

BCCA Protocol Summary for Treatment of Previously Untreated Multiple Myeloma and Not Eligible for Stem Cell Transplant Using Lenalidomide with Low-dose Dexamethasone

Protocol Code	UMYLDF
Tumour Group	Lymphoma, Leukemia/BMT
Contact Physician	Dr. Kevin Song
Contact Pharmacist	Linda Hamata

ELIGIBILITY:

- Patients with newly diagnosed multiple myeloma as per the updated International Myeloma Working Group criteria, who are ineligible for stem cell transplant
- Life expectancy of greater than 3 months
- Patients with renal impairment not on dialysis
- A BC Cancer Agency “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment
- Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca)

EXCLUSIONS:

- Pregnant or lactating women
- Platelet count less than 30×10^9 /L may be considered a relative contraindication
- If absolute neutrophil count (ANC) less than 1.0×10^9 /L may be considered a relative contraindication
- Known hypersensitivity to lenalidomide or pomalidomide or thalidomide
- Dialysis dependence. Bortezomib based therapy should be considered for this population
- Patients who are being considered for stem cell transplant. Lenalidomide can cause difficulty with peripheral blood stem cell collection.

TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, creatinine, LFTs (bilirubin, AST, ALT). If female of child-bearing potential (FCBP): Confirm negative pregnancy test results 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): calcium and serum protein electrophoresis, HBsAg, HBcoreAb, TSH
- Every 2 weeks for the first 4 cycles then may reduce frequency to every 4 weeks: CBC and diff, platelets, creatinine, calcium
- Every 4 weeks (required before treatment): CBC and diff, platelets, creatinine; if female of childbearing potential: pregnancy test (blood)
- Every 4 weeks (required, but results do not have to be available to proceed with treatment): calcium and serum protein electrophoresis; free light chain if clinically indicated
- Every three months (required, but results do not have to be available to proceed with treatment): T3, T4, TSH
- If clinically indicated: bilirubin, AST, ALT, see Precautions #2

PREMEDICATIONS:

None

TREATMENT:

Drug	Dose	BCCA Administration Guideline
lenalidomide	25 mg once daily for 21 days (d1-21)	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

* Dose may vary dependent on tolerability and co-morbidities

- Patients over 75 years of age: consider using dexamethasone 20 mg
- predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance.

Repeat every 28 until progression of the myeloma or unacceptable toxicity

OTHER OPTIONS FOR DEXAMETHASONE DOSING**Option A:**

Oral dexamethasone 20 or 40 mg daily on days 1-4, 9-12, 17-20 x 4 cycles; then 20 or 40 mg daily on days 1-4 only for subsequent cycles. The dose should be adjusted based upon 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.

Option C:

No dexamethasone. Dexamethasone 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 using lenalidomide alone. Dexamethasone may be added for non-response.

Repeat every 28 days until progression of the myeloma or unacceptable toxicity

LENALIDOMIDE DOSE MODIFICATIONS:

Fatigue may respond to dose reduction

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.

Dose Levels	Lenalidomide on Days 1–21 of Every 28-Day Cycle
Standard dose	25 mg/d on Days 1-21
Dose level -1	20 mg/d on Days 1-21
Dose level -2	15 mg/d on Days 1-21
Dose level -3	10 mg/d on Days 1-21
Dose level -4	5 mg/d on Days 1-21
Dose level -5	2.5 mg/d on Days 1-21

1. Hematological

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	1 st Event Dose	2 nd Event Dose	3 rd Event Dose	4 th Event Dose or subsequent
Greater than or equal to 1.0	and	Greater than or equal to 50	100%	100%	100%	100%
0.5 to 0.9	or	25 to 49	Delay* then 100%	Delay* then 100%	Delay* then 100%	Delay* then 100%
Less than 0.5†,‡ or febrile neutropenia	or	Less than 25	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

* Delay until ANC greater than or equal to 1.0 x 10⁹/L and platelets greater than or equal to 50 x 10⁹/L

† Consider G-CSF if clinically indicated and G-CSF is available

‡ If neutropenia is isolated without other toxicity and G-CSF treatments continue, may consider continuing with no dose reduction. G-CSF is not covered as a benefit drug by the BCCA.

Note: Bloodwork monitored every 2 weeks for the first 4 cycles
 Day 15 bloodwork for Cycle 1-4 will be monitored by the physician and physician will be responsible to check and advise patient on dose adjustment, as per suggested guidelines above.

2. Renal dysfunction:

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Lenalidomide Dose
Greater than or equal to 60	25 mg daily†
30-59	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 (d 1-21) 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 the drug

3. Non-hematological/Non-renal

Toxicity	1 st occurrence	2 nd occurrence	3 rd occurrence	4 th 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 0-2

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, 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.
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. **Hypothyroidism:** The use of lenalidomide may result in hypothyroidism. Thyroid function tests should be repeated every 3 months. 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. **Aspirin 81 mg** oral daily should be considered in all patients. For those with higher risk of thromboembolic disease full anti-coagulation should be considered.
7. **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 lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two 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.
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.

Call Dr. Kevin Song (Leukemia/BMT) or Dr Laurie Sehn (Lymphoma) or tumour group delegate with any problems or questions regarding this treatment program. (Leukemia/BMT at (604) 875-4863 or after hours (604) 875-4111; Lymphoma at (604) 877-6000 or 1-800-663-3333)

Date activated: 1 April 2017

Date revised:

References:

1. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and Dexamethasone in Transplant Ineligible patient with Myeloma. *NEJM* 2014; 371 (10):906-17
2. Delforge M, Minuk L. Eisenmann JC et al. Healthrelated Quality-of-Life in Patients with Newly Diagnosed Multiple Myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, Thalidomide. *Hematologica* 2015; 100(6):826-33.
3. Rajkumar SV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014: 15:e538-48