BORTEZOMIB 35d

INDICATIONS

1- Relapsed or refractory multiple myeloma in patients who are at first relapse having received one prior line of therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances [NICE TA129]:
   - the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and
   - the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above). [NICE TA129]

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

3- Bortezomib is on the list of drugs routinely commissioned by NHSE (baseline commissioning) for the following indications:
   - 1st line treatment of multiple myeloma in patients who are not NICE eligible for bortezomib due to presentation with:
     a) Severe renal failure contraindicating standard therapy (< 30 ml/min) or on haemodialysis
     b) Multisystem amyloidosis (on amyloid centre review)
   - 1st line treatment of multiple myeloma in patients for whom transplant is considered unsuitable

4- 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 application

Note: This 35d regimen (unlicensed) adapted from APEX trial is preferred in most patients and particularly in those at high risk of neuropathy. A protocol for a 21d regimen is also approved and may be suitable where a rapid response is required. Unless there is a contraindication to steroids, the use of Dexamethasone, given on the day of and the day after each dose of bortezomib, is recommended to improve response rates.

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)
   - Hevylite analysis (if paraprotein level difficult to quantify)
   - 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
Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ

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.


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. Baseline clinical assessment must be documented in the notes before the first dose of bortezomib is prescribed.

2. 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 as SC bolus as standard.</th>
<th>Days 1, 8, 15 and 22 on a 35 day cycle.</th>
</tr>
</thead>
</table>

WITH

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<thead>
<tr>
<th>Dexamethasone</th>
<th>20 mg PO once daily</th>
<th>Day of and day after each bortezomib dose. This will usually be days 1, 2, 8, 9, 15, 16, 22 &amp; 23.</th>
</tr>
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</table>

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

CYCLE FREQUENCY

Repeat every 35 days until signs of disease progression or unacceptable toxicity. 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. If there is no response after 2 cycles, the addition of Cyclophosphamide to the Bortezomib and Dexamethasone may be clinically appropriate (switch to CyBorDex).

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

The NICE authorisation for first relapse in bortezomib naïve patients states that if patients have failed to reach at least a 50% reduction in paraprotein after 4 cycles, there will be no funding for any further courses and the drug must be stopped. In those circumstances, the manufacturers will refund the cost of the 4 cycles via the established rebate scheme. Patients should have formal assessment of response documented in the notes prior to proceeding to cycle #5. In patients with non-secretory myeloma, this may require a repeat bone marrow aspirate / trephine.
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 platelet count < 70 at the start of each cycle, FBC should be checked before each dose, the drug should be withheld until FBC is through and the dose omitted if 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).

Otherwise withhold at G3 non-haem (excluding neuropathy, see below) or G4 haem toxicities. Once resolved, re-initiate at 25% reduced dose (1.3 mg/m² reduced to 1.0 mg/m²; 1.0 mg/m² reduced to 0.7 mg/m²). If toxicity is not resolved or if it recurs at the lowest dose, discontinue unless benefit outweighs risk.

Peripheral neuropathy

Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

<table>
<thead>
<tr>
<th>Grading of neuropathy</th>
<th>Dose modification</th>
</tr>
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<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</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/m² once per week.</td>
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<tr>
<td>G4 and/or severe autonomic neuropathy</td>
<td>Discontinue</td>
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Hepatic/ Renal impairment:

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
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<tbody>
<tr>
<td>For dialysis patients, bortezomib should be given after dialysis No dose reduction necessary</td>
<td>Bil 1.0−1.5 x ULN: no dose reduction required Bili &gt; 1.5 x ULN: reduce dose 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>
</tbody>
</table>

This is a controlled document and therefore must not be changed
INVESTIGATIONS (at the beginning of each cycle unless otherwise noted)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC (in patients with thrombocytopenia, consider checking FBC prior to each dose of bortezomib)
- U&E, LFTs, Ca++ – every 3 weeks
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib.
- Blood pressure (consider checking for postural drop if symptomatic)
- Ig’s, paraprotein, Freelite assay.
- Consider repeat BM aspirate and trephine after 3 cycles in non-secretory myeloma, and check result prior to starting cycle #5.
- 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 for 3 months after stopping bortezomib
- 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 antagonists at clinician’s discretion.
- Prescribe loperamide if needed for diarrhoea.
- Bone protection as per NSSG Bone Protection protocol MM.3

Extravasation risk: bortezomib-irritant

EMETIC RISK

Low emetic risk

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

- 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.
• **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 medications, 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.

• **Herpes zoster virus reactivation, progressive multifocal leukoencephalopathy (PML).**

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**TREATMENT RELATED MORTALITY**

<5%

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**REFERENCES**

transplantation (TA311). Online. Available at: https://www.nice.org.uk/guidance/TA311/chapter/1-guidance


REVIEW

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</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 Jaimal Kothari</td>
<td>Regimen specific pre assessment included</td>
<td>May 2016</td>
<td>1.3</td>
<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>Funding. Standardisation of assessment, investigations supports, adverse events.</td>
<td>June 2018</td>
<td>1.5</td>
<td>June 2018</td>
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<tr>
<td>Myeloma Protocol Review 2019</td>
<td>Clarification of dosing in hepatic impairment, dose modification, concurrent medications, extravasation risk, update of references</td>
<td>June 2019</td>
<td>1.6</td>
<td>June 2020</td>
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