BC Cancer Protocol Summary for the Treatment of Multiple Myeloma using Bortezomib, Dexamethasone With or Without Cyclophosphamide as Induction Pre-Stem Cell Transplant

Protocol Code	*MYBORPRE*
Tumour Group	*Myeloma*
Contact Physicians	*Dr. Kevin Song* *Dr. Christopher Venner*

ELIGIBILITY:

Patients must:

- Have previously untreated multiple myeloma or amyloid light (AL) chain amyloidosis, and
- Be eligible for autologous stem cell transplant (ASCT)

Notes:

- A referral to the Leukemia/BMT Program of BC must be made for consideration of transplant at the start of the first cycle.
- To maximize stem cell collection efficiency and minimize the risk of collection failure:
    - The last dose of bortezomib and cyclophosphamide should be given at least 14 days prior to stem cell collection
- The addition of cyclophosphamide will increase response and should be used when possible

EXCLUSIONS:

- None

CAUTIONS:

- Platelet count less than 30 x 10^9/L
- ANC less than 0.5 x 10^9/L may require giving filgrastim

TESTS:

- Baseline (required before first treatment): CBC & Diff, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, 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, HBsAb, HBcoreAb, beta-2 microglobulin
- Prior to each cycle (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and serum free light chain levels

- Prior to each cycle (optional, results not mandatory but encouraged prior to each cycle): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM), beta-2 microglobulin
- Prior to each cycle: CBC & Diff, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, 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, random glucose
- If clinically indicated: HBV viral load (see protocol SCHBV)

PREMEDICATIONS:
None

SUPPORTIVE MEDICATIONS:
- High risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating bortezomib. Patients should take valACYclovir 500 mg PO daily
- Routine anti-emetic or anti-diarrheal premedication is not required. These symptoms should be managed symptomatically if they arise
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone or prednisone may be considered

RECOMMENDED TREATMENT:

- The once weekly bortezomib treatment option is preferred over the twice weekly bortezomib treatment option
- Duration of treatment: up to 6 cycles. For further treatment, "Compassionate Access Program" request is required.

ONCE WEEKLY TREATMENT: cycle length 28 days

Drug	Dose	BC Cancer Administration Guideline
bortezomib	1.5 mg/m^2 (may start with 1.3 mg/m^2) on Days 1, 8, 15, 22 of each cycle	Subcutaneously (abdomen or thigh)*
If using: 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
dexamethasone	40 mg** once daily on Days 1, 8, 15 and 22	PO, in the morning with food

* Back of the arm can also be considered as a third option, after abdomen or thigh

** Dexamethasone dose may vary dependent on tolerability and co-morbidities. See also: Other options for steroid dosing, below

TWICE WEEKLY OPTION: cycle length 21 days

Drug	Dose	BC Cancer Administration Guideline
bortezomib*	1.3 mg/m^2 on Days 1, 4, 8, 11 of each cycle (+/- one day maintaining at least 72 h between doses)	Subcutaneously (abdomen or thigh)**
If using: cyclophosphamide	500 mg once weekly on Days 1, 8, and 15 *OR* 50 mg once every 2 days	PO, in the morning may be preferred
dexamethasone	40 mg*** once daily on Days 1, 4, 8, 11 (same days as bortezomib is given)	PO, in the morning with food

* bortezomib 1.5 mg/m^2 cannot be given with the twice weekly bortezomib regimen. This escalated dose can only be given with the weekly bortezomib regimen.

** Back of the arm can also be considered as a third option, after abdomen or thigh

*** Dexamethasone dose may vary dependent on tolerability and co-morbidities. See also: Other options for steroid dosing, below

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 or 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 without high-dose steroids. High-dose steroids may be added for non-response.

