Regimen Monograph

A - Regimen Name

BMP Regimen

Bortezomib-Melphalan (oral)-Prednisone

Disease Site	Hematologic - Multiple Myeloma
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	Previously untreated multiple myeloma patients who are unsuitable for stem cell transplantation
Supplementary Public Funding	**bortezomib** New Drug Funding Program (Bortezomib - Previously Untreated - Multiple Myeloma) (NDFP Website) **melphalan** ODB - General Benefit (melphalan - oral tablets) (ODB Formulary) **prednisone** ODB - General Benefit (prednisone) (ODB Formulary)

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B - Drug Regimen

A: STANDARD REGIMEN [1] ***- Cycles 1 - 9 (every 5 weeks):***

bortezomib[2]	1.3 mg /m²	IV / Subcut	Days 1, 8, 15, 22
melphalan	9 mg /m²	PO	Days 1 to 4
prednisone	60 mg /m²	PO	Days 1 to 4

B: ALTERNATIVE REGIMEN - ***Cycles 1 - 4 (every 6 weeks):***

bortezomib[2]	1.3 mg /m²	IV / Subcut	Days 1, 4, 8, 11, 22, 25, 29, 32
melphalan	9 mg /m²	PO	Days 1 to 4
prednisone	60 mg /m²	PO	Days 1 to 4

ALTERNATIVE SCHEDULE ***- Cycles 5 - 9 (every 6 weeks):***

bortezomib[2]	1.3 mg /m²	IV / Subcut	Days 1, 8, 22, 29
melphalan	9 mg /m²	PO	Days 1 to 4
prednisone	60 mg /m²	PO	Days 1 to 4

[1]Blood 2010;116(23):4745-53.

[2]Missed doses should not be made up. A minimum of 72 hours is required between bortezomib doses

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C - Cycle Frequency

STANDARD REGIMEN:
REPEAT EVERY 5 WEEKS
For a usual total of 9 cycles in the absence of disease progression or unacceptable toxicity

OR ALTERNATIVE REGIMEN:
REPEAT EVERY 6 WEEKS

For a usual total of 9 cycles (4 cycles of initial phase and 5 cycles of maintenance phase) in the absence of disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low
No routine prophylaxis for melphalan PO

Other Supportive Care:

- Allopurinol and hydration to reduce the risk of tumour lysis syndrome are recommended, especially for patients with high tumour load.
- Consider antiviral prophylaxis (ie. acyclovir) for herpes zoster.

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

Dosage with toxicity

Dose levels of bortezomib are 1.3, 1 and 0.7 mg/m^2.

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Dose Modifications for Hematological and Non-Hematological Toxicities:
Patients with symptoms of pneumonitis or ARDS should have treatment withheld and be appropriately investigated.

Table B: In Combination with Melphalan and Prednisone	**Dose modification and delay**
Toxicity Prior Cycle / Day 1 of Cycle	
Day 1 AGC < 1 x 10^9/L or platelets < 70 x 10^9/L	Delay until recovery
Grade 4 AGC or platelets ≥ 5 days or febrile neutropenia or thrombocytopenic bleeding PRIOR cycle	Reduce melphalan dose by 25%
Bortezomib held (≥ 3 times in a cycle during twice weekly administration, or ≥ 2 times in a cycle during weekly administration)	Reduce bortezomib by 1 dose level
Grade 3 or 4 non-hematologic toxicity (see table B for neurotoxicity)	Hold until ≤ grade 1/baseline then restart with 1 dose level ↓. Consider discontinuing for grade 4.
Any grade RPLS/ PML/ pneumonitis or dose-limiting toxicity at 0.7 mg/m^2	Discontinue
Toxicity During Cycle	
ANC ≤ 0.75 x 10^9/L or platelet ≤ 30 x 10^9/L	Hold both bortezomib and melphalan (if applicable)
Grade 3 or 4 non-hematologic toxicity (see table B for neurotoxicity)	Hold until ≤ grade 1/baseline then restart with 1 dose level ↓. Consider discontinuing for grade 4.
Any grade RPLS/ PML/ pneumonitis or dose-limiting toxicity at 0.7 mg/m^2	Discontinue

Dosage for Neurotoxicity: Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment.

