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	*Lymphoma, Leukemia/BMT*
Contact Physician	*Dr. Kevin Song*
Contact Pharmacist	*Louisa Pang*

ELIGIBILITY:
Previously untreated multiple myeloma or light (AL) chain amyloidosis patients who are unsuitable for stem cell transplantation

- Physician may substitute cyclophosphamide for melphalan to reduce myelosupression.
- All patients judged candidates for chemotherapy
- Platelet count less than 50 x 10^9/L may require transfusion support
- Absolute neutrophil count (ANC) less than 0.5 x 10^9/L may require Filgrastim (see PharmaCare guidelines on Filgrastim coverage)

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, urine protein electrophoresis, skeletal survey, HBsAg, HBcoreAntibody, if not previously documented
- Before day 1 (**for bortezomib, melphalan or 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 first 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)**: CBC, differential
- If clinically indicated: skeletal survey X-rays (at least annually)

PREMEDICATIONS:

- 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.
- 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
- 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)	SC (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

Drug	Dose	BC Cancer Administration Guideline
<u>If substituting cyclophosphamide for melphalan</u>:		
cyclophosphamide	300 mg/m^2/day once weekly on days 1, 8, 15, 22 and 29*	PO
predniSONE	100 mg once every 2 days for 2 cycles then 50 mg once every 2 days	PO

*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 or 40 mg daily on days when bortezomib is being given
Option B: predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance
Option C: No steroid. 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 without the steroid. Prednisone or dexamethasone may be added for non-response.

DOSE MODIFICATIONS:
1. Hematological:

For Bortezomib labs on days 1, 8, 15 and 22

ANC ($x10^9$/L)	Platelets ($x10^9$/L)	Dose (bortezomib)
greater than or equal to 0.5	And greater than or equal to 50	100%
less than 0.5	Or less than 50	Delay until recovery checking CBC weekly; consider reducing dose to the next lower level*

*(bortezomib dose levels; 1.3 mg/m^2, 1.0 mg/m^2, 0.7 mg/m^2)

For Melphalan labs on day 1

ANC ($x10^9$/L)	Platelets ($x10^9$/L)	Dose (melphalan)
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 %

For Cyclophosphamide (<u>If substituting for Melphalan)</u> labs on <u>day 1 only</u>

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

2. Peripheral Neuropathy:

For Bortezomib

Severity of Peripheral Neuropathy Signs and Symptoms	Dose (bortezomib)
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:

	Bilirubin	ALT or AST	Bortezomib Dose
Mild	less than or equal to 1.0 x upper limit of normal	greater than the upper limit of normal	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 *<u>or</u>* 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 Melphalan, no dose reduction is necessary for hepatic impairment.
For Cyclophosphamide (If substituting for Melphalan), no dose reduction is necessary for hepatic impairment.

4. Renal dysfunction:

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

For Melphalan, dose modification is necessary for renal failure.

Creatinine clearance (mL/min)	Melphalan Dose
Greater than or equal to 50	100 %
10 to less than 50	75 %
Less than 10	50 %

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

N = 1.04 (Females) and 1.23 (Males)

For Cyclophosphamide (If substituting for Melphalan), 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: 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)

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. 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:

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