BC Cancer Protocol Summary for the Maintenance Therapy of Multiple Myeloma Using Bortezomib for Patients with the High-Risk Chromosome Abnormality

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

ELIGIBILITY:

- Maintenance treatment for patients with newly diagnosed multiple myeloma, following autologous stem cell transplant
- Confirmed chromosomal abnormalities of del 17p or t(4;14) and physician preference
- Minimum of stable disease post- transplant
- 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
- NB: patients progressing on MYBORMTN will still be eligible for MYBORREL as per physician preference and CAP approval. The relapse protocol is more intensive and therefore patients may still respond

EXCLUSIONS:

- none

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, HBsAg, HBcoreAntibody, if not previously documented
- Before Day 1 and before Day 29: CBC, differential, platelets, creatinine, ALT, serum bilirubin. Note: No tests are required before Day 15 and Day 43.
- Before Day 1 and before Day 29 (required, but results do not have to be available to proceed with treatment) calcium, serum protein electrophoresis ***and/or*** serum free light chain levels

Activated: 1 Nov 2015 Revised: 1 Jan 2021 (revised lamivudine duration, clarified bortezomib frequency)

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.

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.

RECOMMENDED TREATMENT:

For 2 years to start 3-4 months post stem cell transplant

Cycle length 56 days

Drug	Dose	BC Cancer Administration Guideline
bortezomib	1.3 mg/m^2 on days 1,15, 29 and 43	SC (abdomen or thigh)*

- **Repeat every 8 weeks for 13 cycles or until disease progression**
- **At time of relapse, Compassionate Access Program (CAP) approval must be obtained to use the more intensive regimen of bortezomib as per MYBORREL**

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

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

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

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
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 to 1.5 x upper limit of normal	Any	100%
Moderate	greater than 1.5 to 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.

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 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 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. H. zoster (shingles) 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. 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)

References:

Neben K1, Lokhorst HM, Jauch A, et al. Administration of bortezomib before and after autologous stem cell transplanation improves outcome in multiple myeloma patients with deletion 17p. Blood 2012;119(4):940-8.