Cancer Chemotherapy Update

Lenalidomide, Bortezomib, and Dexamethasone (RVD) Regimen for Multiple Myeloma

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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. The information presented in this review is based on published data and clinical expertise and includes information not included in the product labeling. Incorporation of such published data provides a more robust assessment of the drugs and assists pharmacists in evaluation of orders for off-label use of these agents.

Regimen name: RVD, VDR, VRD, or VRd

Origin of name: The regimen name is an acronym for the 3 drugs in the regimen: lenalidomide (**R**evlimid), bortezomib (**V**elcade), and **d**examethasone.

INDICATION(S)

Lenalidomide, bortezomib, and dexamethasone (RVD) regimen (Table 1) has been studied in multiple myeloma as induction therapy regardless of transplantation eligibility, consolidation therapy following transplantation or another dexamethasone-based regimen, and salvage therapy for relapsed or refractory cases.¹⁻⁸ Current guidelines recommend RVD as a preferred salvage regimen for previously treated multiple myeloma and as primary therapy in patients irrespective of transplantation eligibility.⁹

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing bortezomib and dispensing lenalidomide and dexamethasone.

A. Lenalidomide

1. Lenalidomide is available as 2.5, 5, 10, 15, 20, and 25 mg capsules.
2. Lenalidomide is available only through a manufacturer-managed limited distribution program called REVLIMID REMS. (See www.celgeneriskmanagement.com or call 1-888-423-5436 for details.)

B. Bortezomib

1. Use bortezomib powder for injection.
2. The manufacturer recommends reconstituting the drug with 0.9% sodium chloride (NS) to a concentration of 1 mg/mL for intravenous administration or 2.5 mg/mL for subcutaneous administration.¹⁰
3. To avoid potential medication errors resulting from the different concentrations, some institutions prepare all bortezomib injections with a concentration of 2.5 mg/mL, regardless of intended route of administration.

C. Dexamethasone

Dexamethasone is available as:

1. 0.5 mg/5 mL and 1 mg/mL oral solution
2. 4 mg/mL and 10 mg/mL intravenous solution
3. 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tablets.

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Table 1. Lenalidomide, bortezomib, and dexamethasone (RVD) regimen^{1,4,7}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Lenalidomide	15 mg to 25 mg	PO	1 through 14	210 mg to 350 mg
Bortezomib	1.3 mg/m ²	IV	1, 4, 8, 11	5.2 mg/m ²
Dexamethasone	40 mg	PO	1, 8, 15	120 mg

Cycle repeats: Every 21 days

Variations:

- Richardson et al gave lenalidomide 15 mg PO days 1 through 14, bortezomib 1 mg/m² IV days 1, 4, 8, 11, and dexamethasone 20 mg PO (cycles 1 through 4) or 10 mg PO (cycles 5 through 8) on days 1, 2, 4, 5, 8, 9, 11, and 12.²
- Jimenez-Zepeda et al gave lenalidomide 15 mg PO days 1 through 14, bortezomib 1 mg/m² or 1.3 mg/m² IV on days 1, 4, 8, 11, and dexamethasone 20 or 40 mg PO on days 1, 2, 4, 5, 8, 9, 11, and 12.³
- Dimopoulous et al gave lenalidomide 15 mg PO days 2 through 14, bortezomib 1 mg/m² IV days 1, 4, 8, 11, and dexamethasone 40 mg PO days 1 through 4.⁵
- Richardson et al gave lenalidomide 25 mg PO days 1 through 14, bortezomib 1.3 mg/m² IV days 1, 4, 8, 11, and dexamethasone PO 20 mg (cycles 1 through 4) or 10 mg (cycles 5 through 8) on days 1, 2, 4, 5, 8, 9, 11, and 12.⁶
- Durie et al gave lenalidomide 25 mg PO days 1 through 14, bortezomib 1.3 mg/m² IV days 1, 4, 8, 11, and dexamethasone 20 mg PO on days 1, 2, 4, 5, 8, 9, 11, and 12.⁸

Note: IV = intravenous; PO = oral.

DRUG ADMINISTRATION

A. Lenalidomide

- Take lenalidomide by mouth daily around the same time of day without regard to food.
- Swallow lenalidomide capsules with liquid.

B. Bortezomib: Administer intravenously as a rapid IV push over 3 to 5 seconds or as a subcutaneous injection.

C. Dexamethasone

- Dexamethasone is usually given orally as a single daily dose.
- To avoid gastric irritation, dexamethasone should be taken with food or after a meal.

3. Promethazine 25 to 50 mg PO.

4. Serotonin antagonist (choose one):

- Dolasetron 100 mg PO.
- Granisetron 1 to 2 mg (total dose) PO.
- Ondansetron 8 to 16 mg (total dose) PO.
- Palonosetron 0.25 mg IV.

