

BCCA Protocol Summary for the Treatment of Multiple Myeloma using Melphalan, Prednisone and Weekly Bortezomib With the Option of Substituting Cyclophosphamide for Melphalan

| | |
|---------------------------|-------------------------------|
| Protocol Code | <i>UMYMPBOR</i> |
| Tumour Group | <i>Lymphoma, Leukemia/BMT</i> |
| Contact Physician | <i>Dr. Kevin Song</i> |
| Contact Pharmacist | <i>Linda Hamata</i> |

ELIGIBILITY:

Previously untreated multiple myeloma patients who are unsuitable for stem cell transplantation

- Physician may substitute cyclophosphamide for melphalan to reduce myelosuppression.
- All patients judged candidates for chemotherapy
- Platelet count less than 50×10^9 /L may require transfusion support
- Absolute neutrophil count (ANC) less than 0.5×10^9 /L may require Filgrastim (see PharmaCare guidelines on Filgrastim coverage)
- A BC Cancer Agency “Compassionate Access Program” request must be approved prior to treatment

EXCLUSIONS:

- none

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, 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, AST, serum bilirubin,
- Before day 1 (required, but results do not have to be available to proceed with first treatment): calcium, serum protein electrophoresis
- Before day 8,15, 22 (**for bortezomib only**): CBC
- 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.
- 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)

TREATMENT: cycle length 35 days (i.e., 5 weeks)

Duration of treatment: up to a maximum of 9 cycles. For further treatment, another “Compassionate Access Program” request is required.

| Drug | Cycle | Dose | BCCA Administration Guideline |
|------------|-------|---|--|
| Bortezomib | 1 - 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) ^{***} OR IV push over 3-5 seconds |
| Melphalan | 1 - 9 | 9 mg/m ² /day on days 1 – 4 ^{****} | PO |
| Prednisone | 1 - 9 | 60 mg/m ² /day on days 1 – 4 | PO |

*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 2 mg

| Drug | Dose | BCCA Administration Guideline |
|---|--|-------------------------------|
| <u>If substituting Cyclophosphamide for Melphalan:</u> Cyclophosphamide | 300 mg/m ² /day once daily on days 1, 8, 15, 22, 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 day 1, 8, 15, 22**

| ANC ($\times 10^9/L$) | Platelets ($\times 10^9/L$) | 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/m², 1.0 mg/m², 0.7 mg/m²)

For Melphalan labs on day 1

| ANC ($\times 10^9/L$) | Platelets ($\times 10^9/L$) | Dose (melphalan) |
|-------------------------|-------------------------------|---|
| greater than 3 | greater than 200 | Increase by 2 mg/day |
| 1-3 | greater than or equal to 100 | 100% of previous dose |
| less than 1 | less than 100 | Check CBC & diff weekly, resume treatment when ANC is greater than 1 and platelets return to baseline. If after 5 weeks ANC is still less than 1 or platelets less than 100, reduce dose of melphalan to 75 % |

For Cyclophosphamide (If substituting for Melphalan) labs on day 1 only

| ANC (x10 ⁹ /L) | Platelets (x10 ⁹ /L) | Dose (cyclophosphamide) |
|---------------------------|---------------------------------|-----------------------------------|
| greater than 1.0 | greater than 80 | 100% |
| less than or equal to 1.0 | less than or equal to 80 | perform weekly CBC until recovery |

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 | 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 | <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 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 50 | 100 % |
| 10-50 | 75 % |
| Less than 10 | 50 % |

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)

For Cyclophosphamide (If substituting for Melphalan), dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis.

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

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: 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 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 <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 (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. 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: 01 Dec 2009

Date revised: 1 July 2011 (include subcutaneous route of administration for bortezomib)

1 Dec 2011 (formatting, bortezomib sc site of administration and protocol contact information)

References:

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