

BCCA Protocol Summary for the Treatment of Relapsed Multiple Myeloma using Bortezomib, Dexamethasone With or Without Cyclophosphamide

Protocol Code	<i>UMYBORREL</i>
Tumour Group	<i>Lymphoma, Leukemia/BMT</i>
Contact Physician	<i>Dr. Kevin Song</i>

ELIGIBILITY:

- For the treatment of multiple myeloma in patients who received at least one prior therapy. Physician may add cyclophosphamide to increase response.
- A BC Cancer Agency “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment

EXCLUSIONS:

- Platelet count less than $30 \times 10^9/L$ may require transfusion support
- If absolute neutrophil count (ANC) less than $0.5 \times 10^9/L$ may require giving filgrastim

TESTS:

- Baseline: CBC, differential, platelets, creatinine, AST, serum bilirubin
- Baseline (required, but results do not have to be available to proceed with first treatment): calcium, serum protein electrophoresis, HBsAg, HBcoreAntibody, if not previously documented
- Before day 1 (**for bortezomib and cyclophosphamide if using**): CBC, differential, platelets, creatinine, AST, serum bilirubin
- Before day 1 (required, but results do not have to be available to proceed with treatment) calcium, serum protein electrophoresis
- Before day 11 (**for bortezomib only, in twice weekly dosing**): If the patient’s platelet count on day 1 is less than $100 \times 10^9/L$, the platelet count should be checked on day 11 and transfusion may be required in platelets less than $20 \times 10^9/L$ on day 11. Platelet levels can improve over subsequent cycles if the myeloma is responsive.
- Before day 8, 15, 22 (**for bortezomib only, in weekly dosing**): CBC

PREMEDICATIONS:

- Routine anti-emetic or anti-diarrheal premedication is not required. These symptoms should be managed symptomatically if they arise.
- Bortezomib is associated with approximately a 10% risk of H. zoster infection (shingles). Patients should take valacyclovir 500 mg PO daily while taking bortezomib and for 4 weeks after its discontinuation (Chanan-Kahn, Analysis of Herpes zoster events among bortezomib-treated patients. *J Clin Oncol* 2008;26:4784-90)

RECOMMENDED TREATMENT:

TWICE WEEKLY TREATMENT OPTION: cycle length 21 days

Duration of treatment: up to a maximum of 8 cycles. For further treatment, another "Compassionate Access Program" request is required.

Drug	Dose	BCCA 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)	SC [*] , ^{**} (abdomen or thigh) ^{***} OR IV push over 3-5 seconds
<u>If using:</u> Cyclophosphamide	300 mg/m ² /day on days 1, 8, 15 ^{****}	PO
Dexamethasone	40 mg on days 1, 4, 8, 11 of each cycle	PO, in the morning may be preferred

*Subcutaneous administration of bortezomib significantly reduces the occurrence of peripheral neuropathy; since it is a hazardous drug, it should only be administered by chemotherapy certified nurses at centres equipped to prepare and handle hazardous (cytotoxic) drugs

**Bortezomib dilution for both the SC and the IV administration is the same and results in a 1 mg/mL concentration

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

****Round dose to nearest 25 mg

ONCE WEEKLY TREATMENT OPTION: cycle length 35 days

Drug	Dose	BCCA Administration Guideline
Bortezomib	1.3 mg/m ² (may start with 1.5 mg/m ²) on days 1, 8, 15, 22 of each cycle	SC [*] , ^{**} (abdomen or thigh) ^{***} OR IV push over 3-5 seconds
<u>If using:</u> Cyclophosphamide	300 mg/m ² /day on days 1, 8, 15, 22, 29 ^{****}	PO
Dexamethasone	40 mg on days 1, 8, 15, 22 of each cycle	PO, in the morning may be preferred

*Subcutaneous administration of bortezomib significantly reduces the occurrence of peripheral neuropathy; since it is a hazardous drug, it should only be administered by chemotherapy certified nurses at centres equipped to prepare and handle hazardous (cytotoxic) drugs

