Bortezomib for Multiple Myeloma

Indication:
NICE approved indication:
Second line therapy for patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation.

Bortezomib may be used for the following indications if funding is agreed as per local process (Cancer Drugs Fund)
- Greater than first relapse (i.e. third-line or more treatment)
- First line therapy for patients who present with renal impairment (CrCl < 30ml/min)

Consider avoiding use in patients with pre-existing severe neuropathy.

Regimen details: Bortezomib 1.3 mg/m² IV Days 1, 4, 8 and 11
There must be a minimum of 72 hours between doses.
There is a 10 day rest period between cycles.

Bortezomib may be used in combination with dexamethasone. The schedule for dexamethasone is:
Dexamethasone 20mg od orally Days 1, 4, 8 and 11

Administration: Bortezomib IV bolus over 3 to 5 seconds

Premedication: None required

Frequency: 21 day cycle, maximum of 8 cycles
Assess response after each cycle (by EBMT criteria)
If complete response (CR) is achieved, give another 2 cycles and stop.
If partial response (PR) or PR plateau is achieved, give another 2 cycles. These responding patients who do not achieve a CR can receive up to 8 cycles.
Minimal response (MR), no change (NC) or progressive disease at 4 cycles, stop treatment.
Progressive disease at any point, stop treatment.

Extravasation: Non-vesicant

Anti-emetics: Mild emetogenicity

Supportive Care: Antiviral prophylaxis as per local policy e.g. aciclovir 200mg bd
PCP prophylaxis as per local policy e.g. co-trimoxazole 960mg od Monday, Wednesday, Friday each week
Consider antifungal prophylaxis as per local policy if the patient is also receiving dexamethasone
PPI or H₂ receptor antagonist e.g. omeprazole 20mg od, if receiving dexamethasone
Allopurinol 300mg od (or 100mg od for renal impairment) for first cycle only
250ml sodium chloride 0.9% over 30 minutes is administered prior to each dose of bortezomib to minimise any symptoms of postural hypotension.
To manage peripheral neuropathy:
Consider Vitamin B and folic acid supplementation
Topical cocoa butter (not supplied by NHS) applied to affected areas twice a day may be beneficial to some patients.
Gabapentin up to 300mg tds for neuropathic pain
Further details as per SELCN Guidelines for the Management of Multiple Myeloma and Related Plasma Cell Disorders

Regular investigations:
FBC D1, 4, 8 and 11
LFTs D1
U&E D1
Serum paraprotein and serum free light chains at the start of each cycle.
Baseline neurological examination.
Baseline vitamin B12 and folate.

Toxicities:
Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation.
Hepatobiliary disorders. The most common haematological toxicity is thrombocytopenia.
Peripheral neuropathy. Orthostatic/postural hypotension. Cardiotoxicity – patients with a known history of heart disease, should have an Echo prior to commencing treatment.
Fatigue. Tumour lysis syndrome. Rash.

Dose Modifications

Haematological Toxicity

Prior to every cycle of bortezomib:

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.0 x 10^9/L</td>
<td>≥75 x 10^9/L</td>
<td>100% dose</td>
</tr>
<tr>
<td>&lt;1.0 x 10^9/L</td>
<td>&lt;75 x 10^9/L</td>
<td>Delay on a weekly basis, until recovery of toxicity.</td>
</tr>
</tbody>
</table>

NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the, day 1 dose will go ahead even if neutrophils <1.0 x 10^9/L and platelets < 75 x 10^9/L. This should be confirmed with a Consultant.

If neutrophils < 1.0 x 10^9/L and platelets < 75 x 10^9/L on day 1 of subsequent cycles (when previously > than these levels), delay until as above, and reduce the bortezomib dose to 1.0 mg/m^2 for all further cycles.

If further toxicity occurs where neutrophils < 1.0 x 10^9/L and platelets < 75 x 10^9/L on day 1, delay until as above, and reduce the bortezomib dose to 0.7 mg/m^2 for all further cycles.
Prior to any day of bortezomib during a cycle (other than D1):

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.75 x 10^9/L</td>
<td>≥ 30 x 10^9/L</td>
<td>100% dose</td>
</tr>
<tr>
<td>&lt; 0.75 x 10^9/L</td>
<td>&lt; 30 x 10^9/L</td>
<td>With hold until recovery of toxicity. Re-initiate treatment at a reduced dose.</td>
</tr>
</tbody>
</table>

NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the doses will go ahead even if neutrophils < 0.75 x 10^9/L and platelets < 30 x 10^9/L. This should be confirmed with a Consultant. Doses not given in a cycle are not made up later.

Consideration should be given to platelet transfusion and GCSF support for haematological toxicity. This must be on the recommendation of a Consultant Haematologist.

Renal Impairment

Bortezomib should be used with caution in patients with CrCl < 20ml/min not undergoing dialysis; however, no specific dosing recommendations have been made. Since dialysis may reduce bortezomib concentrations, bortezomib should be administered after the dialysis procedure.

Hepatic Impairment

There is very limited information available regarding the use of bortezomib in patients with hepatic insufficiency and it should therefore be used with caution.

Non-Haematological toxicities

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paraesthesia, weakness and/or loss of reflexes)</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)</td>
<td>Reduce to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or Grade 3 (interfering with activities of daily living)</td>
<td>Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate bortezomib treatment and reduce dose to 0.7 mg/m² and change treatment schedule to once per week.</td>
</tr>
<tr>
<td>Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis) and/or severe autonomic neuropathy</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>

Doses reduced for toxicity should not be re-escalated

Drug interactions: Bortezomib may increase the levels/effects of citalopram, phenytoin and other CYP2C19 substrates. Levels/effects of bortezomib may be increased by azole antifungals, ciprofloxacin, clarithromycin, erythromycin, verapamil and other CYP3A4 inhibitors.
References:

www.medicines.org.uk
Velcade Response Scheme (VRS) Oct 2007 and NICE TAG 129
Criteria for Evaluating Disease Response and progression in Patients with Multiple Myeloma Treated by High Dose Therapy and Haemopoietic Stem Cell Transplantation. Blade et al BJH 1998; 102: 1115-1123
High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory myeloma: results of a global phase 3B expanded access program. Mikhael JR et al BJH 2008; 144: 169-175
Personal communication with Paul Richardson