BC Cancer Protocol Summary for Therapy of Multiple Myeloma using Carfilzomib, Lenalidomide with Dexamethasone

Protocol Code	*MYCARLD*
Tumour Group	*Myeloma*
Contact Physician	*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 lenalidomide, which includes patients who relapse after maintenance lenalidomide (MYLENMTN), or not previously exposed,
- Sensitivity to bortezomib or not previous exposed, and
- Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca)

EXCLUSIONS:

Patients must not:

- Be refractory to lenalidomide (progression on lenalidomide-containing regimen other than MYLENMTN)
- Have prior refractoriness to carfilzomib,
- Be pregnant or lactating,
- Have a known hypersensitivity to lenalidomide, or
- Have uncontrolled hypertension

CAUTION:

- CrCl less than 30 mL/minute
- History of congestive heart failure
- Platelet count less than 30×10^9/L
- ANC less than 1.0×10^9/L. Consider giving filgrastim
- ALT greater than 3 x ULN, total bilirubin greater than 2 x ULN
- 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, phosphate, 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, phosphate, 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, phosphate, 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:

- dexamethasone (see Treatment table, below)
  - If ordered as part of the treatment regimen, it should be administered in the morning regardless of carfilzomib dosing time
  - If not given as part of the treatment regimen, dexamethasone 4 mg PO or IV may be administered at 30 minutes to 4 hours before carfilzomib if necessary

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 carfilzomib and lenalidomide. Patients should take valACYclovir 500 mg PO daily
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone 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 recurrent nausea is noted, consider:
    - ondansetron 8 mg PO TID prn nausea the day of and the day after carfilzomib
    - olanzapine 2.5 mg PO HS the evening before and the evening of carfilzomib

PREHYDRATION: Hydration must be used with caution given the risk of transient cardiac contractility impairment and fluid overload.

- **Cycle 1:** 250 mL NS IV over 30 minutes prior to carfilzomib
- **Subsequent cycles:** optional IV prehydration

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
dexamethasone	*40 mg once weekly on Days 1, 8,15 and 22	PO, in the morning
lenalidomide	25 mg once daily for 21 days (Days 1 to 21)	PO, in the evening may be preferred
carfilzomib*	**CYCLE 1:** 20 mg/m^2 on Day 1 then 56 mg/m^2 on Days 8 and 15 **CYCLE 2 to 18:** 56 mg/m^2 on Days 1, 8 and 15 *(cap BSA at 2.2)	IV in 100 mL D5W over 30 minutes†

* 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

† Infusion time remains consistent throughout protocol regardless of any dose modifications

Cycle length is 28 days.

- After cycle 18, carfilzomib is discontinued but lenalidomide and dexamethasone are continued until disease progression or unacceptable toxicity using the same protocol.
- Continuation of carfilzomib beyond 18 cycles is not funded by BC Cancer. Beyond 18 cycles, carfilzomib may be obtained compassionately from Amgen. A BC Cancer "Compassionate Access Program" request is required for continuation of carfilzomib beyond 18 cycles. Contact the drug company (Amgen) to enroll patient in the patient assistance program for supply.

Vitals monitoring and observation:

- Vital signs prior to EACH carfilzomib infusion
- For Cycle 1 only, observe patient for 30 minutes following each carfilzomib infusion.

Post-Carfilzomib Hydration:

- Optional IV post-hydration with 250 mL NS IV over 30 minutes after carfilzomib can be considered, especially if there are concerns with renal impairment. Hydration must be used with caution given the risk of transient cardiac contractility impairment and fluid overload.

OTHER OPTIONS FOR STEROID DOSING

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.

DOSE MODIFICATIONS:

Recommended dose level reductions: carfilzomib

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose level -3
carfilzomib	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 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.

Recommended dose level reductions: lenalidomide

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):**

- **Microangiopathy and thrombotic thrombocytopenic purpura is a rare but serious hematologic toxicity. If the clinical picture is suggestive, carfilzomib should be stopped immediately and a hemolytic work up should be initiated:**
  - **CBC & Diff, platelets, peripheral smear, LDH, total and direct bilirubin, Haptoglobin, DAT, creatinine, urea**

ANC (x10^9/L) On Day 1		**Platelets (x10^9/L)** On Day 1	**Carfilzomib 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 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.
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. Non-hematological: Carfilzomib

Toxicity	Carfilzomib Dose
Renal: Creatinine clearance less than 15 mL/min	Hold dose. When CrCl returns to greater than or equal to 15 mL/min, resume dose. If dialysis required, may resume at a maximum dose of 20 mg/m^2 and administer carfilzomib after dialysis
Febrile neutropenia	Delay and if ANC returns to baseline grade and fever resolves, resume at same dose level
Any Grade 3 or 4 non-hematological toxicity	Delay and consider decreasing by one dose level when toxicity has resolved to less than or equal to Grade 2 or baseline; dose may be escalated to previous dose at physician's discretion.

