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Positive Quality Intervention: Bortezomib (Velcade®) in the First-Line Management for Multiple Myeloma

Description: The purpose of this PQI is to discuss the option of using bortezomib for first-line treatment in multiple myeloma (MM).

Background: Bortezomib is a reversible proteasome inhibitor of the chymotrypsin-like activity of the 26S proteasome. It is approved for treatment of transplant-eligible and ineligible adult patients diagnosed with MM and can be administered in various combinations including with lenalidomide, dexamethasone, and daratumumab.[1] Current category 1 recommendations per NCCN include triplet therapy (bortezomib, lenalidomide, dexamethasone) and quadruplet therapy (bortezomib (V), lenalidomide (R), dexamethasone (d), and daratumumab (D).[2] In the phase 3, open-label and randomized SWOG S0777 trial, newly diagnosed MM patients were randomized to bortezomib, lenalidomide, and dexamethasone (RVd) or lenalidomide and dexamethasone (Rd) (see Table 1). RVd was given for eight cycles with each cycle lasting 21 days and Rd was given for six cycles with each cycle lasting 28 days. After completion of induction therapy, maintenance with 25 mg oral lenalidomide with weekly dexamethasone until progression, toxic effects, or patient withdrawal. Median progression-free survival (PFS) was found to be significantly improved with VRd (43 months) as compared to 64 Rd (30 months). Overall survival (OS) was found to be significantly improved at 75 months with VRd versus 64 months with Rd.[3]

Table 1: SWOG S0777 Regimens

		Week 1	Week 2	Week 3	Week 4
VRD	Bortezomib 1.3 mg/m^2	Days 1 and 4	Days 8 and 11	--	--
	Lenalidomide 25 mg	Days 1 – 7	Days 8 – 14	--	--
	Dexamethasone 20 mg	Days 1, 2, 4, 5	Days 8, 9, 11, 12	--	--
RD	Lenalidomide 25 mg	Days 1 – 7	Days 8 – 14	Days 15 - 21	--
	Dexamethasone 40 mg	Days 1	Day 8	Day 15	Day 22

In the phase 2 open-label GRIFFIN trial, newly diagnosed MM patients were randomized to receive induction regimen with four cycles of lenalidomide, bortezomib, and dexamethasone (RVd) alone or combined with daratumumab (D-RVd), followed by consolidation with autologous stem cell transplant (A-SCT) and 2 additional cycles of either RVd or D-RVd and maintenance with lenalidomide alone (R) or lenalidomide-daratumumab (DR) (respectively) with dosing noted in Table 2. The primary endpoint was stringent complete response (sCR) following consolidation, and it favored D-RVd (42.4%) over RVd (32.0%), [(CI 0.87-2.82), p=0.68]. Minimal residual disease (MRD) negativity was found to be significantly improved with D-RVd (51.0%) over RVd (20.4%) [p<0.001].[1]

Table 2: GRIFFIN Regimens

		INDUCTION			CONSOLIDATION
		Cycle 1 – 3	Cycle 4		Cycle 5 – 6
RVD	Lenalidomide 25 mg	Days 1 – 14	Days 1 – 14		--
	Bortezomib 1.3 mg/m^2	Days 1, 4, 8, 11	Days 1, 4, 8, 11		--
	Dexamethasone 20 mg	Days 1, 2, 8, 9, 15, 16	Days 1, 2, 8, 9, 15, 16	A-SCT	Every 4 or 8 weeks
D-RVD	Daratumumab 16 mg/kg	Day 1, 8, 15	Day 1, 8, 15		
	Lenalidomide	15 mg: Days 1 – 21	25 mg: Days 1 – 21		
	Bortezomib 1.3 mg/m^2	Days 1, 4, 8, 11	Days 1, 4, 8, 11		--
	Dexamethasone 20 mg	Days 1, 2, 8, 9, 15, 16	Days 1, 2, 8, 9, 15, 16		Day 22

PQI Process: Upon receipt of bortezomib order:

- 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 injection
    - When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated and injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated[4]
    - If volume is too large, subcutaneous injection may need to be split into 2 doses
        - Commonly set at a max of 2 mL per syringe, per injection site
    - 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: Reconstitute with 0.9% sodium chloride and should be a clear/colorless solution

Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration[4]			
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

- Dose Adjustment
    - No starting dosage adjustment of bortezomib is recommended for patients with mild hepatic impairment (tili ≤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
    - Dose reduction should be considered in patients with pre-existing or who develop peripheral neuropathy during treatment
    - Dose reduction should be considered in case of significant gastro-intestinal toxicity.
- Prior to initiating any cycle of therapy with bortezomib in combination with lenalidomide, dexamethasone, +/- daratumumab:
    - Platelet count should be preferably ≥ 70 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
- All patients started on Bortezomib must receive prophylactic therapy to prevent herpes zoster reactivation with either acyclovir or valacyclovir.

Patient-Centered Activities:

- Provide Intravenous Cancer Treatment Education (IVE) Sheet
    - 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
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Vorhees PM< Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood* 2020; 136(8): 936-945.
2. National Comprehensive Cancer Network. Multiple Myeloma (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed May 4, 2023.
3. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *The Lancet* 2017; 389:519-527.
4. Velcade® (bortezomib) [prescribing information].