MELPHALAN, BORTEZOMIB (VELCADE), PREDNISOLONE (MelBorPred)

INDICATION

1- First-line treatment of multiple myeloma in patients who are unable to tolerate, or have contraindications to, thalidomide and who are unsuitable for stem cell transplantation (NICE TA228).

2- May have a role in the treatment of progressive multiple myeloma at second or subsequent relapse in patients who have not received prior bortezomib containing regimen.

Note: MelBorPred may be particularly suitable for patients over the age of 75 or those with marked pre-existing neuropathy. As it uses weekly Bortezomib for 4 weeks over a 35 day cycle, the incidence of serious neuropathy is likely to be less than with twice weekly administration. This protocol has been modified from the VISTA trial. In this study a maximum of 51 doses of Bortezomib were given.

TREATMENT INTENT
Disease Modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - PT and APTT or Coagulation profile
   - U&Es
   - LFTs
   - Calcium
   - Uric acid
   - CRP
   - Virology: HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Calculated creatinine clearance (CrCl), urine protein/creatinine ratio,
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   - Serum free light chain assay (Freelite)
   - Hevylite analysis (if paraprotein level difficult to quantify)
   - Albumin & β2 microglobulin for ISS staging
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions. Samples should be sent to Wessex Regional Genetics Laboratory (address below)
   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
   - Group and save
   - Imaging as per NICE/network guidance and clinical presentation
   - Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)
ADDITIONAL INVESTIGATIONS

- Plasma viscosity if hyperviscosity suspected.

2. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.

3. Fertility - all patients should be offered fertility advice, as appropriate.

4. Hydration - fluid intake of at least 3 litres /day should be attempted.


6. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE -ASSESSMENT

Evaluate for presence of neuropathy. This is usually done by clinical assessment although nerve conduction studies may be useful in occasional patients to document the extent of neurological damage prior to treatment with Bortezomib. Baseline clinical assessment must be documented in the notes before the first dose of Bortezomib is prescribed.

Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1

DRUG REGIMEN

<table>
<thead>
<tr>
<th>Bortezomib</th>
<th>1.3 mg/m² given SC bolus</th>
<th>Days 1, 8, 15, 22</th>
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<tbody>
<tr>
<td>WITH</td>
<td></td>
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<tr>
<td>Melphalan</td>
<td>7 mg/m² PO daily (tablets are 2 mg in strength)</td>
<td>Days 1 - 4</td>
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<tr>
<td>Prednisolone</td>
<td>60 mg/m² PO daily (5 mg and 25 mg in strength)</td>
<td>Days 1 - 4</td>
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<td>NB: Dose of prednisolone may be reduced in the very elderly or if significant toxicity occurs</td>
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</table>

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

Repeat every 35 days, continue until signs of disease progression or unacceptable toxicity. It is recommended that patients receive up to 12 treatment cycles particularly in a newly diagnosed patient to ensure optimal Bortezomib exposure. In a relapsed setting in patients with a confirmed maximal response receive 2 additional cycles of treatment to a total of 8 cycles.

DOSE MODIFICATIONS

Dose adjustments during treatment and re-initiation of treatment for combination therapy

Prior to initiating a new cycle of therapy:
• Platelets ≥ 70 x 10^9/L and ANC ≥ 1.0 x 10^9/L
• Non-haem toxicities should resolve to G1 or baseline

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Posology modification or delay</th>
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<tbody>
<tr>
<td><strong>Haematological toxicity during a cycle</strong></td>
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<tr>
<td>• If prolonged G4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle</td>
<td>Reduce melphalan dose by 25% in the next cycle.</td>
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<tr>
<td>• If platelet ≤ 30 x 10^9/L or ANC ≤ 0.75 x 10^9/L on a Bortezomib dosing day (other than Day 1)</td>
<td>Withhold Bortezomib</td>
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<tr>
<td>• If several Bortezomib doses in a cycle are withheld ≥ 2 doses during weekly administration</td>
<td>Bortezomib reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)</td>
</tr>
<tr>
<td><strong>G ≥ 3 non-haem toxicities</strong></td>
<td>Bortezomib withheld until symptoms resolved to G1 or baseline. Bortezomib reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)</td>
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<tr>
<td><em>(see below for neuropathic pain and/or peripheral neuropathy)</em></td>
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**Bortezomib-related neuropathy:**

