BC Cancer Protocol Summary for Therapy of Relapsed Multiple Myeloma Using Lenalidomide with Dexamethasone

Protocol Code	***MYLDREL***
Tumour Group	***Lymphoma, Leukemia/BMT***
Contact Physicians	***Dr. Christopher Venner***

ELIGIBILITY:

Patients must have:

- Relapsed and refractory multiple myeloma,
- Received at least one prior therapy (which can include autologous stem cell transplant),
- Sensitivity to lealidomide, which includes patients who relapse after maintenance lenalidomide (MYLENMTN), 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,
- Have a known hypersensitivity to lenalidomide, pomalidomide or thalidomide, or
- Have lenalidomide-refractory disease (progressed during or after active lenalidomide therapy)

CAUTIONS:

- Platelet count less than 30 x 10^9/L may be considered a relative contraindication.
- Absolute neutrophil count (ANC) less than 1.0 x 10^9/L may be considered a relative contraindication. Consider giving filgrastim

TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, creatinine, LFTs (bilirubin, ALT). 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): serum protein electrophoresis ***and*** serum free light chain levels, immunoglobulin panel (IgA, IgG, IgM), HBsAg, HBcoreAb, TSH, calcium,
- If cytopenias a concern, every 2 weeks for the first 4 cycles: CBC and diff, platelets, creatinine, calcium

- Every 4 weeks (required before treatment): CBC and diff, platelets, creatinine; 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, and calcium
- Every 4 weeks (optional, results do not have to be available to proceed with treatment): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM)
- 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
- If clinically indicated: bilirubin, ALT, see Precautions #2

PREMEDICATIONS:

None

SUPPORTIVE MEDICATIONS:

- 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) PO or low molecular weight heparin (LMWH) SC daily continuing for the duration of treatment with lenalidomide

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
lenalidomide	25 mg once daily for 21 days (d 1-21)	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
OPTIONAL cyclophosphamide¥	500 mg once weekly on days 1, 8, 15 and 22 *OR* 50 mg once every 2 days	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.

¥Cyclophosphamide may be added per physician discretion to increase response

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

OTHER OPTIONS FOR DEXAMETHASONE DOSING

Option A: Oral dexamethasone 20 mg or 40 mg daily on days 1-4, 9-12, 17-20 x 4 cycles; then 20 mg or 40 mg daily on days 1-4 only for subsequent cycles. The dose should be adjusted based upon toxicity and patient tolerance. (e.g. dexamethasone 4 - 40 mg PO once weekly)
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 - 100mg PO once weekly)
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.

LENALIDOMIDE DOSE MODIFICATIONS:

Fatigue may respond to dose reduction

NB: Use one of the 25 mg, 20 mg, 15 mg, 10 mg or 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 on Days 1-21
Dose level -1	20 mg on Days 1-21
Dose level -2	15 mg on Days 1-21
Dose level -3	10 mg on Days 1-21
Dose level -4	5 mg on Days 1-21
Dose level -5	2.5 mg on Days 1-21

1. Hematological Day 1

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose or subsequent
Greater than or equal to 1.0	and	Greater than or equal to 50	100%	100%	100%	100%
Less than 1.0†	or	Less than 50	Delay* then consider decreasing by one dose level when dosing resumed	Delay* then consider decreasing by one dose level when dosing resumed	Delay* then consider decreasing by one dose level when dosing resumed	Delay* then consider decreasing by one dose level when dosing resumed Do not dose below 2.5 mg

* Follow hematology weekly and delay until ANC greater than or equal to 1.0 x 10^9/L and platelets greater than or equal to 50 x 10^9/L and no evidence of hemostatic failure (i.e., bleeding or petechiae)

† Consider filgrastim if clinically indicated and filgrastim is available

Day 15:

For Cycles 1-4: Physician will monitor Day 15 bloodwork and physician will be responsible to advise patient on dose adjustment based on ANC and platelets. Note: For ANC less than 0.5 x 10^9/L or platelets less than 30 x 10^9/L, consider omitting lenalidomide for remainder of cycle; restart on Day 1 of next cycle if counts have recovered; consider decreasing by one dose level when dosing resumed.

For females of child-bearing potential on weekly pregnancy test during cycle 1, physician will be responsible for checking results

2. Renal dysfunction:

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Dose
greater than or equal to 60	25 mg†
30-59	10 mg†‡
less than 30, not requiring dialysis	15 mg every other day for 21 days, then rest for 7 days (i.e. 28-day cycle)
less than 30, dialysis dependent	5 mg† (administer after dialysis on dialysis day)

*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	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 consider decreasing by one dose level when dosing resumed at next cycle	Delay* then consider decreasing by one dose level when dosing resumed at next cycle	Delay* then consider decreasing by one dose level when dosing resumed at next cycle	Delay* then consider decreasing 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

CYCLOPHOSPHAMIDE DOSE MODIFICATIONS:

1. **Hematological, for low counts on day 1 lab work due to treatment**

ANC ($x10^9$/L)	Platelets ($x10^9$/L)	Dose (all drugs)
greater than or equal to 1.0	greater than or equal to 50	100%
less than 1.0	less than 50	Delay until recovery

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 HBcoreAb. If either test is positive, such patients should be treated with Lamivudine 100 mg PO daily, for the entire duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA 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 they are 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 previously treated multiple myeloma patients, for those receiving lenalidomide with dexamethasone, the incidence rate of SPM was increased (3.98 per 100 person years) compared to controls (1.38 per 100 person years). The non-invasive SPM were basal cell or squamous cell skin cancers, while most of the invasive SPM were solid tumour malignancies. The risk of occurrence of SPM must be taken into account before initiating treatment with lenalidomide in relapsed multiple myeloma patients. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of secondary 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. Kevin Song (Leukemia/BMT) or Dr. Christopher Venner (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)

References:

1. Dimopoulos M, Spencer A, Attal M, et al. Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-32.
2. Weber DM, Chen C, Niesvizky R, et al. Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-42.
3. Palumbo A, Rajkumar SV, Dimopoulos MA et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-23.
4. Kevin Song MD, Personal communication. BC Cancer Agency Leukemia/BMT Tumour Group; September 2009.
5. Celgene REVLIMID® product monograph. Oakville, Ontario; 15 February, 2017