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Positive Quality Intervention: Bortezomib (Velcade®) Management for Multiple Myeloma and Mantle Cell Lymphoma

Description: The purpose of this PQI is to discuss the option of using bortezomib for multiple myeloma (MM) and mantle cell lymphoma (MCL) patients.

Background: Bortezomib is a reversible proteasome inhibitor of the chymotrypsin-like activity of the 26S proteasome and is approved for treatment of adult patients with multiple myeloma (MM) or mantle cell lymphoma (MCL). In a randomized, open-label study in patients with previously untreated MM, patients who received bortezomib, melphalan, and prednisone (Vc-MP) had a median time to progression of 20.7 months versus 15 months with melphalan and prednisone (MP) (HR=0.54); at a median follow-up of 60.1 months, the median overall survival (OS) was 56.4 months versus 43.1 months (HR 0.695). The bortezomib arm had complete and partial response rates of 30% and 40% respectively whereas the MP arm reported 4% and 30% complete and partial response rates.[2,3] For newly diagnosed MCL**,** a phase 3, randomized, open-label study reported a median PFS of 25 months in the VcR-CAP regimen arm (bortezomib with rituximab, cyclophosphamide, doxorubicin, and prednisone) vs 14 months in the R-CHOP arm (HR=0.63); the median OS was 91 months versus 56 months at a median follow-up of 78.5 months (HR=0.66).[4] In an integrated safety analysis of single agent bortezomib in 1163 patients with relapsed MM or relapsed MCL, the most commonly reported (>20%) adverse reactions were nausea (49%), diarrhea (46%), asthenic conditions including fatigue (41%) and weakness (11%), peripheral neuropathies (38%), thrombocytopenia (32%), vomiting (28%), constipation (25%), and pyrexia (21%). Eleven percent (11%) of patients experienced at least one episode of ≥ Grade 4 toxicity, most commonly thrombocytopenia (4%) and neutropenia (2%).[1]

PQI Process: Upon order of bortezomib:

- Verify dosing of bortezomib is 1.3 mg/m^2 with a concentration of 1 mg/mL intravenously or at a concentration of 2.5 mg/mL subcutaneously
    - Bortezomib is for intravenous or subcutaneous use only
    - When administered intravenously, administer as a 3 to 5 second bolus intravenous injection
    - Retreatment may be considered for patients with MM who had previously responded to treatment with bortezomib and who have relapsed at least six months after completing prior bortezomib treatment. Treatment may be started at the last tolerated dose
- Bortezomib is available in single-dose vials containing 3.5 mg of lyophilized powder for reconstitution and withdrawal of the appropriate individual patient dose
- Preparation: Bortezomib should only be reconstituted with 0.9% sodium chloride and should be a clear/colorless solution

Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration[1]			
Route of Administration	**Bortezomib (mg/vial)**	**Diluent (0.9% Sodium Chloride)**	**Final Bortezomib Concentration (mg/mL)**
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

PQI Process Continued:

- Dose Adjustment
  - No starting dosage adjustment of bortezomib is recommended for patients with mild hepatic impairment (tbili ≤1x ULN and AST > ULN, or tbili >1 to 1.5x ULN and any AST)
  - Consider reducing the starting dose in patients with moderate (tbili >1.5 to 3x ULN and any AST) or severe (tbili >3x ULN and any AST) hepatic impairment to 0.7 mg/m^2 in the first cycle
    - Consider dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability
  - No starting dose adjustment of bortezomib for patients with renal impairment
    - In patients requiring dialysis, bortezomib should be given after dialysis procedure
- For Previously Untreated MM, bortezomib is administered in combination with oral melphalan and oral prednisone for 9, six-week treatment cycles as shown in Table 1
- Prior to initiating any cycle of therapy with bortezomib in combination with melphalan and prednisone:
  - Platelet count should be at least 70 x 10^9/L and absolute neutrophil count (ANC) ≥ 1 x 10^9/L
  - Nonhematological toxicities should have resolved to Grade 1 or baseline
  - If any of these requirements are not met, review prescribing information for dose modifications

Table 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma[1]

Twice Weekly Bortezomib (Cycles 1 to 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib (1.3 mg/m2)	Day 1	--	--	Day 4	Day 8	Day 11	Rest period	Day 22	Day 25			Rest period
Melphalan (9 mg/m2) Prednisone (60 mg/m2)	Day 1	Da 2	Day 3	Day 4	--	--	Rest period	--	--	--	--	Rest period
Once Weekly Bortezomib (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib (1.3 mg/m2)	Day 1	--	--		Day 8		Rest period	Day 22		Day 29		Rest period
Melphalan (9 mg/m2) Prednisone (60 mg/m2)	Day 1	Day 2	Day 3	Day 4	--	--	Rest period	--	--	--	--	Rest period

- For previously untreated MCL, bortezomib is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (VcR-CAP) for 6, three week treatment cycles as shown in Table 2
  - Bortezomib is administered first followed by rituximab
  - If response first documented at cycle 6, two additional VcR-CAP cycles are recommended
  - At least 72 hours should elapse between consecutive doses of bortezomib
- Prior to the first day of each cycle (other than Cycle 1):
  - Platelet count should be at least 100 x 10^9/L and ANC should be at least 1.5 x 10^9/L
  - Hemoglobin should be at least 8 g/dL (at least 4.96 mmol/L)
  - Nonhematologic toxicity should have recovered to Grade 1 or baseline
  - If any of these requirements are not met, review prescribing information for dose modifications
  - Hold at the onset of Grade 3 toxicities, excluding neuropathy managed without holding

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PQI Process Continued:

Table 2: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma[1]								
Twice Weekly Bortezomib (6, Three-Week Cycles)*								
Week	**1**					**2**		**3**
Bortezomib (1.3 mg/m^2)	Day 1	--	--	Day 4	--	Day 8	Day 11	Rest period
Rituximab (375 mg/m^2) Cyclophosphamide (750 mg/m^2) Doxorubicin (50 mg/m^2)	Day 1	--	--			--	--	Rest period
Prednisone (100 mg/m^2)	Day 1	Day 2	Day 3	Day 4	Day 5	--	--	Rest period

*Dosing may continue for two more cycles (8 cycles total) if response is seen at cycle 6

- Administration
  - When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site
  - If local injection site reactions occur following subcutaneous administration, a less concentrated solution (1 mg/mL) may be administered subcutaneously. Intravenous route can be considered

Patient Centered Activities:

- Patient Education
  - Counsel patient on common side effects including peripheral neuropathy, headache, diarrhea, constipation, nausea/vomiting, and appropriate management of side effects
    - See **Chemotherapy Induced Peripheral Neuropathy** PQI
    - See **Chemotherapy Induced Nausea and Vomiting** PQI and **CINV Assessment Tool**
    - See **Chemotherapy, Oncolytic, Antiemetic Induced Constipation** PQI
    - See **Oncolytic Induced Diarrhea** PQI
- Velcade® Reimbursement Assistance Program (VRAP) - https://www.velcade.com/paying-for-treatment
  - Takeda Oncology Here2Assist
  - View online at www.Here2Assist.com or by calling 1-844-817-6468, Option 2
  - Provide Velcade® starter kit

References:

1. Velcade® (bortezomib) [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals, Inc.
2. 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; 359:906-917.
3. San Miguel JF, Schlag R, Khuageva NK et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol 2013; 31(4):448-55.
4. Robak T, Jin J, Pylypenko H, et al. Frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma: final overall survival results of a randomised, open-label, phase 3 study. The Lancet. Oncology. 2018;19(11):1449–1458.