BORTEZOMIB THALIDOMIDE AND DEXAMETHASONE (VTD) 21 day cycle

INDICATIONS

1- Induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation [NICE TA311].

1- Appropriate therapy for relapsed or refractory multiple myeloma in patients who are at second or more relapse and who have not received prior bortezomib based therapy. Funding from the Cancer Drugs Fund is required. Requires Blueteq approval

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Baseline random blood glucose level
   - 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)
   - β2 microglobulin
   - LDH
   - 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)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Additional Investigations
- Plasma viscosity if hyperviscosity suspected
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology

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. Document patient’s performance status
7. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE-ASSESSMENT

1. 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
2. The conditions of the Thalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the Celgene Pregnancy Prevention Programme
3. Clinical assessment of thrombo-embolic risk
4. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1

DRUG REGIMEN

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Schedule</th>
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</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² given S/C bolus</td>
<td>Days 1, 4, 8 and 11</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>50 - 100 mg PO (preferably nocte) Start at 50mg and increase as tolerated</td>
<td>Daily</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20 mg PO once daily</td>
<td>Days 1, 2, 4, 5, 8, 9, 11 and 12 - i.e. day of and day after each bortezomib dose</td>
</tr>
</tbody>
</table>

At least 72 hours should elapse between consecutive doses of bortezomib.
Bortezomib can also be administered weekly on days 1, 8 and 15 in a 21 days cycle.

If neurotoxicity precludes completing planned therapy, consider completing VTD following autologous transplant.
CYCLE FREQUENCY

Repeat every 21 days. It is recommended that patients with a confirmed maximal response receive 2 additional cycles of treatment beyond confirmation of this status to a maximum of 8 treatment cycles (total 24 doses of bortezomib).

Allowable number of doses is as follows
- 24 doses for transplant eligible patients (first line of treatment)
- 51 doses for transplant ineligible (first line of treatment) patients
- 32 doses at first relapse

DOSE MODIFICATIONS

Haematological toxicity

BORTEZOMIB:
Thrombocytopenia due to Bortezomib is transient and very rarely causes significant bleeding. If baseline platelet count is > 70, then the risk of severe thrombocytopenia is very low.

In such patients, FBC should be checked only at the start of the cycle and does not need to be repeated before each dose.

In patients with plts < 70 at the start of each cycle, the FBC should be checked before each dose, the drug should be withheld until FBC is through and the dose omitted if the platelets are < 25 unless thrombocytopenia is thought to be mainly due to marrow infiltration by myeloma. In those circumstances, consider proceeding with treatment with platelet transfusion support.

In all other circumstances, if these levels are not reached, then treatment should be withheld and subsequent doses reduced by 25% (i.e. from 1.3 mg/m² to 1.0 mg/m² or from 1.0 mg/m² to 0.7 mg/m²).

Peripheral neuropathy

BORTEZOMIB:
If there are symptoms of peripheral neuropathy, the dose reduction schedule must be invoked (see below). The drug should be stopped if symptoms or signs progress despite this.

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<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/m² or Change treatment schedule to 1.3 mg/m² once per week if currently is twice per week</td>
</tr>
<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/m² once per week.</td>
</tr>
<tr>
<td>G4 and/or severe autonomic neuropathy</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

THALIDOMIDE:  
Thalidomide should be stopped or dose reduced if there are symptoms of progressive peripheral neuropathy causing functional disability (grade 2 or above). Consider cautious re-introduction of thalidomide at a dose of 50mg daily if symptoms resolve to grade 1 or better after a two-week gap. Subsequent cautious dose escalation should be considered if symptoms permit. Switching to
CyBorDex is a reasonable alternative.

**Renal & Hepatic impairment:**

<table>
<thead>
<tr>
<th>BORTEZOMIB</th>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>For dialysis patients, bortezomib should be given after dialysis.</td>
<td>Bil 1.0-1.5 x ULN: no dose reduction required</td>
<td>Bili &gt; 1.5 x ULN: reduce to 0.7 mg/m² in the first treatment cycle. Consider dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.</td>
</tr>
<tr>
<td>No dose reduction necessary</td>
<td></td>
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<tr>
<th>THALIDOMIDE</th>
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**INVESTIGATIONS (at the beginning of each cycle)**

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&Es, LFTs, Ca²⁺
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle.
- Blood pressure (consider checking for postural drop if symptomatic)
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

**CONCURRENT MEDICATIONS**

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and 3 months post therapy.
- Prophylactic fluconazole 50mg OD
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton Pump Inhibitor or H2 antagonist at clinician’s discretion
- Thromboprophylaxis/anticoagulation- see VTE section below
- Bone protection as per NSSG Bone Protection protocol MM.3

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.
Extravasation risk: bortezomib-irritant

EMETIC RISK
Low

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

- **Teratogenic**: The Celgene Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention programme.

- **Peripheral 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. Caution in patients with existing peripheral neuropathy.

- **Venous thromboembolism (VTE)**: There is an increased risk of thrombosis with thalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:
  1. Prophylactic low-molecular weight heparin OR
  2. Prophylactic NOAC e.g. apixaban 2.5mg bd (check product specific information)

  Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors.

  If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- **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 500ml intravenous 0.9% sodium chloride with each dose of bortezomib.

- **Gastrointestinal**: Nausea, diarrhoea, vomiting and constipation are very common and ileus has been reported.

- **Drowsiness, somnolence and sedation**: Take the thalidomide dose at night time. Thalidomide may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking thalidomide.

- **Skin toxicity**: in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.
Other warnings: Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

TREATMENT RELATED MORTALITY

<5%

REFERENCES


2. Bortezomib (Velcade®) eMC UK Summary of Product Characteristics for, Janssen, February 2019


6. Thalidomide, Celgene® eMC UK Summary of Product Characteristics for April 2019

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 modification, contraindication section removed</td>
<td>May 2016</td>
<td>1.3</td>
<td>May 2018</td>
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<tr>
<td>Dr J. Kothari Consultant</td>
<td>Regimen specific pre assessment included</td>
<td>May 2016</td>
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<td>May 2018</td>
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<tr>
<td>Faouzi Djebbari (Haematology Pharmacist)</td>
<td>Updated haematological toxicity, renal and hepatic impairment, concurrent medications, adverse effects and references</td>
<td>July 2017</td>
<td>1.4</td>
<td>June 2018</td>
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<tr>
<td>Nadjoua Maouche</td>
<td>Indications. Standardise assessment, investigations, concurrent medication, VTE assessment, adverse effects.</td>
<td>June 2018</td>
<td>1.5</td>
<td>June 2019</td>
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<tr>
<td>Myeloma Protocol Review 2019</td>
<td>Update of indication, addition of allowable number of doses per treatment line, clarification of dosing in hepatic impairment, extravasation risk, update of references</td>
<td>June 2019</td>
<td>1.6</td>
<td>June 2020</td>
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