Bortezomib, Melphalan and Prednisolone (VMP)

**Indication**
First line treatment of multiple myeloma in patients who are intolerant of or have contraindications to thalidomide, and are unsuitable for bone marrow transplantation.

(NICE TA228)

**ICD-10 codes**
Codes with a pre-fix C90

**Regimen details**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,8,15 and 22</td>
<td>Bortezomib</td>
<td>1.3 mg/m²</td>
<td>SC</td>
</tr>
<tr>
<td>1-4</td>
<td>Melphalan</td>
<td>9 mg/m²</td>
<td>PO</td>
</tr>
<tr>
<td>1-4</td>
<td>Prednisolone</td>
<td>60 mg/m² OM</td>
<td>PO</td>
</tr>
</tbody>
</table>

* Consider reducing melphalan to 7mg/m² if significant co-morbidities, poor performance status.

At least 72 hours must elapse between doses of bortezomib

**Cycle frequency**
35 days

**Number of cycles**
Maximum of 8 cycles

**Administration**
Bortezomib is administered by SC injection. At least 72 hours must elapse between doses of bortezomib.

Melphalan is available as 2mg tablets. Melphalan tablets are cytotoxic. Tablets should be swallowed whole with a glass of water and should not be broken, crushed or chewed.

Prednisolone is available as 5mg and 25mg tablets. The dose should be taken once a day in the morning, with or after food.

**Pre-medication**
Nil

**Emetogenicity**
This regimen has moderate emetogenic potential.

**Additional supportive medication**
- H₂ antagonist or proton pump inhibitor
  - Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden, for the first cycle only
  - Bisphosphonates as per local policy
- Antifungal, antiviral and PCP prophylaxis as per local policy
- Loperamide if required.
**Extravasation**
Bortezomib is neutral (group 1).

**Investigations – pre first cycle**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC and film</td>
<td>7 days</td>
</tr>
<tr>
<td>Clotting screen</td>
<td>7 days</td>
</tr>
<tr>
<td>U+Es (including creatinine)</td>
<td>7 days</td>
</tr>
<tr>
<td>LFTs</td>
<td>7 days</td>
</tr>
<tr>
<td>Calcium</td>
<td>7 days</td>
</tr>
<tr>
<td>Blood pressure (lying and standing)</td>
<td>On day 1</td>
</tr>
</tbody>
</table>

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)
Bone marrow aspirate and trephine
Consider baseline echocardiogram (risk of bortezomib-induced cardiomyopathy)

**Investigations – pre subsequent cycles**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC*</td>
<td>96 hours</td>
</tr>
<tr>
<td>U+Es (including creatinine)</td>
<td>7 days</td>
</tr>
<tr>
<td>LFTs</td>
<td>7 days</td>
</tr>
<tr>
<td>Calcium</td>
<td>7 days</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>On day 1</td>
</tr>
</tbody>
</table>

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)

* In addition FBC is required on days 8, 15 and 22 within 24 hours of bortezomib administration.

**Standard limits for administration to go ahead**

If blood results not within range, authorisation to administer **must** be given by prescriber/consultant

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>≥ 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 70 x 10⁹/L</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>≥ 50 mL/min</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt; 1.5 x ULN</td>
</tr>
</tbody>
</table>

**Dose modifications**

Doses of bortezomib are modified according to the following table:

<table>
<thead>
<tr>
<th></th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full dose</td>
<td>1.3 mg/m²</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>1.0 mg/m²</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>0.7 mg/m²</td>
</tr>
<tr>
<td>Third dose reduction</td>
<td>0.5 mg/m²</td>
</tr>
</tbody>
</table>

- **Haematological toxicity**

Treatment on day 1 should only be initiated if neutrophils ≥ 1.0 x 10⁹/L and platelets ≥ 70 x 10⁹/L.

If cytopenia considered to be disease related, treatment may be given at consultant discretion.

On days 8, 15 and 22 if neutrophils ≤ 0.75 x 10⁹/L or platelets ≤ 30 x 10⁹/L withhold bortezomib. If several doses within a cycle are withheld, consider dose reduction of bortezomib for subsequent cycles.

If prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding, reduce melphalan dose to 75% for subsequent cycles.
• **Renal impairment**
  
  **Bortezomib:**
  If CrCl < 20mL/min use with caution. If patient is on dialysis, bortezomib should be administered after dialysis.

  **Melphalan:**
  
  $\text{CrCl (mL/min)}$ | $\text{Melphalan dose}$
  --- | ---
  > 50 | 100%
  10-50 | 75%
  < 10 | 50%

• **Hepatic impairment**
  
  **Bortezomib:**
  If bilirubin > 1.5 x ULN consider starting dose of 0.7mg/m$^2$ for cycle 1. For subsequent cycles consider increasing dose to 1mg/m$^2$ or reducing dose to 0.5mg/m$^2$ according to tolerability.

  There are no dose modification recommendations for melphalan in hepatic impairment, however, if excess toxicity experienced, consider dose reduction for subsequent cycles.

• **Other toxicities**
  
  **Neuropathy:**
  
  $\text{Grade}$ | $\text{Bortezomib dose}$
  --- | ---
  Grade 1 with no pain | 100%
  Grade 1 with pain or grade 2 but not interfering with daily living | 1.0mg/m$^2$
  Grade 2 with pain or grade 3 | Withhold until symptoms resolved Restart at dose of 0.7mg/m$^2$
  Grade 4 | Discontinue

  Any other ≥ grade 3 non-haematological toxicity: withhold bortezomib until ≤ grade 1. Recomence with 1 level dose reduction.

**Adverse effects** - for full details consult product literature/reference texts

• **Serious side effects**
  
  Myelosuppression
  Tumour lysis syndrome
  Cardiac failure
  Pulmonary hypotension
  Acute respiratory distress syndrome

• **Frequently occurring side effects**
  
  Myelosuppression
  Constipation, diarrhoea
  Nausea and vomiting
  Fatigue
  Peripheral neuropathy
  Headache
  Rash

• **Other side effects**
  
  Altered LFTs
  Decreased appetite
  Confusion
  Depression
Significant drug interactions – for full details consult product literature/ reference texts

**Bortezomib:**

**Antihypertensives:** Risk of additive hypotensive effect. Close monitoring of BP is required.

**Oral anti diabetic agents:** Hyper and hypo glycermia has been reported. Close monitoring of blood glucose is required.

**Ciclosporin:** increased risk of severe neuropathy: avoid concomitant use.

**Vitamin C:** reduced efficacy of bortezomib: avoid concomitant use.

**Cytochrome P34A inhibitors** (ketoconazole and otherazole antifungals, clarithromycin, erythromycin) may increase bortezomib levels: avoid concomitant use.

**Cytochrome P34A inducers** (rifampicin, carbamazepine, phenytoin, St Johns Wort) may reduce bortezomib levels: avoid concomitant use.

**Additional comments**

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**References**

- Morabito et al. Bortezomib, melphalan, prednisone (VMP) versus melphalan, prednisone, thalidomide (MPT) in elderly newly diagnosed multiple myeloma patients: a retrospective case-matched study/ Am J Hematology. 2014: 89 (4); 355-362

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