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

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

ELIGIBILITY:

- For the treatment of multiple myeloma in patients who received at least one prior therapy.
- Patients must be sensitive to lenalidomide and bortezomib or not previously exposed.
- Life expectancy of greater than 3 months
- A BC Cancer "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:

- Prior progression on lenalidomide including maintenance lenalidomide post-auto-transplant.
- Prior exposure to carfilzomib
- Pregnant or lactating women
- Creatinine Clearance less than 30 mL/minute
- LVEF <40%
- Uncontrolled hypertension
- 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
- ALT greater than 3x upper limit of normal (ULN), bilirubin greater than 2x ULN
- Known hypersensitivity to lenalidomide or pomalidomide or thalidomide

TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, creatinine, sodium, potassium, urea, calcium, magnesium, phosphate, glucose, alkaline phosphatase, ALT, serum bilirubin, albumin total protein, uric acid, Blood Pressure measurement. 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): serum protein electrophoresis ***and/or*** serum free light chain levels, HBsAg, HBcoreAb, TSH
- Every 2 weeks (for lenalidomide) during the first 4 cycles then may reduce frequency to every four weeks: CBC and diff, platelets, creatinine, calcium
- Every three months (required for lenalidomide, but results do not have to be available to proceed with treatment): TSH
- Day 1: CBC, diff, platelets, creatinine, sodium, potassium, urea, calcium, magnesium, phosphate, glucose, alkaline phosphatase, ALT, serum bilirubin, albumin, total protein, uric acid, Blood Pressure measurement; if female of childbearing potential: pregnancy test (blood)
- Day 1(required, but results do not have to be available to proceed with treatment): serum protein electrophoresis ***and/or*** free light chain
- Cycle 1
    - Day 8 and 15: CBC, diff, platelets, creatinine, sodium, potassium, calcium, phosphate, glucose, uric acid
- Cycle 2 to 18
    - Day 15: CBC and diff, platelets, creatinine, sodium, potassium, calcium, phosphate, glucose, uric acid

PREMEDICATIONS/PREHYDRATION:

At least 24 hours prior to Cycle 1 Day 1, the following treatments should be started:

- Antiviral prophylaxis is recommended prior to initiating carfilzomib for patients who have a history of varicella zoster virus infection (chicken pox and shingles). Patients should take valACYclovir 500 mg PO daily while taking carfilzomib and for 4 weeks after its discontinuation.
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone
- Aspirin (enteric coated) PO daily continuing for the duration of treatment with lenalidomide

Dexamethasone

- 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.

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 daily on days 1, 8, 15 and 22 (Note: not given on days 2, 9 and 16)	PO, in the morning
lenalidomide	25 mg once daily for 21 days (d 1-21)	PO, in the evening may be preferred
carfilzomib*	CYCLE 1: 20 mg/m^2 on days 1 and 2 27 mg/m^2 on days 8, 9, 15 and 16 CYCLE 2-12: 27 mg/m^2 on days 1, 2, 8, 9, 15 and 16 CYCLE 13-18: 27 mg/m^2 on days 1, 2, 15 and 16 *(cap BSA at 2.2)	IV in 100 mL D5W over 10 minutes†

*Dose may vary dependent on tolerability and co-morbidities. For older patients i.e.,

75 y, the starting dose of dexamethasone should be 20 mg PO weekly

Cycle length is 28 days. After cycle 18 carfilzomib is discontinued but lenalidomide and dexamethasone are continued until disease progression or unacceptable toxicity

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

Vital signs prior to EACH carfilzomib infusion

For Cycle 1 only, observe patient for one hour following each carfilzomib infusion.

OTHER OPTIONS FOR STEROID DOSING

Option A: **Oral dexamethasone 20 mg daily on days 1, 8, 15 and 22**
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.

CARFILZOMIB DOSE MODIFICATIONS:

Recommended dose level reductions

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose level -3
carfilzomib	27 mg/m^2	20 mg/m^2	15 mg/m^2	Discontinue carfilzomib

1. Hematological:

ANC (x10^9/L)		Platelets (x10^9/L)	Carfilzomib Dose
Greater than or equal to 0.5	**and**	Greater than or equal to 10	Maintain dose level
Less than 0.5	**or**	If evidence of bleeding or platelets less than 10	Delay until ANC greater than or equal to 0.5 and platelets greater than or equal to 10* and then restart at same dose level
Reoccurrence of less than 0.5	**or**	Reoccurrence of less than 10	Delay until ANC greater than or equal to 0.5 and platelets greater than or equal to 10* and then consider decreasing by one dose level

*follow hematology weekly

2. Non-hematolgical:

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/m2 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

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.

1. **Hematological:**

Agent	**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**

ANC (x10^9/L)	**Platelets (x10^9/L)**	**Lenalidomide Dose**
Day 1 of Cycle less than 1.0	**Day 1 of Cycle** less than 30	Hold until ANC greater than or equal to 1.0 and platelets greater than or equal to 30† then consider dose reduction by 1 dose level* Carfilzomib start should also be delay when lenalidomide cycle is being delayed.
Day 15 of Cycle‡ less than 1.0	**Day 15 of Cycle‡** less than 30	Omit for remainder of cycle; restart on Day 1 of next cycle if ANC greater than or equal to 1.0 and platelets greater than or equal to 30; consider reducing by 1 dose level*

*if filgrastim (5 mcg/kg) is available resume at the same dose if delay due to ANC. Filgrastim is not covered as a benefit at the BC Cancer.
† follow hematology weekly
‡ 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. **Non-hematolgical:**

Renal dysfunction

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 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.

PRECAUTIONS:

1. **Infusion reactions** are common with carfilzomib. Premedication with dexamethasone, at least 30 minutes but no more than 4 hours, prior to carfilzomib has been reported to reduce the incidence and severity of these reactions. However, local experience has found premedication with dexamethasone may not be beneficial in reducing the incidence of infusion reactions. 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.
2. **Cardiac Toxicities:** New onset or worsening of pre-existing cardiac failure (e.g., pulmonary edema, decreased ejection fraction, congestive heart failure), QT prolongation, myocardial ischemia and infarction have been observed with carfilzomib. 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, or angina. 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**, 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. See CARFILZOMIB DOSE MODIFICATION SECTION.
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. **Hypothyoidism:** 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.
10. **Venous thrombosis/embolism: Aspirin 81mg** oral daily should be considered in all patients. For those with higher risk of thrombo-embolic 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 HBcoreAb. 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.

15. **VZV prophylaxis:** Antiviral prophylaxis is recommended prior to initiating carfilzomib for patients who are VZV seropositive. Patients should take valACYclovir 500 mg PO daily while taking carfilzomib and for 4 weeks after its discontinuation. Of note, VZV serology if often not reliable, even in patients previously exposed. Most clinicians choose to prescribe valACYclovir without testing for VZV serology.
16. **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.
17. **Live vaccines**: Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
18. **Need for irradiated blood products:** potentially life-threatening transfusion-related graft-versus-host-disease can occur in previously treated myeloma patients. Patients receiving carfilzomib for myeloma should receive irradiated blood products, effectively eliminating this risk.

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)

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.