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	*Myeloma*
Contact Physicians	*Dr. Kevin Song* *Dr. Christopher Venner*

ELIGIBILITY:

Patients must have:

- Newly diagnosed multiple myeloma, following an autologous stem cell transplant,
- Confirmed chromosomal abnormalities of del 17p or t(4;14) and physician preference, and
- Minimum of stable disease post- transplant

Note: Patients progressing on MYBORMTN will still be eligible for MYBORREL as per physician preference. The relapse protocol is more intensive and therefore patients may still respond

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, platelets, 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, HBcoreAb, beta-2 microglobulin
- Every 4 weeks Days 1 and 29 (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and serum free light chain levels

- Every 4 weeks Days 1 and 29 (optional, results not mandatory but encouraged prior to each cycle): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM), beta-2 microglobulin
- Every 4 weeks Days 1 and 29: CBC & Diff, platelets, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
- Days 15 and 43 (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

PREMEDICATIONS:
None

SUPPORTIVE MEDICATIONS:
- If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per current guidelines
- 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

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	Subcutaneously (abdomen or thigh)*

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

- **Repeat every 8 weeks until disease progression or unacceptable toxicity or up to a maximum of 13 cycles**

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: (based on pre-cycle labwork)

ANC (x10^9/L) On Day 1		**Platelets (x10^9/L)** On Day 1	**Bortezomib Dose**
Greater than or equal to 0.5	and	Greater than or equal to 50	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.
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 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:

	Total 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	

4. Renal Failure:

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

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 – 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)

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:** All myeloma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with hepatitis B prophylaxis according to current guidelines. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every three 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.
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:

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.