DOSE MODIFICATIONS:

- **Bortezomib dose levels:**

Dose level 0	Dose level -1	Dose level -2	Dose level -3	Dose level -4
1.5 mg/m^2	1.3 mg/m^2	1 mg/m^2	0.7 mg/m^2	0.5 mg/m^2

1. Hematological: (based on pre-cycle labwork)

ANC ($x10^9$/L) On Day 1		**Platelets ($x10^9$/L)** On Day 1	**Bortezomib Dose**	**Cyclophosphamide Dose (if using)**
Greater than or equal to 0.5	and	Greater than or equal to 50	100%	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 decrease by one dose level if felt to be treatment-related.	
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. Peripheral Neuropathy:

Severity of Peripheral Neuropathy Signs and Symptoms	Bortezomib Dose
Grade 1 (paresthesia and/or loss of reflexes) without pain or loss of function	100%
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 1.3 mg/m^2 (for once weekly dosing) or 1 mg/m^2 (for twice weekly dosing)
Grade 2 with pain or Grade 3 (interfering with activities of daily living	Delay until recovery. When resolved, reduce dose to 1 mg/m^2 weekly x 2 doses q 21 days (for once weekly dosing) or 0.7 mg/m^2 weekly x 2 doses q 21 days (for twice weekly dosing)
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

3. Hepatic Impairment:

<table>
<tr><th></th><th>Total bilirubin</th><th>ALT or AST</th><th>Bortezomib Dose</th><th>Cyclophosphamide Dose (if using)</th></tr>
<tr><td rowspan="2">Mild</td><td>less than or equal to 1 x upper limit of normal</td><td>greater than the upper limit of normal</td><td>100%</td><td rowspan="4">100%</td></tr>
<tr><td>greater than 1 to 1.5 x upper limit of normal</td><td>Any</td><td>100%</td></tr>
<tr><td>Moderate</td><td>greater than 1.5 to 3 x upper limit of normal</td><td>Any</td><td rowspan="2">▪ Reduce dose to 0.7 mg/m^2 in the first cycle.
▪ Consider dose escalation to 1 mg/m^2 <u>or</u> further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.</td></tr>
<tr><td>Severe</td><td>greater than 3 x upper limit of normal</td><td>Any</td></tr>
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4. Renal Failure:

- For bortezomib, no dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis.
- For cyclophosphamide, dose reduction is necessary per table, below. 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 = $\frac{N \times (140 - Age) \times weight\ (kg)}{Serum\ Creatinine\ (micromols/L)}$

N = 1.04 (Females) and 1.23 (Males)

5. Diarrhea

Diarrhea grading system

Grade 1	Grade 2	Grade 3	Grade 4
Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; IV fluids indicated for less than 24 hrs; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of greater than 7 stools per day over baseline; incontinence; IV fluids for greater than 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)

Treatment of Diarrhea during cycle		
At first loose stool:	Start loperamide 2 mg po q 2 h while awake and q 4 h while sleeping. Continue around the clock until 12 h diarrhea free	• If diarrhea free greater than 12 h, stop loperamide. If new episode, retreat with loperamide. • If grade 3 diarrhea or diarrhea accompanied by mucus or dehydration, hold doses of bortezomib (if applicable) and hydrate.

Diarrhea management: Next Cycle Dosing Delay next cycle until diarrhea has resolved (less than 2 watery bowel movements / day)	
Severity of diarrhea with last cycle:	Bortezomib dose this cycle
less than or equal to grade 2	no change from previous cycle
greater than or equal to grade 3 or associated with mucus or dehydration	Reduce dose to 80% of that used in the last course or consider once a week dosing. (if two dose reductions have already occurred further treatment with bortezomib must be individualised and should only continue if a clearly useful clinical response in the myeloma has occurred)

PRECAUTIONS:

1. Neutropenia: fever or other evidence of infection must be assessed promptly and treated aggressively.

2. 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.

3. Green tea avoidance: Some of the components in green tea and preparations made from green tea block the activity of bortezomib in in vitro experiments. Green tea or preparations made from green tea should be avoided by patients taking bortezomib.

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

5. Hepatitis B Reactivation: See SCHBV protocol for more details.

6. **Peripheral Neuropathy:** occurs in 36–37% of patients receiving IV bortezomib with 8–14% resulting in grade 3–4 severity of symptoms. This is a common and often dose limiting side effect. Administration of bortezomib via the subcutaneous route instead of IV push significantly reduces the occurrence of peripheral neuropathy.

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.

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