BC Cancer Protocol Summary for the Treatment of Relapsed Multiple Myeloma Using Bortezomib, Dexamethasone With or Without Cyclophosphamide

Protocol Code	*MYBORREL*
Tumour Group	*Lymphoma, Leukemia/BMT*
Contact Physician	*Dr. Kevin Song*

ELIGIBILITY:

- For the treatment of multiple myeloma or light (AL) chain amyloidosis in patients who received at least one prior therapy. Physician may add cyclophosphamide to increase response.
- Re-treatment appropriate if disease progression occurs at least one month after the completion of bortezomib treatment. Evidence of disease progression should be documented.

EXCLUSIONS:

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

TESTS:

- Baseline: CBC, differential, platelets, creatinine, serum bilirubin, ALT
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): calcium, serum protein electrophoresis ***and/or*** serum free light chain levels, beta-2-microglobulin, HBsAg, HBcoreAntibody, if not previously documented
- Before day 1(**for bortezomib and cyclophosphamide if using**): CBC, differential, platelets, creatinine, ALT, serum bilirubin
- Before day 1 (required, but results do not have to be available to proceed with treatment) calcium, serum protein electrophoresis ***and/or*** serum free light chain levels
- If CBC prior to day 1 show ANC less than 1.5 x 10^9/L or platelets less than 100 x 10^9/L, then:
  - Before day 8, 15, 22 (**for bortezomib only, in weekly dosing**): CBC, differential
  - Before day 11 (**for bortezomib only, in twice weekly dosing**): CBC, differential

PREMEDICATIONS:

- Routine anti-emetic or anti-diarrheal premedication is not required. These symptoms should be managed symptomatically if they arise.
- Antiviral prophylaxis is recommended prior to initiating bortezomib for patients who have a history of varicella zoster virus (VZV) infection (chicken pox and shingles). Patients should take valACYclovir 500 mg PO daily while taking bortezomib and for 4 weeks after its discontinuation.

Activated: 1 Oct 2010 (replacing UMYBORTEZ) Revised: 1 Mar 2021 (clarified cyclophosphamide dosing in renal dysfunction, updated references)

SUPPORTIVE MEDICATIONS:
If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the 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.

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: 8 cycles, see ELIGIBILTY for re-treatment

ONCE WEEKLY TREATMENT OPTION: cycle length 35 days

Drug	**Dose**	**BC CANCER 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)*
<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, 29 of each cycle	PO, in the morning may be preferred

* Back of the arm can also be considered as a third option, after abdomen or thigh
**Round dose to nearest 25 mg

TWICE WEEKLY TREATMENT 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)	SC (abdomen or thigh)**
If using: 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

* Bortezomib 1.5mg/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
***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:

Option A: Oral dexamethasone 20 mg daily on days 1, 8, 15, 22, 29 of each cycle
Option B: predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance (e.g. 100 mg PO on alternate days or 50 mg PO on alternate days)
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

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 (<u>If using</u>) lab on <u>day 1 only</u>

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

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	ALT or 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	▪ 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	

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.

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

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:** 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. **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	• 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 individualized 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 HBcoreAb. If either test is positive, such patients should be treated with lamiVUDine during 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 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. **VZV prophylaxis:** Antiviral prophylaxis is recommended prior to initiating bortezomib for patients who are VZV seropositive. Patients should take valACYclovir 500 mg PO daily while taking bortezomib and for 4 weeks after its discontinuation. Of note, VZV serology if often not reliable, even in patients previously exposed. Most clinicians choose to prescribe valACYclovir without testing for VZV serology.

8. **Platelet counts:** If the patient's platelet count on day 1 is less than 100 $x10^9$/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 x 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)

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