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

Protocol Code  UMYCARDEX
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. Physician may add cyclophosphamide to increase response.
- 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

EXCLUSIONS:
- Prior exposure to carfilzomib
- Refractory to bortezomib
- Pregnant or lactating women
- Creatinine Clearance less than 15 mL/minute
- LVEF <40%
- Uncontrolled hypertension
- Platelet count less than $30 \times 10^9/L$ may be considered a relative contraindication
- Absolute neutrophil count (ANC) less than $1.0 \times 10^9/L$ may be considered a relative contraindication. Consider giving filgrastim
- ALT greater than 3x upper limit of normal (ULN), bilirubin greater than 2x ULN
TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, creatinine, electrolytes (including potassium), urea, calcium, magnesium, phosphate, glucose, alkaline phosphatase, ALT, serum bilirubin, albumin, total protein, uric acid, Blood Pressure measurement.
- 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 (if indicated), HBsAg, HBcoreAb
- Day 1, and 15: CBC and diff, platelets
- Day 1: Creatinine, electrolytes (including 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/or free light chain (if clinically indicated)
- Cycle 1
  - Day 8 and 15: CBC and diff, platelets, creatinine, electrolytes (including potassium), calcium, phosphate, glucose, uric acid
- Cycle 2 and beyond
  - Day 15: Creatinine, electrolytes (including 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.

Premedicate with dexamethasone on days when dexamethasone and carfilzomib are given the same day as part of the treatment regimen i.e., when dexamethasone 20 mg is given on days 1, 2, 8, 9, 15 and 16 it should be administered 30 minutes to 4 hours before carfilzomib. Of note, if dexamethasone is not given as part of the treatment regimen, premedication with dexamethasone is not necessary but 4 mg PO or IV administered 30 minutes to 4 hours before carfilzomib may be given if deemed necessary by the clinician.

**Cycle 1:** 250 mL NS IV over 30 minutes prior to carfilzomib.

**Subsequent cycles:** optional IV prehydration
**TREATMENT:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>dexamethasone</td>
<td>20 mg once daily on days 1, 2, 8, 9, 15, 16, 22 and 23</td>
<td>PO, in the morning may be preferred, at least 30 minutes but no more than 4 hours prior to carfilzomib</td>
</tr>
<tr>
<td>carfilzomib*</td>
<td><strong>CYCLE 1:</strong> 20 mg/m² on days 1 and 2 and if tolerated escalate to 56 mg/m² on days 8, 9, 15 and 16&lt;br&gt;&lt;br&gt;<strong>CYCLE 2-onward:</strong> 56 mg/m² on days 1, 2, 8, 9, 15 and 16&lt;br&gt;&lt;br&gt;* (cap BSA at 2.2)</td>
<td>IV in 100 mL D5W over 30 minutes†</td>
</tr>
<tr>
<td>If using:</td>
<td>cyclophosphamide</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>300 mg/m²/day on days 1, 8, 15 (round to nearest 25 mg)</td>
<td></td>
</tr>
</tbody>
</table>

Repeat every 28 days 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.
### CARFILZOMIB DOSE MODIFICATIONS:

**Recommended dose level reductions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Level 0</th>
<th>Dose Level -1</th>
<th>Dose Level -2</th>
<th>Dose level -3</th>
<th>Dose level -4</th>
</tr>
</thead>
<tbody>
<tr>
<td>carfilzomib</td>
<td>56 mg/m²</td>
<td>45 mg/m²</td>
<td>36 mg/m²</td>
<td>27 mg/m²</td>
<td>Discontinue carfilzomib</td>
</tr>
</tbody>
</table>

1. **Hematological:**

<table>
<thead>
<tr>
<th>ANC (x10⁹/L)</th>
<th>Platelets (x10⁹/L)</th>
<th>Carfilzomib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 0.5 and Greater than or equal to 10</td>
<td>Maintain dose level</td>
<td></td>
</tr>
<tr>
<td>Less than 0.5 or Less than 10</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Reoccurrence of less than 0.5 or Reoccurrence of less than 0.5</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

*follow hematology weekly*
For Cyclophosphamide (if using) lab on day 1 only

<table>
<thead>
<tr>
<th>ANC (x10⁹/L)</th>
<th>Platelets (x10⁹/L)</th>
<th>Dose (cyclophosphamide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than 1.0</td>
<td>greater than 80</td>
<td>100%</td>
</tr>
<tr>
<td>less than or equal to 1.0</td>
<td>less than or equal to 80</td>
<td>Consider delay until recovery checking CBC weekly</td>
</tr>
</tbody>
</table>

2. Non-hematological:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Carfilzomib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal</strong>: Serum creatinine equal to or greater than 2 × baseline, or Creatinine clearance less than 15 mL/min</td>
<td>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</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td>Delay and if ANC returns to baseline grade and fever resolves, resume at same dose level</td>
</tr>
<tr>
<td>Any Grade 3 or 4 non-hematological toxicity</td>
<td>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</td>
</tr>
</tbody>
</table>

*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.

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Cyclophosphamide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 10</td>
<td>100 %</td>
</tr>
<tr>
<td>Less than 10</td>
<td>75 %</td>
</tr>
</tbody>
</table>

Calculated creatinine clearance = N x (140 – Age) x weight (kg) / Serum Creatinine (micromols/L)

N = 1.04 (Females) and 1.23 (Males)
PRECAUTIONS:

1. **Infusion reactions** are common with carfilzomib. Premedication with dexamethasone, at least 30 minutes but no more than 4 hours, prior to carfilzomib reduces the incidence and severity of these 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;
the choice of antithrombotic agent should be based on patient’s underlying risk and clinical status. Or do we want to be more specific and state? **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/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.

10. **Live vaccines:** Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.

11. **Need for irradiated blood products:** potentially life-threatening transfusion-related graft-versus-host-disease can occur in previously treated myeloma patients. Patients receiving Bortezomib 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: