

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

Protocol Code

MYCARDEX

Tumour Group

Lymphoma, Leukemia/BMT

Contact Physician

Dr. Christopher Venner

ELIGIBILITY:

Patients must have:

- Relapsed/refractory multiple myeloma and have received at least one prior therapy. Physician may add cyclophosphamide to increase response.
- Life expectancy of greater than 3 months and

EXCLUSIONS:

Patients must not:

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

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

CAUTION:

- Creatinine Clearance less than 15 mL/minute (monitor renal function closely in patients with CrCl less than 30 mL/min)
- LVEF less than 40%
- Uncontrolled hypertension
- Platelet count less than 30×10^9 /L
- Absolute neutrophil count (ANC) less than 1.0×10^9 /L. Consider giving filgrastim.
- ALT greater than 3x upper limit of normal (ULN), bilirubin greater than 2 x ULN

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, MUGA, Blood Pressure measurement,
- 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
- Day 1: CBC and diff, platelets, creatinine, sodium, potassium, urea, calcium, magnesium, phosphate, glucose, alkaline phosphatase, ALT, serum bilirubin, albumin, total protein, uric acid, Blood Pressure measurement
- Day 1: (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis **and** serum free light chains
- Day 1 (optional, results do not have to be available to proceed with treatment): immunoglobulin panel (IgA, IgG, IgM), urine protein electrophoresis
- Day 8 (for cycle 1 only) and Day 15: CBC and diff, platelets, creatinine, sodium, potassium, calcium, phosphate, glucose, uric acid

PREMEDICATIONS/PREHYDRATION:

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 H₂ antagonist for the duration of treatment with dexamethasone may be considered

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 weekly on Days 1, 8,15 and 22	PO, in the morning
carfilzomib*	<p>CYCLE 1: 20 mg/m² on Day 1 then 70 mg/m² on Days 8 and 15</p> <p>CYCLE 2-onward: 70 mg/m² on Days 1, 8, 15 *(cap BSA at 2.2)</p>	IV in 100 mL D5W over 30 minutes†
<u>If using:</u> cyclophosphamide	300 mg/m ² /day weekly on Days 1, 8, 15 (round to nearest 25 mg)	PO

Repeat every 28 days until disease progression or unacceptable toxicity

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

*Dose may vary dependent on tolerability and co-morbidities. For older patients i.e. 75 years old, the starting dose of dexamethasone should be 20 mg PO weekly

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:

Dexamethasone 20 mg PO once weekly (or dexamethasone 4 - 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 – 100 mg 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.

CARFILZOMIB DOSE MODIFICATIONS:

Recommended dose level reductions

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose level -3	Dose level -4	Dose level -5
carfilzomib	70 mg/m ²	56 mg/m ²	45 mg/m ²	36 mg/m ²	27mg/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	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

For Cyclophosphamide (If using) lab on Day 1 only

ANC (x10 ⁹ /L)	Platelets (x10 ⁹ /L)	Dose (cyclophosphamide)
greater than 1.0	greater than 80	100%
less than or equal to 1.0	less than or equal to 80	Consider delay until recovery checking CBC weekly

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

For Cyclophosphamide, no dose reduction is necessary for hepatic impairment.

For Cyclophosphamide, dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis. Physician may consider giving full dose of cyclophosphamide irrespective of renal function if deemed to be of benefit.

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

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

Serum Creatinine (micromols/L)

N = 1.04 (Females) and 1.23 (Males)

PRECAUTIONS:

- 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 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**, 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. See CARFILZOMIB DOSE MODIFICATION SECTION.
7. **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.
8. **Venous thrombosis/embolism:** Carfilzomib with dexamethasone is known to increase the risk for thromboembolic disease. Thromboprophylaxis is recommended; **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.
9. **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.

10. **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 is often not reliable, even in patients previously exposed. Most clinicians choose to prescribe valACYclovir without testing for VZV serology.
11. **Live vaccines:** Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
12. **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 (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. 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