B. Breakthrough Nausea and Vomiting^{11,12}: Patients should receive an antiemetic prescription to treat breakthrough nausea. One of the following regimens is suggested:

- Metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed.
- Prochlorperazine 10 mg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed.
- Prochlorperazine 25 mg rectally every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.
- Promethazine 25 to 50 mg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.

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

SUPPORTIVE CARE

A. Acute Emesis Prophylaxis: The RVD regimen is predicted to cause acute emesis in less than 30% of patients.^{11,12} Some of the studies reviewed did not report nausea or emesis^{1,7,8}; other studies reviewed reported nausea of any grade in 23% to 32% of patients^{2,3,6} and grade 3 or 4 nausea in 2% of patients.^{4,5} Because dexamethasone is one of the components of the RVD regimen, additional corticosteroids as part of the antiemetic regimen generally are not necessary. One of the following regimens is suggested on the days when lenalidomide is given^{11,12}:

- Metoclopramide 10 to 20 mg orally (PO).
- Prochlorperazine 10 mg PO.

less than 10%, routine prophylactic use of CSFs is not recommended.¹³ Febrile neutropenia was reported in 2% to 16% of patients,^{1,4} while (grade 3 or 4) neutropenia was reported in 7% to 35% of patients.^{1-6,8} Prophylactic use of CSFs is not recommended. CSFs should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of RVD.

D. Venous Thromboembolism: Lenalidomide combined with dexamethasone in the treatment of multiple myeloma has been associated with an 8% to 75% incidence of venous thromboembolism (VTE).¹⁴ VTE (grade 3 or 4) was reported in 4% to 8% of patients in the RVD studies reviewed,^{5,6,8} and in all studies patients received anticoagulation prophylaxis with aspirin, warfarin, or low molecular weight heparin.¹⁻⁸ One study suggests that daily low dose aspirin is as effective as low molecular weight heparin or warfarin in the prevention of thromboembolic events secondary to regimens containing dexamethasone and thalidomide, a drug similar to lenalidomide.¹⁵ Current guidelines suggest low dose aspirin in myeloma patients receiving lenalidomide-, thalidomide-, or pomalidomide-based regimens who are at low risk for thromboembolic events and low molecular weight heparin or warfarin international normalized ratio (INR) 2 to 3 for such patients at high risk of thromboembolic events.¹⁶

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://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities; but make, or consider, 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 1%.

- A. Cardiovascular:** Atrial fibrillation (all grades) 5%,² (grade 3) 2% to 3%,^{2,6}; cardiac arrhythmia (grade 3 or 4) 8%,⁵; hypotension (all grades) 5%,² (grade 3) 2%,²; QTc interval (all grades) 6%,⁶ (grade 3) 3%,⁶; thrombosis (grade 3 or 4 with 160 mg dexamethasone per week) 4%,⁵; thrombosis or embolism (grade 3 or 4 with dexamethasone 80 mg per week) 8%,⁸; thrombosis, thrombus, or pulmonary embolism (all grades with 80 mg dexamethasone per week) 6%,⁶ (grade 3 or 4 with 80 mg dexamethasone per week) 5%.⁶
- B. Constitutional:** Constitutional (all grades) 35%,⁷ (grade 1 or 2) 18%,⁸ (grade 3) 13%,⁷; fatigue (all grades) 50% to 64%,^{2,6} (grade 1 or 2) 70%,³ (grade 3) 3% to 5%,^{2,6} (grade 3 or 4) 7% to 22%,^{4,5,8}; fever without neutropenia (all grades) 11%,² (grade 3) 2%.²
- C. Dermatologic:** Dry skin (all grades) 14%,⁶ (grade 3) 2%,⁶; pruritus (grades 1 or 2) 18% to 23%,^{3,6}; rash (all grades) 27%,³ (grade 3 or 4) 3%,^{1,3}; rash or desquamation (all grades) 14% to 36%,^{2,6} (grade 3) 2%.^{2,6}
- D. Endocrine:** Hyperglycemia (all grades) 27% (dexamethasone 80 mg per week),⁶ (grade 1 or 2) 10% (dexamethasone 80 mg to 160 mg per week),³ (grade 3) 2% (dexamethasone 80 mg per week),⁶ (grade 3 or 4) 7% (dexamethasone 80 mg per week).⁸
- E. Gastrointestinal:** Constipation (grade 1 or 2) 30% to 61%,^{2,3,6}; diarrhea (all grades) 41%,² (grade 1 or 2) 33% to 35%,^{3,6} (grade 3) 3%,² (grade 3 or 4) 8%,⁸; gastrointestinal toxicity (all grades) 22%,⁷ (grade 3) 9%,⁷; nausea (grade 1 or 2) 23% to 32%,^{2,3,6} (grade 3 or 4) 2%,^{4,5}; stomach hemorrhage (grade 3) 2%.⁶
- F. Hematologic:** Anemia (all grades) 6% to 87%,^{2,3,6} (grade 3) 2%,^{2,6} (grade 3 or 4) 3% to 20%,^{1,3,4,5,8}; febrile neutropenia (grade 3 or 4) 2% to 16%,^{1,4}; leukopenia (all grades) 17%,² (grade 3) 3% to 9%,^{2,6} (grade 3 or 4) 14%,⁸; lymphopenia (grade 3) 11%,² (grade 3 or 4) 2% to 23%,^{4,6,8}; neutropenia (all grades) 15% to 70%,^{2,3,6} (grade 3 or 4) 7% to 35%,^{1-6,8}; thrombocytopenia (all grade) 18% to 70%,^{2,3,6} (grade 3 or 4) 6% to 22%.^{1-6,8}
- G. Hepatic:** Alanine transaminase (all grades) 12%,⁶ (grade 3) 3%.⁶
- H. Infection:** Infection (all grades) 86%,³ (grade 3) 2% to 4%,^{6,7} (grade 3 or 4) 16% to 26%,^{3,5}; lung infection with grade 0 to 2 neutropenia (all grades) 3%,² (grade 3) 2%,²; pneumonia (grade 3 or 4) 5%.⁴
- I. Metabolic/Nutrition:** Dehydration (grade 3 or 4) 8%,⁸; hyperkalemia (all grades) 9%,⁶ (grade 3) 2%,⁶; hypokalemia (grade 3 or 4) 9%,⁸; hyponatremia (all grades) 9% to 11%,^{2,6} (grade 3) 2% to 8%,^{2,6}; hypophosphatemia (all grades) 9%,⁶ (grade 3) 5%,⁶ (grade 3 or 4) 9%,²; metabolic (all grades) 18%,⁷ (grade 3) 9%.⁷

