BC Cancer Protocol Summary for Therapy of Multiple Myeloma using Carfilzomib and Dexamethasone With or Without Cyclophosphamide

Protocol Code	*MYCARDEX*
Tumour Group	*Myeloma*
Contact Physician	*Dr. Christopher Venner*

ELIGIBILITY:

Patients must have:

- Relapsed/refractory multiple myeloma, and
- Received at least one prior therapy.

Note:

- Physician may add cyclophosphamide to increase response.

EXCLUSIONS:

Patients must not:

- Have prior refractoriness to carfilzomib*, or
- Be pregnant or lactating

*does not include patients previously exposed or refractory to bortezomib and ixazomib

CAUTIONS:

- CrCl less than 15 mL/minute (monitor renal function closely in patients with CrCl less than 30 mL/min)
- History of congestive heart failure
- Uncontrolled hypertension
- 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

TESTS:

- Baseline (required before first treatment): CBC & Diff, platelets, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, phosphate, LDH, random glucose
- 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, 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
- 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

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. 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
- 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
carfilzomib**	**CYCLE 1:** 20 mg/m^2 on Day 1 then 70 mg/m^2 on Days 8 and 15 **CYCLE 2-onward:** 70 mg/m^2 on Days 1, 8, 15 ** (cap BSA at 2.2)	IV in 100 mL D5W over 30 minutes†
<u>If using</u>: 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. 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

Repeat every 28 days until disease progression or unacceptable toxicity

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 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

- 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.

CARFILZOMIB DOSE MODIFICATIONS:

Recommended dose level reductions

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose level -3	Dose level -4
carfilzomib	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2	27mg/m^2

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 and differential, 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**	**Cyclophosphamide Dose (if using)**
Greater than or equal to 0.5	and	Greater than or equal to 50	Maintain dose level	100%
Greater than or equal to 0.5	and	30 to 49	Notify provider. Proceed but consider dose reduction by one dose level for low platelets.	Delay until recovery
Less than 0.5†	or	Less than 30*	May proceed but consider decrease by one dose level if felt to be treatment related.	
Reoccurrence of less than 0.5†	or	Reoccurrence of less than 30*	For recurrence 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:

Toxicity	Carfilzomib Dose
Renal*: Serum creatinine equal to or greater than 2 × baseline, or Creatinine clearance less than 15 mL/min	Delay and decrease by one dose level when renal function has recovered to within 25% of baseline; dose may be escalated to previous dose at physician's discretion
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

*for patients receiving dialysis carfilzomib should be administered after the dialysis procedure

Non-hematological: cyclophosphamide

- Hepatic impairment: no dose reduction is necessary.
- Renal failure: 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)

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 clinical 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, have been reported in multiple myeloma patients treated with carfilzomib. Hold treatment upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose of 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. **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.
10. **Live vaccines**: Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
11. **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. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. The Lancet Oncology 2016;17(1):27-38.
2. Boccia RV, Bessudo A, Agajanian R, et al. A multicenter, open-label, phase 1b study of carfilzomib, cyclophosphamide and dexamethasone in newly diagnosed multiple myeloma patients (CHAMPION-2). Clin Lymphoma Myeloma and Leuk 2017;17(7):433-37
3. Bringhen S, Petrucci MT, Larocca A, et al. Carfilzomib, cyclophosphamide and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood 2014;124(1):63-9
4. Amgen Canada Inc. KYPROLIS® product monograph. Mississauga, Ontario; 20 December 2016.
5. Moreau P, Mateos MV, Berenson J et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. The Lancet Oncology 2018; 19: 953-64.
6. Dimopoulos M, Sonneveld P, Leung N et al. International Myeloma Working Group Recommendations for the diagnosis and Management of Myeloma-Related Renal Impairment. J Clin Oncol 2016; 34 (13): 1544-57
7. 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.