Bortezomib, Melphalan and Prednisolone Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of adult patients with previously untreated multiple myeloma who are NOT eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.</td>
<td>C90</td>
<td>00275a</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined*, the indication has yet to be assessed through the formal HSE reimbursement process.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Bortezomib is administered subcutaneously in combination with oral melphalan and oral prednisolone as shown in the treatment table below. A 6-week period is considered a treatment cycle. Treatment is administered for 9 bortezomib treatment cycles or until disease progression or unacceptable toxicity develops.

- In Cycles 1-4, bortezomib is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In Cycles 5-9, bortezomib is administered once weekly on days 1, 8, 22 and 29.
- Melphalan and prednisone should both be given orally on days 1, 2, 3 and 4 of the first week of each cycle.
- As an alternative, bortezomib may be given once weekly on days 1, 8, 15 and 22 of a 5 week cycle in select patients at the treating clinician’s discretion.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 4, 8, 11, 22, 25, 29, 32</td>
<td>Bortezomib</td>
<td>1.3 mg/m²</td>
<td>SC (abdomen or thigh)</td>
<td>1-4 (every 6 weeks)</td>
</tr>
<tr>
<td>1, 8, 22 and 29</td>
<td>Bortezomib</td>
<td>1.3 mg/m²</td>
<td>SC (abdomen or thigh)</td>
<td>5-9 (every 6 weeks)</td>
</tr>
<tr>
<td>1-4</td>
<td>Melphalan</td>
<td>9 mg/m²</td>
<td>PO</td>
<td>1-9 (every 6 weeks)</td>
</tr>
<tr>
<td>1-4</td>
<td>Prednisolone</td>
<td>60 mg/m²</td>
<td>PO</td>
<td>1-9 (every 6 weeks)</td>
</tr>
</tbody>
</table>

Note: In individual cases where approved by Consultant, bortezomib may be administered as IV bolus over 3-5 seconds through a peripheral or central intravenous catheter followed by a flush with 0.9% NaCl. Note the concentration of bortezomib solution should be 1mg/ml when administered via the IV route.

*The solution should be injected subcutaneously, at a 45-90° angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered SC or a switch to intravenous injection is recommended.*

At least 72 hours should elapse between consecutive doses of bortezomib.

Bortezomib is a proteasome inhibitor and is neurotoxic. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer.

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron, melphalan or any of the excipients
- Acute diffuse infiltrative pulmonary and pericardial disease

NCCP Regimen: Bortezomib, Melphalan and Prednisolone

Published: 08/08/2016
Review: 12/10/2020
Version number: 2

Tumour Group: Myeloma
NCCP Regimen Code: 00275

IHS Contributors: Dr John Quinn

Page 1 of 7

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NCCP Chemotherapy Regimen

PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:
- FBC, renal, liver and bone profile
- Uric acid
- Clotting screen
- Blood pressure, blood glucose (patients on oral hypoglycaemics).
- Assessment of peripheral neuropathy status.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), C and HIV

**Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. 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 (Refer to local policy). 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 stopping chemotherapy.

Regular tests:
- FBC; monitor platelet count at a minimum of day 1 and day 11 each cycle
- Renal, liver and bone profile prior to each cycle.
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)

Disease monitoring:
Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:
- Any dose modification should be discussed with a Consultant

Haematological:
Prior to initiating a new cycle of therapy
- Platelets ≥70 x 10^9/L and ANC ≥1 x 10^9/L
- Non-haematological toxicities should have resolved to Grade 1 or baseline

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Table 1: Dose modifications for haematological toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>If prolonged Grade 4 Neutropenia (ANC &lt; 0.5 x 10^9/L) or Thrombocytopenia (Platelets &lt; 25 x 10^9/L) or thrombocytopenia with bleeding observed in the previous cycle</td>
<td>Consider reduction of the melphalan dose by 25% in the next cycle.</td>
</tr>
<tr>
<td>If platelet ≤ 30x10^9/L or ANC ≤ 0.75 x 10^9/L on a bortezomib dosing day (other than day 1)</td>
<td>Withhold bortezomib</td>
</tr>
<tr>
<td>If several bortezomib doses in a cycle are withheld (≥ 2 doses)</td>
<td>Reduce bortezomib from 1.3mg/m^2 to 1mg/m^2 or from 1mg/m^2 to 0.7mg/m^2</td>
</tr>
</tbody>
</table>

Renal Impairment:

Table 2: Dose modifications in renal impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hepatic Impairment:

Table 3: Dose modifications for bortezomib in hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade of Hepatic Impairment*</th>
<th>Bilirubin Level</th>
<th>SGOT (AST) levels</th>
<th>Modification of starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>Mild</td>
<td>≤1 x ULN</td>
<td>&gt; ULN</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1 - 1.5 x ULN</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>&gt;1.5 - 3 x ULN</td>
<td>Any</td>
<td>Reduce dose to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability.</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>&gt; 3 x ULN</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td></td>
<td></td>
<td></td>
<td>No dose changes recommended. If excessive toxicity, consider dose reduction on subsequent cycles</td>
</tr>
</tbody>
</table>

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).
Neuropathic pain and/or peripheral neuropathy:

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or</td>
<td>None</td>
</tr>
<tr>
<td>loss of function</td>
<td></td>
</tr>
<tr>
<td>Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of</td>
<td>Reduce dose to 1 mg/m² Or</td>
</tr>
<tr>
<td>Daily Living (ADL))</td>
<td>Change treatment schedule to 1.3mg/m2 once every week</td>
</tr>
<tr>
<td>Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)</td>
<td>Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves</td>
</tr>
<tr>
<td></td>
<td>re-initiate treatment and reduce dose to 0.7mg/m² once every week</td>
</tr>
<tr>
<td>Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>autonomic neuropathy</td>
<td></td>
</tr>
</tbody>
</table>

Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

Dose reductions for other toxicities:

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 Non-haematological toxicity</td>
<td>Withhold bortezomib until symptoms resolved to Grade 1 or baseline then reinitiate with one</td>
</tr>
<tr>
<td></td>
<td>dose level reduction from 1.3mg/m² to 1 mg/m² or from 1mg/m² to 0.7mg/m²</td>
</tr>
<tr>
<td>New or worsening pulmonary symptoms (e.g. cough, dyspnoea)</td>
<td>Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be</td>
</tr>
<tr>
<td></td>
<td>considered prior to continuing bortezomib therapy.</td>
</tr>
<tr>
<td>Posterior Reversible Encephalopathy Syndrome (PRES)</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:
Bortezomib- Low (Refer to local policy).
Melphalan – Minimal (Refer to local policy)

PREMEDICATIONS: Not usually required. Ensure patient remains well hydrated during treatment

OTHER SUPPORTIVE CARE:
- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- Consider the use of a H₂ antagonist or proton pump inhibitor (Refer to local policy).
- Tumour Lysis Syndrome prophylaxis (Refer to local policy).
- Consider PJP prophylaxis (Refer to local policy)
- Antiviral prophylaxis (Refer to local policy).

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ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Haematological toxicity:** Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore platelet counts should be monitored prior to each dose of bortezomib and bortezomib should be withheld when the platelet count is < 25x 10⁹ cells/L. Potential benefit of treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding. Complete blood counts with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate.

- **Progressive multifocal leukoencephalopathy (PML):** Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PM is suspected patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.

- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

- **Seizures:** Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

- **Hypotension:** Treatment is commonly associated with orthostatic/postural hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting.

- **Posterior Reversible Encephalopathy Syndrome (PRES):** In patients developing PRES, treatment with bortezomib should be discontinued.

- **Heart Failure:** Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.

- **Hepatic Impairment:** Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities.

- **Tumour Lysis Syndrome:** Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

- **Myelosuppression:** Melphalan is a potent myelosuppressive agent.

- **Renal Impairment:** Clearance of melphalan may be reduced in patients with renal impairment who may also have uraemic bone marrow suppression. Dose reduction may therefore be necessary and these patients should be closely observed.

- **Mutagenecity:** Chromosome aberrations have been observed in patients treated with melphalan.

- **Carcinogenecity:** There have been reports of acute leukaemia occurring after melphalan treatment for multiple myeloma.

**DRUG INTERACTIONS:**
- Additive hypotensive effect with antihypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of antihypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving...
bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics

- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.
- Impaired renal function has been described in bone marrow patients who were pre-conditioned with high dose IV Melphalan and who subsequently received cyclosporine to prevent graft-versus-host disease.
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>L01XX32</td>
</tr>
<tr>
<td>Melphalan</td>
<td>L01AA03</td>
</tr>
</tbody>
</table>

**REFERENCES:**

NCCP Chemotherapy Regimen

## Version History

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>08/08/2016</td>
<td></td>
<td>Dr John Quinn</td>
</tr>
<tr>
<td>2</td>
<td>12/10/2018</td>
<td>Updated with new NCCP regimen template and Hepatitis B recommendations</td>
<td>Dr John Quinn</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System  
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes  
Further details on the Cancer Drug Management Programme is available at;  
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/