- J. Musculoskeletal:** Bone pain (grade 3 or 4) 3%¹; extremity pain (all grades) 23% to 30%,^{2,6} (grade 3) 2% to 3%^{2,6}; limb edema (all grades) 34%,^{3,4} (grade 1 or 2) 45% to 50%,^{3,6} (grade 3) 3%²; muscle cramps (grade 1 or 2) 13%³; muscle pain (all grades) 44%,⁶ (grades 1 or 2) 39%,² (grade 3) 2%⁶; muscle weakness (all grades) 60%,³ (grade 3 or 4) 7% to 26%.^{3,8}
- K. Neurologic:** Motor neuropathy (all grades) 14% to 18%,^{2,6} (grade 3) 2% to 3%^{2,6}; neuropathy, any (all grades) 52% to 71%,^{4,5,7} (grade 3) 14% to 35%,^{5,7} (grade 3 or 4) 17% to 24%^{4,8}; pain, neuropathic (all grades) 32%,⁶ (grade 1 or 2) 10% to 17%,^{1,2} (grade 3) 3%⁶; sensory neuropathy (all grades) 80%,⁶ (grade 1 or 2) 53% to 80%,¹⁻³ (grade 3) 2%,⁶ (grade 3 or 4) 23%⁸; pain, any (all grades) 22%,⁷ (grade 3) 13%.⁷
- L. Otic:** Auditory (all grades) 6%,⁶ (grade 3) 2%.⁶
- M. Ophthalmic:** Blurred vision (all grades) 14%,⁶ (grade 3) 2%.⁶
- N. Psychiatric:** Agitation (all grades) 6%,⁶ (grade 3) 2%⁶; anxiety (all grades) 14%,⁶ (grade 1 or 2) 33%,³ (grade 3) 2%⁶; confusion (all grades) 3%,² (grade 4) 2%²; insomnia (all grades) 30%,⁶ (grade 1 or 2) 28% to 30%,^{2,3} (grade 3) 2%⁶; mental status (all grades) 11%,⁶ (grade 3) 2%⁶; psychosis (grade 4) 2%.²
- N. Respiratory:** Apnea (grade 3) 2%²; dyspnea (grade 1 or 2) 18%⁶; other pulmonary or upper respiratory (all grades) 9%,⁶ (grade 3) 3%,⁶ (grade 3 or 4) 5%.²
- O. Renal:** Increased serum creatinine (all grades) 3%,⁶ (grade 3) 2%,⁶ (grade 3 or 4) 8%.⁵
- P. Treatment-Related Death:** Bronchopneumonia 2%.²