**Bortezomib dilution for both the SC and the IV administration is the same and results in a 1 mg/mL concentration

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

****Round dose to nearest 25 mg

Other Steroid Schedules can be used, dose should be adjusted based upon toxicity and patient tolerance. Some examples included below:

<p>Option A: Oral dexamethasone 20 mg daily on days when bortezomib is being given</p>
<p>Option B: Prednisone may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance</p>
<p>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 bortezomib alone. Dexamethasone may be added for non-response</p>

DOSE MODIFICATIONS:

1. Hematological:

ANC (x10 ⁹ /L)	Platelets (x10 ⁹ /L)	Bortezomib Dose
greater than or equal to 0.5	And greater than or equal to 30	100%
less than 0.5	Or less than 30	Consider delay until recovery checking CBC weekly; reduce dose to 1 mg/m ² or consider once a week dosing (see above) at the same dose
reoccurrence of less than 0.5	reoccurrence of less than 30	Consider delay until recovery checking CBC weekly; further reduce dose to 0.7 mg/m ² or consider once a week dosing (see above) at the same dose

For Cyclophosphamide (If using) lab on day 1 only

ANC (x10 ⁹ /L)	Platelets (x10 ⁹ /L)	Dose (cyclophosphamide)
greater than 1	greater than 80	100%
less than or equal to 1	less than or equal to 80	perform weekly CBC until recovery

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 mg/m ²
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 weekly x 2 doses q 21 days or consider once weekly dosing (see above)
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

3. Hepatic Impairment:

	Bilirubin	AST	Bortezomib Dose
Mild	less than or equal to 1 x upper limit of normal	greater than the upper limit of normal	100%
	greater than 1 – 1.5 x upper limit of normal	Any	100%
Moderate	greater than 1.5-3 x upper limit of normal	Any	<ul style="list-style-type: none"> ▪ Reduce dose to 0.7 mg/m² in the first cycle. ▪ Consider dose escalation to 1.0 mg/m² <u>or</u> further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.
Severe	greater than 3 x upper limit of normal	Any	

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

4. Renal Failure:

For Bortezomib, no dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis.

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

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

N = 1.04 (Females) and 1.23 (Males)

PRECAUTIONS:

1. **Neutropenia:** fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **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.
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. 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 – 6 stools per day over baseline; IV fluids indicated for less than 24hrs; 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	<ul style="list-style-type: none"> • If <u>diarrhea free greater than 12 h</u>, stop loperamide. If new episode, retreat with loperamide. • If <u>grade 3 diarrhea</u> or diarrhea accompanied by <u>mucus or dehydration</u>, <u>hold doses of Bortezomib</u> (if applicable) and hydrate.
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Diarrhea management: Next Cycle Dosing

Delay next cycle until diarrhea has resolved (less than 2 watery bowel movements / day)

Severity of diarrhea with <u>last</u> cycle:	Bortezomib dose <u>this</u> 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)

5. **Live vaccines:** Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
6. **Hepatitis B Reactivation:** All lymphoma/myeloma patients should be tested for both HBsAg and HBcoreAntibody. 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.
7. **H. zoster (shingles) prophylaxis:** Bortezomib is associated with ~10% risk of H. zoster infection (shingles). Patients should take valacyclovir 500 mg PO daily while taking bortezomib and for 4 weeks after its discontinuation (Chanan-Kahn, Analysis of Herpes zoster events among bortezomib-treated patients. J Clin Oncol 2008;26:4784-90)
8. **Platelet counts:** If the patient's platelet count on day 1 is less than $100 \times 10^9/L$, the platelet count should be checked on day 11 and that day's dose should be omitted if the platelet count is less than $30 \times 10^9/L$ on day 11.
9. **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. 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)

Date activated:	1 Oct 2010 (replacing UMYBORTEZ)
Date revised:	1 July 2011 (include subcutaneous route of administration for bortezomib) 1 December 2011 (formatting, bortezomib sc site of administration and protocol contact information)

References:

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