BC Cancer Protocol Summary for Treatment of Multiple Myeloma using Lenalidomide, Bortezomib and Dexamethasone as Induction Pre-Stem Cell Transplant

Protocol Code	*MYBLDPRE*
Tumour Group	*Myeloma*
Contact Physician	*Dr. Christopher Venner*

ELIGIBILITY:

Patients must:

- Have previously untreated multiple myeloma,
- Be eligible for autologous stem cell transplant (ASCT)

Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca) is required.

Notes:

- A referral to the Leukemia/Bone Marrow Transplant Program of BC must be made for consideration of transplant at the start of the first cycle.
- To maximize stem cell collection efficiency and minimize the risk of collection failure:
    - The last dose of bortezomib should be given at least 14 days prior to stem cell collection
    - The last dose of lenalidomide should be given at least 21 days prior to stem cell collection

EXCLUSIONS:

Patients must not:

- Be pregnant or lactating
- Have a known hypersensitivity to lenalidomide

CAUTIONS:

- ANC less than 1.0×10^9/L
- Platelet count less than 30×10^9/L
- Total bilirubin greater than or equal to 1.5 x upper limit of normal
- Known hypersensitivity to pomalidomide or thalidomide

TESTS:

- Baseline (required before first treatment): CBC & Diff, platelets, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose. If female of child-bearing potential (FCBP): Confirm negative pregnancy test results via a quantitative beta-hCG blood test obtained 7 to 14 days and 24 hours prior to initial prescription.
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): serum protein electrophoresis and serum free light chain levels, immunoglobulin panel (IgA, IgG, IgM), HCAb, HBsAg, HBcoreAb, TSH, beta-2 microglobulin
- Every 4 weeks (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and serum free light chain levels
- Every 4 weeks (optional, results not mandatory but encouraged prior to each cycle): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM), beta-2 microglobulin
- Every 4 weeks: CBC & Diff, platelets, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose; if female of childbearing potential: quantitative beta-hCG blood test
- Days 8, 15, 22 (optional if pre-cycle cytopenias, hypercalcemia, hepatic or renal dysfunction, or steroid-induced diabetes a concern. Results do not have to be available to proceed with treatment. Provider to review results, no dose modifications indicated for mid-cycle bloodwork): CBC & Diff, platelets, creatinine, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, random glucose
- Every three months (required for lenalidomide, but results do not have to be available to proceed with treatment): TSH
- If female of childbearing potential: Every week for 4 weeks during cycle 1: quantitative beta-hCG blood test. Provider responsible for checking results.

PREMEDICATIONS:

None

SUPPORTIVE MEDICATIONS:

- Routine anti-emetic or anti-diarrheal premedication is not required. These symptoms should be managed symptomatically if they arise
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone or prednisone may be considered
- ASA (enteric coated), warfarin, direct oral anticoagulant (DOAC) or low molecular weight heparin (LMWH) subcutaneously daily continuing for the duration of treatment with lenalidomide
- If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per current guidelines
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating bortezomib and lenalidomide. Patients should take valACYclovir 500 mg PO daily

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
bortezomib	1.5 mg/m^2 (may start with 1.3 mg/m^2) on Days 1, 8, 15, and 22	Subcutaneously (abdomen or thigh)*
lenalidomide	25 mg once daily for 21 days (Days 1 to 21)	PO, in the evening may be preferred
dexamethasone	40 mg** once daily on Days 1, 8, 15 and 22	PO, in the morning may be preferred

* Back of the arm can also be considered as a third option, after abdomen or thigh

** Dexamethasone dose may vary dependent on tolerability and co-morbidities. See also: Other options for steroid dosing, below

Repeat every 28 days.

- Patients are eligible for up to 6 cycles.
- Stem cells are ideally collected after 3 to 4 cycles of treatment, but timing may vary based on the clinical situation. Examples:
  - 4 cycles prior to stem cell collection and 2 cycles post-transplant,
  - All 6 cycles pre-transplant
- Treatment may also be given to 'bridge' between stem cell collection and transplant

OTHER OPTIONS FOR STEROID DOSING

- Can be used (but may result in lower efficacy). Dose should be adjusted based upon toxicity and patient tolerance. Some examples included below:

Option A: dexamethasone 20 mg PO once weekly (or dexamethasone 4 to 40 mg PO once weekly based on toxicity and patient tolerance)
Option B: predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance. (e.g. predniSONE 10 to 100 mg PO once weekly)
Option C: No dexamethasone or predniSONE. High-dose steroids may need to be avoided in certain patients who are intolerant or have difficulty with side-effects. It is expected that the response will be inferior than without high-dose steroids. High-dose steroids may be added for non-response.

