BC Cancer Protocol Summary for Maintenance Therapy of Multiple Myeloma using Lenalidomide

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

ELIGIBILITY:

Patients must have:

- Newly diagnosed multiple myeloma following autologous stem cell transplant,
- Minimum of stable disease post- transplant, and

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

EXCLUSIONS:

Patients must not:

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

CAUTIONS:

- Platelet count less than 30 x 10^9/L
- ANC less than 1.0 x 10^9/L. Consider giving filgrastim
- Creatinine Clearance less than 30 mL/min
- Known hypersensitivity to thalidomide or pomalidomide

TESTS:

- Baseline (required before first treatment): CBC & Diff, creatinine, 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): calcium, serum protein electrophoresis and serum free light chain levels, immunoglobulin panel (IgA, IgG, IgM), HCAb, HBsAg, HBsAb, HBcoreAb, TSH, beta-2 microglobulin
- 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, creatinine, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, random glucose

- Every 4 weeks (required before treatment): CBC & Diff, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose; if female of childbearing potential: quantitative beta-hCG blood test
- 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): immunoglobulin panel (IgA, IgG, IgM), urine protein electrophoresis, beta-2 microglobulin
- Every three months (required, 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.
- If clinically indicated: HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

None

SUPPORTIVE MEDICATIONS:

- High risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating lenalidomide. Patients should take valACYclovir 500 mg PO daily
- ASA (enteric coated), warfarin, direct oral anticoagulant (DOAC) or low molecular weight heparin (LMWH) subcutaneously daily continuing for the duration of treatment with lenalidomide

TREATMENT:

- Start 3 to 4 months post stem cell transplant.

Drug	Dose	BC Cancer Administration Guideline
lenalidomide	10 mg* once daily for 21 days (Days 1 to 21)** **OR** 10 mg* once daily continuously (Days 1 to 28)	PO, in the evening may be preferred

* May consider increasing dose to 15 mg (for either 21/28 day dosing or for continuous dosing, Days 1 to 28) after 3 months if patient tolerating and ANC greater than 1.0 x 10^9/L, platelets greater than 75 x 10^9/L

** Dosing for 21/28 days preferred for majority of patients. Consider continuous dosing for 28/28 days per provider discretion

- Repeat every 28 days until progression or unacceptable toxicity.

DOSE MODIFICATIONS:

- NB: Use one of the 15 mg, 10 mg, 5 mg, or 2.5 mg capsules for dosing. The use of two 5 mg capsules for a 10 mg dose etc., has significant budgetary implications.

Lenalidomide dose levels:

Dose Level +1*	Dose Level 0	Dose Level -1	Dose Level -2
15 mg	10 mg	5 mg	2.5 mg

* May consider increasing dose to 15 mg continuously (Days 1 to 28) after 3 months if patient tolerating and ANC greater than 1.0 x 10^9/L, platelets greater than 75 x 10^9/L

1. Hematological (based on pre-cycle lab work):

ANC (x10^9/L) On Day 1		**Platelets (x10^9/L)** On Day 1	**Lenalidomide Dose**
Greater than or equal to 1.0	and	Greater than or equal to 50	100%
0.5 to 0.99†	or	30 to 49	Notify provider. Proceed but at next lower dose level, above, or maintain dose but decrease to *21/28 days* if not yet done.
Less than 0.5 or febrile neutropenia (ANC less than 1.0 with oral temperature greater than or equal to 38.0° Celsius)	or	less than 30*	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, or maintain dose but decrease to *21/28 days* if not yet done.

* 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
Greater than or equal to 60	100%
30 to 59	• If currently on 15 mg or 10 mg daily for 28/28 days consider decreasing dose to 10 mg daily *21/28 days* and reassess in four weeks to attempt to re-escalate • If currently on 10 mg daily for *21/28 days,* maintain dose
Less than 30, not requiring dialysis	15 mg every other day for *21/28 days*
Less than 30, dialysis dependent	5 mg daily for *21/28 days* (administer after dialysis on dialysis days)

*as reported in patient's laboratory report

**Further decrease in dose is not necessary for stable eGFR/creatinine clearance greater than 30 providing other patient parameters are adequate e.g., ANC and platelets

3. Non-hematological/Non-renal: lenalidomide

Toxicity	1st occurrence	2nd occurrence	3rd occurrence	4th or subsequent occurrence
Grade 3 or greater exfoliative rash, SJS, TEN	Discontinue			
Pneumonitis	For suspected pneumonitis, hold and investigate; discontinue if confirmed			
Grade 3-4 (any other toxicity)	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle Do not dose below 2.5 mg

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

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. **Hepatotoxicity:** Hepatic failure, including fatal cases, have 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.
3. **Constipation**: Patients should be warned that constipation may occur in patients taking lenalidomide.
4. **Fatigue**: Patients should be warned that lenalidomide may cause fatigue.
5. **Hypothyoidism:** 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.
6. **Venous thrombosis/embolism:** Lenalidomide with dexamethasone is known to increase the risk for thromboembolic disease. The risk is lower with lenalidomide maintenance but ASA 81mg oral daily should be considered in all patients. For those

with higher risk of thrombo-embolic disease full anti-coagulation should be considered.

7. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
8. **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.
9. **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.
10. **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

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. McCarthy PL, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1770-81.
2. Palumbo A, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2014;371:895-905.
3. Attal M, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1782-91.
4. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol. 2020 Jun;7(6):e456-e468.
5. Jackson GH, Davies FE, Pawlyn C, et al.; UK NCRI Haemato-oncology Clinical Studies Group. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019 Jan;20(1):57-73.
6. Cherniawsky HM, Kukreti V, Reece D, et al. The survival impact of maintenance lenalidomide: an analysis of real-world data from the Canadian Myeloma Research Group national database. Haematologica. 2021 Jun 1;106(6):1733-1736.