (bortezomib, melphalan, prednisolone) regimen for newly diagnosed Korean myeloma patients who are not eligible for transplantation [abstract 5379]. *Proc Am Soc Hematol*. 2013. <http://www.bloodjournal.org/content/122/21/5379>. Accessed September 8, 2014.

12. Niesvizky R, Flinn I, Rifkin RM, et al. Efficacy and safety of three bortezomib-based induction and maintenance regimens in previously untreated, transplant-ineligible multiple myeloma (MM) patients (Pts): Final results from the randomized, phase 3b, US community-based UPFRONT study (NCT00507416) [abstract 1966]. *Proc Am Soc Hematol*. 2013. <http://www.bloodjournal.org/content/122/21/1966>. Accessed September 8, 2014.

13. Mateos MV, Martinez-López J, Hernandez MT, et al. Comparison of sequential vs alternating administration of bortezomib, melphalan and prednisone (VMP) and lenalidomide plus dexamethasone (Rd) in elderly patients with newly diagnosed multiple myeloma (MM) patients: GEM2010MAS65 trial [abstract 403]. *Proc Am Soc Hematol*. 2013. <http://www.bloodjournal.org/content/122/21/403>. Accessed: September 8, 2014.

14. Larocca A, Cavallo F, Magarotto V et al. Reduced dose-intensity subcutaneous bortezomib plus prednisone (VP) or plus cyclophosphamide (VCP) or plus melphalan (VMP) for newly diagnosed multiple myeloma patients older than 75 years of age [abstract 539]. *Proc Am Soc Hematol*. 2013. <http://www.bloodjournal.org/content/122/21/539>. Accessed September 8, 2014.

15. *Velcade* [prescribing information]. New York: Pfizer Labs; 2013. http://www.velcade.com/files/PDFs/VELCADE_PRESCRIBING_INFORMATION.pdf. Accessed September 8, 2014.

16. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomized, phase 3, non-inferiority study. *Lancet Oncol*. 2011;12(6):431-440.

17. Koh Y, Lee SY, Kim I, et al. Bortezomib-associated peripheral neuropathy requiring medical treatment is decreased by administering the medication by subcutaneous injection in Korean multiple myeloma patients. *Cancer Chemother Pharmacol*. 2014;74(3):653-657.

18. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol*. 1997;15(1):103-109.

19. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines – Antiemesis. V.2.2014. http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed September 8, 2014.

20. Basch E, Prestrud AA, Hesketh PJ et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update: 2011. *J Clin Oncol*. 2011;29(31):4189-4198.

21. Multinational Association for Supportive Care in Cancer. MASCC/ESMO Antiemetic Guidelines. 2013. http://www.mascc.org/assets/documents/mascc_guidelines_english_2013.pdf. Accessed September 8, 2014.

22. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24(19):3187-3205.

23. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology – Myeloid Growth Factors. V.2.2014. http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed September 8, 2014.

24. Jagannath S, Barlogie B, Berenson JR, et al. Bortezomib in recurrent and/or refractory multiple myeloma: Initial clinical experience in patients with impaired renal function. *Cancer*. 2005;103(6):1195-1200.

25. Aronoff GR, Bennett WM, Berns JS, et al, eds. *Drug Prescribing in Renal Failure*. 5th ed. Philadelphia: American College of Physicians; 2007.

26. *Alkeran* (melphalan) tablets [US package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/014691s029lbl.pdf. Accessed June 9, 2014.

27. Prednisone tablet [US package insert]. <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=10fe5a3b-84dc-4600-87c2-b80c97ce18cf>. Accessed June 9, 2014.

28. LoRusso PM, Venkatakrishnan K, Ramanathan RK, et al. Pharmacokinetics and safety of bortezomib in patients with advanced malignancies and varying degrees of liver dysfunction: Phase I NCI Organ Dysfunction Working Group Study NCI-6432. *Clin Cancer Res*. 2012;18(10):2954-2963. ■