DOSE MODIFICATIONS:

- **Bortezomib dose levels:**

Dose level 0	Dose level -1	Dose level -2	Dose level -3	Dose level -4
1.5 mg/m^2	1.3 mg/m^2	1 mg/m^2	0.7 mg/m^2	0.5 mg/m^2

- **Lenalidomide dose modifications:**

  NB: Use one of the 25 mg, 20 mg, 15 mg, 10 mg, 5 mg or 2.5 mg capsules for dosing. Currently there is no evidence to support the use of other dosing regimens (i.e., there is no clinical reason or research available to support the use of a combination of lenalidomide capsules for dosing, however the use of such dosing does have significant budgetary implications).
- Dexamethasone should continue to be taken even if lenalidomide is held due to a dose limiting toxicity.

Lenalidomide dose levels:

Lenalidomide Dose on Days 1 to 21 of Every 28-Day Cycle					
Dose level 0	**Dose level -1**	**Dose level -2**	**Dose level -3**	**Dose level -4**	**Dose level -5**
25 mg	20 mg	15 mg	10 mg	5 mg	2.5 mg

1. Hematological: (based on pre-cycle labwork)

ANC (x10^9/L) On Day 1		**Platelets (x10^9/L)** On Day 1	**Bortezomib Dose**	**Lenalidomide Dose**
Greater than or equal to 1.0	and	Greater than or equal to 50	Maintain dose level	100%
0.5 to 0.99†	or	30 to 49	Notify provider. Proceed but consider dose reduction by one dose level for low platelets.	Notify provider. Proceed but at next lower dose level, above.
Less than 0.5†	or	Less than 30*	May proceed but decrease by one dose level if felt to be treatment-related.	Hold until ANC greater than or equal to 1.0 and platelets greater than or equal to 30, then restart at next lower dose level, above.
Reoccurrence of less than 0.5†	or	Reoccurrence of less than 30*	For reoccurrence of ANC less than 0.5, may proceed but consider decrease by one dose level if felt to be treatment-related. Delay until platelets greater than or equal to 30, then consider decreasing by one dose level	

* follow hematology weekly and consider arrangements for transfusion support as required.

† Consider weekly filgrastim if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer.

2. Renal dysfunction:

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Lenalidomide Dose	Bortezomib Dose
Greater than or equal to 60	25 mg daily†	100% For patients on hemodialysis, give dose after dialysis.
30 to 59	10 mg daily†‡	
Less than 30, not requiring dialysis	15 mg every other day for 21 days, then rest for 7 days (i.e. 28-day cycle)	

* As reported in patient's laboratory report
† Dosing for 21 days (Days 1 to 21) of each 28-day cycle
‡ Dose can be escalated to 15 mg after 2 cycles if patient is not responding to treatment and is tolerating the drug; may consider escalating to 25 mg if patient continues to tolerate

3. Hepatic Impairment: Bortezomib

	Total bilirubin	ALT	Bortezomib Dose
Mild	less than or equal to 1 x upper limit of normal	greater than the upper limit of normal	100%
	greater than 1 to 1.5 x upper limit of normal	Any	100%
Moderate	greater than 1.5 to 3 x upper limit of normal	Any	▪ Reduce dose 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.
Severe	greater than 3 x upper limit of normal	Any	

4. Non-hematological/Non-renal: Lenalidomide

Toxicity	Management
Grade 3 or greater exfoliative rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis	Discontinue
Pneumonitis	Hold and investigate; discontinue if confirmed. Note this is a very rare side-effect and alternative causes must be ruled out.
Grade 3 to 4 (any other toxicity)	Delay* then decrease by one dose level when dosing resumed at next cycle

* Stop treatment immediately and delay until toxicity resolved to Grade 0 to 2

5. Peripheral Neuropathy: bortezomib

Severity of Peripheral Neuropathy Signs and Symptoms	Dose
Grade 1 (paresthesia and/or loss of reflexes) without pain or loss of function	100%
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 1.3 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Delay until recovery. When resolved, reduce dose to 1 mg/m^2 x 2 doses
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