*carfilzomib should be administered after dialysis

3. **Renal Dysfunction: Lenalidomide**

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

*as reported in patient's laboratory report
†dosing for 21 days (Day 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.

PRECAUTIONS:

1. **Infusion reactions** to carfilzomib are rare but can occur. Must be differentiated from fluid overload and congestive heart failure. Reactions can occur immediately following or within 24 hours of carfilzomib infusion. Symptoms may include: fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, and/or angina. For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX: Management of Infusion-Related Reactions to Systemic Therapy Agents.
2. **Cardiac Toxicities:** New onset or worsening of pre-existing cardiac failure (e.g., pulmonary edema, decreased ejection fraction, congestive heart failure) is the main concern with carfilzomib. The mechanism of action is transient effects on myocardial contractility. It is reversible and can respond to standard CHF management often not necessitating discontinuation of therapy. Also reported are myocardial ischemia and infarction. Patients at high risk of cardiac complications include: those who are age 75 years or older, prior history of heart failure, recent myocardial infarction, conduction abnormalities, angina or presence of AL amyloidosis. Although adequate hydration is required prior to cycle 1, **monitor patients for volume overload and tailor fluid requirements as necessary in patients with pre-existing or at high risk of cardiac failure**. During treatment, monitor patients for signs and symptoms of cardiac failure/ischemia. Withhold carfilzomib until recovery for Grade 3 or 4 cardiac adverse events. Carfilzomib may be restarted at a reduced dose following risk/benefit assessment. Following reconstitution, each mL of carfilzomib contains 0.3 mmols (7 mg) of sodium. This should be taken into consideration for patients on a controlled sodium diet.
3. **Hypertension** including hypertensive crisis has occurred with carfilzomib; hypertension should be well-controlled prior to initiation of treatment.
4. **Hemorrhage**, related to hematologic toxicity both serious and fatal, including gastrointestinal, pulmonary and intracranial hemorrhage as well as serious cases of epistaxis may occur. Carfilzomib dose reduction or temporary discontinuation may be required following signs of blood loss.
5. **Hepatotoxicity:** Hepatic failure, including fatal cases, has been reported with carfilzomib and lenalidomide in combination with dexamethasone. Hold treatment for Grade 3 toxicity or greater. After return to baseline values, treatment at a lower dose of lenalidomide and carfilzomib may be considered.
6. **Renal Toxicity** occurs in up to 10% of carfilzomib patients and may require dose reduction, interruption, or therapy discontinuation. The risk of renal failure may be greater in patients with a reduced creatinine clearance at baseline. Ensure patient is adequately hydrated to mitigate the risk of renal toxicity. **Must monitor for thrombotic microangiopathy as noted above.** See Dose Modifications, above.
7. **Pulmonary toxicities** including Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease, such as pneumonitis and interstitial lung disease have been reported with carfilzomib. Some of these events have been fatal. Hold carfilzomib until these events resolve; consider the benefits and risks when deciding if treatment should be re-initiated.

8. **Posterior Reversible Encephalopathy Syndrome (PRES)** cases have been reported with carfilzomib. Symptoms include seizure, headache, lethargy, confusion, blindness, altered consciousness, and/or other visual and neurological disturbances, along with hypertension. Hold treatment if suspected and evaluate by neuro-radiological imaging.
9. **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.
10. **Venous thrombosis/embolism: Aspirin 81mg** oral daily should be considered in all patients. For those with higher risk of thromboembolic disease full anti-coagulation should be considered.
11. **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.
12. **Constipation**: Patients should be warned that constipation may occur in patients taking lenalidomide.
13. **Fatigue**: Patients should be warned that lenalidomide may cause fatigue. Fatigue may respond to dose reduction.
14. **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.
15. **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.
16. **Live vaccines**: Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
17. **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. Stewart KA, Rajkumar V, Dimopoulos MA, et al. Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. N Engl J Med. 2015 Jan;372(2):142-152.
2. Amgen Canada Inc. KYPROLIS® product monograph. Mississauga, Ontario; 20 December 2016
3. Celgene REVLIMID® product monograph. Mississauga, Ontario; 9 December, 2016.
4. Biran N, Siegel D, Berdja J et al. Weekly carfilzomib, lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: A phase 1b study. Am J Hematol. 2019; 94: 794-802.
5. Richez V, Gruchet C, Guidez S et al. Carfilzomib weekly 20/56mg/m2, lenalidomide and dexamethasone for early relapsed refractory multiple myeloma. Am J Hematol 2019;94(1): E17-E20.
6. Georgiopoulos G, Makris N, Laina A, et al. Cardiovascular Toxicity of Proteasome Inhibitors: Underlying Mechanisms and Management Strategies: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncol. 2023 Feb 21;5(1):1-21.