PRETREATMENT LABORATORY STUDIES NEEDED

A. Baseline

1. AST/ALT
2. Total bilirubin
3. Serum creatinine
4. CBC with differential

B. Prior to Each Treatment

1. CBC with differential

C. Recommended Pretreatment Values: The minimally acceptable pretreatment CBC values required to begin a cycle with full-dose therapy in the protocols reviewed were:

1. Absolute neutrophil count (ANC): Greater than or equal to 1,000 cells/mcL.^{2,4,6}

2. Hemoglobin: Greater than or equal to 8 g/dL.^{2,6}
3. Platelet count:
  - a. Greater than or equal to 50,000 to 70,000 cells/mcL.^{2,4,6}
  - b. In clinical practice, a pretreatment platelet count of 75,000 cells/mcL is usually considered acceptable.
4. Serum creatinine: Less than or equal to 2.5 mg/dL.^{2,4,6}
5. Creatinine clearance: Greater than 50 mL/minute.¹
6. ALT/AST: Less than 2 to less than or equal to 3 times ULN.^{1,2,4,6}
7. Total bilirubin:
  - a. Less than 2 mg/dL.¹
  - b. Less than or equal to 3 times ULN.⁴
8. Alkaline phosphatase: Less than 3 times ULN.¹

DOSAGE MODIFICATIONS

A. Renal:

1. Lenalidomide:
  - a. CrCl 30 mL/min to less than or equal to 50 mL/min: 10 mg every 24 hours. If patient does not experience dose-limiting toxicity, dose can be increased to 15 mg following completion of 2 cycles.^{17,18}
  - b. CrCl less than 30 mL/min not requiring dialysis: 15 mg every 48 hours.¹⁷
  - c. CrCl less than 30 mL/min requiring dialysis: 5 mg once daily after dialysis¹⁷ or 15 mg three times weekly.¹⁸
2. Bortezomib: No dosage reduction required.^{10,19}
3. Dexamethasone: No dosage reduction required.²⁰

B. Hepatic Function

1. Lenalidomide: No dosage reduction required.¹⁷
2. Bortezomib: Bilirubin level greater than 1.5 times the ULN: For the first cycle, lower the dose to 0.7 mg/m². Depending on tolerability, may increase to 1 mg/m² or decrease to 0.5 mg/m² for future cycles.^{10, 21}
3. Dexamethasone: No dosage guidelines available.²²

C. Myelosuppression

1. Lenalidomide:
  - a. ANC less than 1,000 cells/mcL: Hold lenalidomide and monitor CBC weekly. When ANC is greater than or equal to 1,000 cells/mcL¹⁷:
    - (1) Restart at 25 mg or original dose if this is the first occurrence of neutropenia and is the only toxicity.

- (2) If there are other toxicities in addition to neutropenia, restart at next lower available intact capsule dosage.
  - (3) After the first occurrence of neutropenia, restart at next lower available intact capsule dosage each time ANC is less than 1,000 cells/mcL.
  - (4) When making dosage adjustments, refrain from dosing below 2.5 mg daily.
  - b. Platelet count less than 30,000 cells/mcL: Hold lenalidomide until platelet count is greater than or equal to 30,000 cells/mcL. Resume at next lower available intact capsule dosage, but avoid dosing below 2.5 mg daily.¹⁷
  2. Bortezomib: If any grade 4 hematological toxicities occur, hold bortezomib. When symptoms improve, restart at 25% reduced dose.¹⁰
  3. Dexamethasone: No dosage reduction recommended.²²
  4. For any grade 4 hematologic adverse event, reduce lenalidomide dose by 5 mg, bortezomib by 0.3 mg/m², and dexamethasone by 50% until toxicity reassessed.⁶
- D. Neurologic**
1. Lenalidomide: No specific dosage guidelines available. See below for nonhematologic toxicity dosage reductions.
  2. Bortezomib^{10,23}:
    - a. Grade 1 without pain or loss of function, no dosage reduction required.
    - b. Grade 1 with pain or grade 2, lower dose to 1 mg/m².
    - c. Grade 2 with pain or grade 3, hold and restart at 0.7 mg/m² once weekly.
    - d. Grade 4, stop bortezomib.
    - e. Bortezomib administered subcutaneously versus intravenously is associated with decreased incidence of neuropathy, and its use is especially advantageous in patients with risk factors or history of neuropathy.^{10,24} Multiple myeloma guidelines were recently updated with the recommendation for preference of subcutaneous bortezomib in these patient populations.⁹
  3. Dexamethasone: No dosage reduction necessary.
- E. Other:** For nonhematologic grade 3 or 4 toxicities, hold all drugs and restart lenalidomide with a 5 mg reduction, bortezomib with a 0.3 mg/m² reduction, and dexamethasone with a 50% reduction when toxicity has resolved to less than or equal to grade 2.^{6,10,17}

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