Indication: Relapsed Multiple Myeloma.
          Newly diagnosed Multiple Myeloma as per SELCN Guidelines.
          Consider avoiding use in patients with pre-existing severe neuropathy.

Regimen details: Cyclophosphamide 500mg orally Days 1, 8, 15
          Bortezomib 1.3 mg/m² IV Days 1, 4, 8 and 11
          Dexamethasone 20mg od orally 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.

Administration: Bortezomib IV bolus over 3 to 5 seconds
               Cyclophosphamide and dexamethasone orally.

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 if receiving dexamethasone
                Allopurinol 300mg od (or 100mg od for renal impairment) for first cycle only / until plateau
                250ml sodium chloride 0.9% over 30 minutes is administered prior to each dose of
                bortezomib to minimise any symptoms of postural hypotension.
Bortezomib (Velcade®), Cyclophosphamide, Dexamethasone (VCD) for Multiple Myeloma

To manage peripheral neuropathy:
- Vitamin B compound strong, one tablet once a day
  (NB one Vitamin B compound strong tablet contains: 20mg nicotinamide, 2mg pyridoxine, 2mg riboflavin, 5mg thiamine)
- Folic acid 5mg once a week
- Cocoa butter (not supplied from GSTFT) applied to affected areas twice a day
- Gabapentin up to 300mg tds for neuropathic pain

Regular investigations:
- FBC D1, 4, 8 and 11
- LFTs D1
- U&Es 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 < 1.5 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) with no pain or loss of function</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>

Dexamethasone toxicities: Dexamethasone should be reduced to 20mg od, should a dose reduction be required.

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](http://www.medicines.org.uk)

Personal communication with Paul Richardson

Davies F.E. et al. 2007 The combination of cylophosphamide, velcade and dexamethasone (CVD) induces high response rates with comparable toxicity to velcade alone (V) and velcade plus dexamethasone (VD). Haematologica 92:1149-1150.