NCCP Chemotherapy Regimen

Bortezomib and Dexamethasone 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 progressive multiple myeloma who have</td>
<td></td>
<td>C90</td>
<td>Hospital</td>
</tr>
<tr>
<td>received at least one prior therapy</td>
<td></td>
<td>00270a</td>
<td></td>
</tr>
</tbody>
</table>

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.

Treatment with bortezomib is administered twice weekly for two weeks on days 1, 4, 8 and 11 followed by a 10 day rest period on days 12-21. This 3-week period is considered a treatment cycle.

Dexamethasone is administered orally on days 1, 2, 4, 5, 8, 9, 11 and 12 of the bortezomib treatment cycle.

Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 4, 8, 11</td>
<td>Bortezomib a, b</td>
<td>1.3mg/m²</td>
<td>SC (abdomen or thigh)</td>
</tr>
<tr>
<td>1, 2, 4, 5, 8, 9, 11 and 12</td>
<td>Dexamethasone</td>
<td>20mg once daily</td>
<td>PO</td>
</tr>
</tbody>
</table>

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

b 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.

c 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 IV injection is recommended.

d 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 IV injection is recommended.

e Dexamethasone to be taken once daily in the morning with food.

ELIGIBILITY:

- Indication as above
- ECOG 0-2

NCCP Regimen: Bortezomib and Dexamethasone Therapy  
Published: 05/04/2017  
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Version number: 3

Tumour Group: Myeloma  
NCCP Regimen Code: 00270  
IHS Contributors: Dr Patrick Hayden, Dr John Quinn

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NCCP Chemotherapy Regimen

- Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment. Caution should be exercised as further treatment may result in severe prolonged neuropathy.

EXCLUSIONS:
- Hypersensitivity to bortezomib, boron, dexamethasone or any of the excipients.
- Acute diffuse infiltrative pulmonary and pericardial disease.

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
- Blood pressure
- Blood glucose* if being treated with oral hypoglycaemics (*See Drug Interactions)
- Assessment of peripheral neuropathy status
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), Hepatitis C and HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:
- FBC; monitor platelet count at a minimum of day 1 and day 11 each cycle.
- Renal, liver and bone profile
- Blood pressure
- Assessment of peripheral neuropathy status
- 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.

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Renal impairment:

Table 1: Dose Modification of Bortezomib in Renal Impairment

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to Moderate</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>CrCl &gt;20ml/min/1.73m²</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>It is unknown if the pharmacokinetics of bortezomib are influenced in severe renal impairment (CrCl &lt; 20ml/min/1.73m²) not undergoing dialysis. Dialysis may reduce bortezomib concentrations; it should be administered after the dialysis procedure.</td>
</tr>
<tr>
<td>CrCl &lt;20ml/min/1.73m²</td>
<td></td>
</tr>
</tbody>
</table>

Hepatic impairment:

Table 2: Dose Modification of Bortezomib in Hepatic Impairment

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Bilirubin Level</th>
<th>SGOT (AST level)</th>
<th>Modification of starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≤1 x ULN</td>
<td>&gt; ULN</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>&gt;1 - 1.5 x ULN</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;1.5 - 3 x ULN</td>
<td>Any</td>
<td>Reduce dose to 0.7mg/m² in the first treatment cycle. Consider dose escalation to 1mg/m² or further dose reduction to 0.5mg/m² in subsequent cycles based on patient tolerability.</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;3 x ULN</td>
<td>Any</td>
<td></td>
</tr>
</tbody>
</table>

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Abbreviations: SGOT=serum glutamic oxaloacetic transaminase; AST=aspartate aminotransferase; ULN=upper limit of the normal range.

Dose reductions for other toxicities:

Table 3: Dose Modification of Bortezomib for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 Haematological toxicity (ANC &lt; 0.5 x10⁹/L)</td>
<td>Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at a 25% reduced dose (1.3mg/m² reduced to 1mg/m²; 1mg/m² reduced to 0.7mg/m²). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.</td>
</tr>
<tr>
<td>Grade 3 Non-haematological toxicity</td>
<td>Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.</td>
</tr>
<tr>
<td>New or worsening pulmonary symptoms (e.g. cough, dyspnoea)</td>
<td>Withhold treatment.</td>
</tr>
</tbody>
</table>
Neuropathic pain and/or peripheral neuropathy:

Table 4: Dose modifications for Bortezomib Related 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 loss of function</td>
<td>None</td>
</tr>
<tr>
<td>Grade 1 with pain or Grade 2</td>
<td>Reduce dose to 1 mg/m² or Change treatment schedule to 1.3 mg/m² once every week</td>
</tr>
<tr>
<td>Grade 2 with pain or Grade 3</td>
<td>Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7 mg/m² once every week</td>
</tr>
<tr>
<td>Grade 4 and/or severe autonomic neuropathy</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>

Grading based on NCI Common Toxicity Criteria CTCAE v 4

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (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.
- H₂-antagonist or PPI in patients receiving dexamethasone therapy (Refer to local policy).
- Low dose antiviral prophylaxis (Refer to local policy).
- Consider PJP prophylaxis (Refer to local policy).
- Tumour Lysis Syndrome prophylaxis (Refer to local policy).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.
- Peripheral Neuropathy: Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- 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.
- Gastrointestinal toxicity: Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment.
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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.

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 < 25 x 10⁹/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.

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.

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.

Renal Impairment: Patients with renal impairment should be monitored closely.

Steroid use: Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).

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 anti-viral therapy. (Refer to local infectious disease policy). These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Additive hypotensive effect with anti-hypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of anti-hypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral anti-diabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their anti-diabetic medications.
- 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.
- Current drug interaction databases should be consulted for more information.
REFERENCES:
2. Jagannath S, Richardson PG et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone Haematologica 2006; 91: 929-934