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Posology modification</th>
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<tr>
<td>G1 with no pain or loss of function</td>
<td>None</td>
</tr>
<tr>
<td>G1 with pain or G2</td>
<td>Reduce to 1.0 mg/m^2</td>
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<tr>
<td>G2 with pain or G3</td>
<td>Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m^2 once per week.</td>
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<tr>
<td>G4 and/or severe autonomic neuropathy</td>
<td>Discontinue</td>
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</table>

**Bortezomib:**

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
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<tr>
<td>- For dialysis patients, bortezomib should be given after dialysis No dose reduction necessary</td>
<td>Bili &gt; 1.5x ULN: reduce to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.</td>
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**Melphalan:**

<table>
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<th>Renal</th>
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<tr>
<td>GFR 10 – 50 mL/min</td>
<td>50% dose</td>
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<tr>
<td>GFR &lt; 10 mL/min</td>
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**INVESTIGATIONS (at the beginning of each cycle unless otherwise noted)**

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC (prior to each Bortezomib dose if known thrombocytopenia)
- U&E, LFTs, Ca++
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib.
- Blood pressure (consider checking for postural drop if symptomatic)
- Igs, Paraprotein,
- Serum free light chain
- Consider repeat BM aspirate and trephine after 3 courses in non-secretory myeloma and check result prior to starting cycle 5
- Random blood glucose/ blood sugar

**CONCURRENT MEDICATIONS**

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prophylactic aciclovir 200 mg bd to tid for the duration of treatment and 3 months post therapy.
- Bone protection as per NSSG Bone Protection protocol MM Proton Pump Inhibitor or H2 antagonist at clinician’s discretion.
- Consider prophylactic fluconazole.
- Consider prophylactic co-trimoxazole, particularly if heavily pre-treated or previous autograft.
- Prescribe loperamide if needed for diarrhoea.

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, antivirals, isoniazid, nitrofurantoin or statins), or with a decrease in blood pressure.

Patients on Bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). The concomitant use of bortezomib with strong CYP3A4-inducers (rifampicin, carabamazepine, phenytoin, phenobarbital, and St John’s wort) is not recommended as efficacy may be reduced.

Patients on oral hypoglycaemic may require close monitoring of blood sugar levels.

**EMETIC RISK**

Low emetic risk.
ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

- **Painful neuropathy**: Patients should be advised to report pain hypersensitivity prickling, numbness and paraesthesia, if these occur see above dose reductions and consider use of Amitriptyline, Gabapentin and Pain Team referral. Neuropathy assessment tools are available in DTU.

- **Dizziness and orthostatic hypotension**: Patients should be advised that bortezomib may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position. Caution in patients with history of syncope, receiving medications associated with hypotension and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells. Patients who experience dizziness or low blood pressure may benefit from 500 mL intravenous 0.9% sodium chloride with each bortezomib dose.

- **Gastrointestinal**: Nausea, diarrhoea, vomiting and constipation are very common and ileus has been reported.
- Caution in patients with history of syncope, receiving medications associated with hypotension and patients who are dehydrated.
- Herpes zoster virus reactivation, progressive multifocal leukoencephalopathy (PML)
- Caution in patients with existing peripheral neuropathy ( > Grade 2).

TREATMENT RELATED MORTALITY

<5%

REFERENCES


6. eMC UK Summary of Product Characteristics for Velcade, Janssen, March 2017


10. eMC UK Summary of Product Characteristics for Melphalan 2mg tabs, Aspen, March 2014

11. eMC UK Summary of Product Characteristics for Prednisolone 1mg and 5 mg tablets, Wockhardt UK Ltd, November 2015

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**REVIEW**

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<tbody>
<tr>
<td>Nadjoua Maouche Pharmacist</td>
<td>Formatting, adverse effects and pre assessment section, dose regimen contraindication section removed</td>
<td>May 2016</td>
<td>1.7</td>
<td>May 2018</td>
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<tr>
<td>Dr J. Kothari Consultant</td>
<td>Regimen specific pre assessment section included</td>
<td>May 2016</td>
<td>1.7</td>
<td>May 2018</td>
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<tr>
<td>Faouzi Djebbari (Haematology Pharmacist)</td>
<td>Updated renal and hepatic impairment, concurrent medication, adverse effects and references</td>
<td>July 2017</td>
<td>1.8</td>
<td>June 2018</td>
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