BC Cancer Protocol Summary for the Treatment of Multiple Myeloma using Melphalan, predniSONE and Weekly Bortezomib With the Option of Substituting Cyclophosphamide for Melphalan

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

ELIGIBILITY:

Patients must:

- Have previously untreated multiple myeloma or light (AL) chain amyloidosis, and
- Be ineligible for stem cell transplantation

Note:

- Physician may substitute cyclophosphamide for melphalan to reduce myelosupression.

EXCLUSIONS:

- None

CAUTIONS:

- Platelet count less than 30 x 10^9/L
- ANC less than 0.5 x 10^9/L may require 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
- Before Day 1 (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and serum free light chain levels
- Before Day 1 (optional, results not mandatory but encouraged prior to each cycle): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM), beta-2 microglobulin
- Before Day 1: 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, 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
- No premedication required for melphalan and predniSONE
- Routine anti-emetic or anti-diarrheal premedication for bortezomib 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

TREATMENT: cycle length 35 days (i.e., 5 weeks)

Duration of treatment: up to a maximum of 9 cycles. For further treatment, "Compassionate Access Program" request is required.

Drug	Cycle	Dose	BC Cancer Administration Guideline
bortezomib	1 to 9	1.3 mg/m^2 on Days 1, 8, 15 and 22 of each cycle (+/- one day maintaining at least 72 h between doses)	Subcutaneously (abdomen or thigh)*
melphalan	1 to 9	9 mg/m^2/day on Days 1 to 4**	PO
predniSONE	1 to 9	60 mg/m^2/day*** on Days 1 to 4	PO

*back of the arm can also be considered as a third option, after abdomen or thigh
**Round dose to nearest 2 mg
*** predniSONE dose may vary dependent on tolerability and co-morbidities. See also: Other options for steroid dosing, below

Drug	Dose	BC Cancer Administration Guideline
<u>If substituting cyclophosphamide for melphalan</u>: cyclophosphamide	500 mg once weekly on Days 1, 8, 15, 22 and 29 *OR* 50 mg once every 2 days	PO, in the morning may be preferred
predniSONE†	100 mg*** once every 2 days for 2 cycles then 50 mg once every 2 days	PO, in the morning with food

*** predniSONE dose may vary dependent on tolerability and co-morbidities. See also: Other options for steroid dosing, below
† Round dose to nearest 25 mg, available in 50 mg and 5 mg tablets

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
1.3 mg/m^2	1 mg/m^2	0.7 mg/m^2	0.5 mg/m^2

1. Hematological:

For bortezomib and cyclophosphamide (if using). 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. 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.

For melphalan (if using). Based on pre-cycle labwork.

ANC (x10^9/L) On Day 1	**Platelets (x10^9/L)** On Day 1	**Melphalan Dose (if using)**
Greater than or equal to 3.0	Greater than or equal to 200	Increase by 2 mg/day
1.0 to less than 3.0	Greater than or equal to 100	100% of previous dose
Less than 1.0†	Less than 100	Check CBC & diff weekly, resume treatment when ANC is greater than 1.0 and platelets return to baseline. If after 5 weeks ANC is still less than 1.0 or platelets less than 100, reduce dose of melphalan to 75 %

† Consider weekly filgrastim if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer.

2. Peripheral Neuropathy: Bortezomib

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 mg/m^2, or consider dropping Day 22 dose of bortezomib
Grade 2 with pain or Grade 3 (interfering with activities of daily living	Delay until recovery. When resolved, reduce dose to 0.7 mg/m^2, or drop Day 8 and Day 22 dose.
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

3. Hepatic Impairment:

	Total bilirubin	ALT or AST	Bortezomib Dose	Cyclophosphamide or Melphalan Dose (if using)
Mild	less than or equal to 1.0 x upper limit of normal	greater than the upper limit of normal	100%	100 %
	greater than 1.0-1.5 x upper limit of normal	Any	100%	
Moderate	greater than 1.5-3 x upper limit of normal	Any	▪ Reduce dose to 0.7 mg/m^2 in the first cycle. ▪ Consider dose escalation to 1 mg/m^2 *or* further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.	
Severe	greater than 3 x upper limit of normal	Any		

4. Renal dysfunction:

- For bortezomib, no dose reduction is necessary. For patients on hemodialysis, give dose after dialysis.
- For cyclophosphamide (If substituting for melphalan), 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.
- For melphalan, dose modification is necessary per table, below.

Creatinine clearance (mL/min)	Melphalan Dose (if using)	Cyclophosphamide Dose (if using)
Greater than 50	100 %	100%
10 to 50	75 %	
Less than 10	50 %	75%

5. Diarrhea: for Bortezomib

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 – 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 (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.

References:

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