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Table B: Severity of Peripheral Neuropathy	Bortezomib Dosage and Regimen Modification
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
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)	Hold bortezomib until toxicity resolves. When toxicity resolves, reinitiate at a reduced dose of 0.7mg/m^2 and give once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue permanently

Hepatic Impairment

Melphalan: No adjustment required

Bortezomib is metabolized by liver enzymes and exposure is increased in patients with moderate to severe hepatic impairment. Patients with hepatic impairment should be treated with extreme caution and should be closely monitored for toxicities, and dose reduction should be considered.

Suggested dose modifications:

Bilirubin	AST	Bortezomib Starting Dose
≤ 1 x ULN	> ULN	No change
> 1 – 1.5 x ULN	Any	No change
> 1.5 – 3 x ULN	Any	First cycle: ↓ to 0.7mg/m^2. Subsequent cycles: Consider ↑ dose to 1mg/m^2 or further ↓ dose to 0.5mg/m^2 based on patient tolerability.
> 3 x ULN	Any	

Renal Impairment

Bortezomib: Dose adjustments are not necessary in patients with renal insufficiency.† Patients with compromised renal function should be monitored carefully when treated with bortezomib, especially

if creatinine clearance is less than 30mL/min. Bortezomib should be given after dialysis.†
(†Information obtained from bortezomib US prescribing information, January 2012)

Melphalan: Increased incidence of severe myelosuppression has been observed in patients with BUN ≥ 10.7 mmol/L. Dose reduction should be considered in patients with renal insufficiency receiving melphalan.

Creatinine clearance (mL/min)	**% Melphalan usual dose**
10-50	75% and monitor
<10	50% and monitor

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F - Adverse Effects

Refer to bortezomib, melphalan, prednisone drug monograph(s) for additional details of adverse effects

Most Common Side Effects	**Less Common Side Effects, but may be Severe or Life-Threatening**
• Fatigue • Nausea and vomiting • Diarrhea • Neuropathy (may be severe) • Constipation • Anorexia, weight loss • Myelosuppression +/- bleeding, infection (may be severe) • Cough/dyspnea (may be severe) • Hypotension / hypertension (may be severe) • Pain • Rash (may be severe) • Fertility effects • Steroid effects (weight gain, myopathy, hyperglycemia, gastric irritation, insomnia, mood changes, osteoporosis)	• Arterial thromboembolism • Venous thromboembolism • Tumour lysis syndrome • Disseminated intravascular coagulation • Renal failure • RPLS • GI obstruction • GI perforation • Pancreatitis • ↑ LFTs • Hypersensitivity • Seizure • Cardiotoxcitiy • ↑ QTc • Pulmonary hypertension • Fluid retention/effusions • Secondary malignancies

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G - Interactions

Refer to bortezomib, melphalan, prednisone drug monograph(s) for additional details

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H - Drug Administration and Special Precautions

Refer to bortezomib, melphalan, prednisone drug monograph(s) for additional details

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- Blood glucose levels, especially in patients using antidiabetic medications
- CBC; at each visit
- CXR; baseline
- CXR and lung function assessment, if ILD is suspected
- Liver and renal function tests, electrolytes; baseline and regular
- Routine toxicity ratings of fatigue, neuropathy, infection, bleeding, respiratory symptoms, tumour lysis syndrome, muscle weakness, ophthalmic, cardiovascular and GI side effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- LVEF monitoring in patients with cardiac risk factors

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	16.369 minutes
Nursing Workload (average time per visit)	27.5 minutes

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K - References

Brinjhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010; 116(23);4745-4753.

Channan-Khan A, Sonneveld P, Schuster MW et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 2008; 26: 4784-90.

Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncology 2011;12:431-40.

San Miguel JF, Schlag R, Nuriet K, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. NEJM 2008; 359: 906-17.

PEBC Advice Documents or Guidelines

- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

May 2019 Updated emetic risk category; added PEBC guideline link

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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