6. Diarrhea: Bortezomib

Diarrhea grading system

Grade 1	Grade 2	Grade 3	Grade 4
Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; IV fluids indicated for less than 24 h; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of greater than 7 stools per day over baseline; incontinence; IV fluids for greater than 24 h; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)

Treatment of Diarrhea During Cycle		
At first loose stool:	Start loperamide 2 mg po q 2 h while awake and q 4 h while sleeping. Continue around the clock until 12 h diarrhea free	• If *diarrhea free greater than 12 h*, stop loperamide. If new episode, retreat with loperamide. • If *Grade 3* diarrhea or diarrhea accompanied by *mucus or dehydration*, *hold doses of bortezomib* (if applicable) and hydrate.

Diarrhea management: Next Cycle Dosing

- Delay next cycle until diarrhea has resolved (less than 2 watery bowel movements per day)

Severity of diarrhea with *last* cycle:	**Bortezomib dose *this* cycle**
less than or equal to Grade 2	no change from previous cycle
greater than or equal to Grade 3 or associated with mucus or dehydration	Reduce dose to next dose level (if two dose reductions have already occurred, further treatment with bortezomib must be individualized and should only continue if a clearly useful clinical response in the myeloma has occurred)

PRECAUTIONS:

1. **Teratogenicity**: If lenalidomide is taken during pregnancy, it may cause severe birth defects or death to the fetus. Lenalidomide should never be used by females who are pregnant or who could become pregnant while taking the drug. Even a single dose taken by a pregnant woman may cause birth defects.
2. **Neutropenia**: fever or other evidence of infection must be assessed promptly and treated aggressively
3. **Hepatotoxicity:** Hepatic failure, including fatal cases, has been reported in multiple myeloma patients treated with lenalidomide in combination with dexamethasone during post-marketing. The mechanism of severe drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes and concomitant medications may be risk factors. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered. Dose modification for bortezomib may be required, see dose modifications, above.
4. **Hypothyroidism:** The use of lenalidomide may result in hypothyroidism. Treatment with thyroid replacement should be considered even for subclinical hypothyroidism. Lenalidomide can be continued if hypothyroidism can be easily managed.
5. **Venous thrombosis/embolism:** Lenalidomide with dexamethasone is known to increase the risk for thromboembolic disease. **ASA 81 mg** oral daily should be considered in all patients. For those with higher risk of thromboembolic disease full anti-coagulation should be considered.
6. **Hepatitis B Reactivation**: All myeloma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with hepatitis B prophylaxis according to current guidelines. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every three months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
7. **Skin Rashes**: Lenalidomide may cause skin rashes although in general it is not severe. Minor rashes can be treated with diphenhydramine and/or steroid creams and lenalidomide can be continued. Moderate rashes may require holding lenalidomide until resolution of the rash. For more severe rashes (greater than or equal to Grade 3: severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering greater than or equal to 50% BSA) lenalidomide should be discontinued.
8. **Second Primary Malignancies (SPM)**: In clinical trials of newly diagnosed multiple myeloma patients, for those receiving lenalidomide with dexamethasone, the hematological SPM incidence rate (0.14 per 100 person-years) was not increased as compared to patients on thalidomide in combination with melphalan and prednisone (0.91 per 100 person-years). The risk of occurrence of SPM must be taken into account before initiating treatment with lenalidomide. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

9. **Need for irradiated blood products:** Patients receiving an autotransplant require irradiated blood products from 7 days prior to collection to 3 months post-transplant (6 months if total body irradiation conditioning) to eliminate the risk of potentially life-threatening transfusion-related graft-versus-host-disease. All other myeloma patients do not require irradiated blood products.
10. **Green tea avoidance.** Some of the components in green tea and preparations made from green tea block the activity of bortezomib in *in vitro* experiments. Green tea or preparations made from green tea should be avoided by patients taking bortezomib.

Call Dr. Christopher Venner or tumour group delegate at 604-877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017 Apr 6;376(14):1311-1320.
2. Richardson PG, Jacobus SJ, Weller EA, et al; DETERMINATION Investigators. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. N Engl J Med. 2022 Jul 14;387(2):132-147.
3. CADTH Reimbursement Review. Provisional Funding Algorithm. Multiple Myeloma. May 2022.