BC Cancer 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	*Myeloma*
Contact Physicians	*Dr. Kevin Song,* *Dr. Christopher Venner*

ELIGIBILITY:

Patients must:
- Have newly diagnosed multiple myeloma as per the updated International Myeloma Working Group criteria,
- Be ineligible for stem cell transplant, and
- Have a BC Cancer "Compassionate Access Program" request with appropriate clinical information approved prior to treatment

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,
- Known hypersensitivity to or 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, 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:

- 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 lenalidomide. Patients should take valACYclovir 500 mg PO daily
- 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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
lenalidomide	25 mg once daily for 21 days (Days 1 to 21)	PO, in the evening may be preferred
dexamethasone	*40 mg once weekly 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

* Dexamethasone dose may vary dependent on tolerability and co-morbidities. For older patients i.e. 75 years of age or older, the starting dose of dexamethasone should be 20 mg PO weekly. See also: Other options for steroid dosing, below

¥Cyclophosphamide may be added per physician discretion to increase response

Repeat every 28 days until progression or unacceptable toxicity.

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/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 with high-dose steroids. High-dose steroids may be added for non-response.

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:

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose level -3	Dose level -4	Dose level -5
lenalidomide	25 mg	20 mg	15 mg	10 mg	5 mg	2.5 mg

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

ANC ($x10^9$/L) On Day 1		Platelets ($x10^9$/L) On Day 1	Lenalidomide Dose	Cyclophosphamide Dose (if using)
Greater than or equal to 1.0	and	Greater than or equal to 50	100%	100%
0.5 to 0.99†	or	30 to 49	Notify provider. Proceed but at next lower dose level, above	Delay until recovery
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 lenalidomide 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.	

* 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: Lenalidomide

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Lenalidomide Dose
Greater than or equal to 60	25 mg daily†
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)
Less than 30, dialysis dependent	5 mg† (administer after dialysis on dialysis days)

*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 the drug

Renal dysfunction: cyclophosphamide

- Dose reduction is necessary per table, below. Physician may consider giving full dose of cyclophosphamide irrespective of renal function if deemed to be of benefit.
- For patients on hemodialysis, give dose after dialysis.

Creatinine clearance (mL/min)	Cyclophosphamide Dose
Greater than or equal to 10	100 %
Less than 10	75 %

Calculated creatinine clearance = $\frac{N \times (140 - Age) \times weight\ (kg)}{Serum\ Creatinine\ (micromols/L)}$

N = 1.04 (Females) and 1.23 (Males)

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, 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. **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. **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.
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 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.
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. 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
4. Jackson GH, Pawlyn C, Cairns DA et al. Optimising the value of immunomodulatory drugs during induction and maintenance in transplant ineligible patients with newly diagnosed multiple myeloma: results from Myeloma XI, a multicentre, open-label, randomised, Phase III trial. Br J Haematol. 2021; 192(5):853-868.