CYCLOPHOSPHAMIDE / BORTEZOMIB / DEXAMETHASONE (CycloBorDex)

INDICATIONS

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- Induction treatment of adult patients with previously untreated MM who are eligible for high dose chemotherapy with hematopoietic stem cell transplantation [NICE TA311]

3- An option for first-line treatment of multiple myeloma in patients unsuitable for stem cell transplantation and with advanced renal failure (dialysis either current or imminent) (Baseline commissioning)

4- 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]

5- 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

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   o FBC & film
   o Clotting screen
   o U&Es
   o LFTs
   o Calcium
   o Albumin
   o Uric acid
   o CRP
o Baseline random blood glucose level
o Virology: HIV, Hepatitis B (including core antibody), and Hepatitis C
o Calculated creatinine clearance (CrCl), urine protein/creatinine ratio
o Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
o Serum free light chain assay (Freelite)
o Hevylite analysis (if paraprotein level difficult to quantify)
o β₂ microglobulin
o LDH
o 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)
o Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
o Group and save
o Imaging as per NICE/network guidance and clinical presentation
o 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>Drug</th>
<th>Dosage</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² given as SC bolus</td>
<td>Days 1, 8 and 15</td>
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<tr>
<td>WITH</td>
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<tr>
<td>Dexamethasone</td>
<td>20 mg PO once daily</td>
<td>On the day of and day after each Bortezomib dose. This will usually be days 1, 2, 8, 9, 15 &amp; 16</td>
</tr>
<tr>
<td>WITH</td>
<td></td>
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<tr>
<td>Cyclophosphamide</td>
<td>500 mg PO or IV weekly or, 50 mg daily PO</td>
<td>Days 1, 8 and 15 for weekly dosing</td>
</tr>
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</table>

At least 72 hours should elapse between consecutive doses of Bortezomib. **Bortezomib is given once weekly over 21 days with no break between cycles.**
Consider reduction of dexamethasone dose in elderly patients.

## CYCLE FREQUENCY

Repeat every 21 days, continue until signs of disease progression or unacceptable toxicity. 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 states that for patients treated at first relapse, if they 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: Prior to initiating a new cycle of therapy:
- Platelets $\geq 70 \times 10^9/L$ and ANC $\geq 1.0 \times 10^9/L$
- 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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</thead>
<tbody>
<tr>
<td>If prolonged G4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle</td>
<td>Omit cyclophosphamide 1 week (continue dexamethasone). Restart at same dose when neutrophils and platelets recovered as above. If recurrent, i.e. if neutrophils $&lt; 1.0 \times 10^9/L$ and platelets $&lt; 50 \times 10^9/L$ on day 1 of subsequent cycles (when previously $&gt;$ than these levels), omit cyclophosphamide and consider dose reduction of cyclophosphamide for subsequent doses. If the patient was receiving 500 mg weekly, reduce to 400 mg, if 400 mg reduce to 300 mg, if 300 mg reduce to 200 mg. If patients receiving 50 mg daily omit for a week and consider reduced frequency.</td>
</tr>
<tr>
<td>If platelet $\leq 30 \times 10^9/L$ or ANC $\leq 0.75 \times 10^9/L$ on a bortezomib dosing day (other than Day 1)</td>
<td>Withhold bortezomib</td>
</tr>
<tr>
<td>If several bortezomib doses in a cycle are withheld ($\geq 3$ doses during twice weekly administration or $\geq 2$ doses during weekly administration)</td>
<td>Reduce bortezomib 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>G $\geq 3$ non-haem toxicities (see above for neuropathic pain and/or peripheral neuropathy)</td>
<td>Withhold bortezomib until symptoms resolved to G1 or baseline then reinitiate 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>
</tr>
</tbody>
</table>

### Bortezomib-related neuropathy:

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Posology 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/m$^2$</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/m$^2$ once per week.</td>
</tr>
<tr>
<td>G4 and/or severe autonomic neuropathy</td>
<td>Discontinue</td>
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### Renal/Hepatic Impairment:

#### Bortezomib:

<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</td>
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<tr>
<td></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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</tbody>
</table>
Cyclophosphamide:

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
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</thead>
<tbody>
<tr>
<td>Clinical decision</td>
<td>Exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary.</td>
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<tr>
<td>GFR &gt; 20ml/min</td>
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<tr>
<td>100% dose</td>
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<tr>
<td>GFR 10 – 20ml/min</td>
<td>Clinical decision.</td>
</tr>
<tr>
<td>75% dose</td>
<td></td>
</tr>
<tr>
<td>GFR &lt; 10ml/min</td>
<td></td>
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<tr>
<td>50% dose</td>
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Cyclophosphamide related toxicities include: leucopenia, amenorrhoea, haematuria, hair loss, mucosal ulceration, anorexia, nausea and vomiting, pigmentation (typically affecting the palms and nails of the palms and the soles of the feet) and interstitial pulmonary fibrosis. Dexamethasone related toxicities include: mood changes, restlessness, withdrawal effects, glucose intolerance.

**INVESTIGATION** (at the beginning of each cycle unless otherwise noted)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC (weekly)
- 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).
- 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 3 months post therapy.
- Consider 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.
- Prescribe loperamide if needed for diarrhoea.
- 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, carbamazepine, phenytoin, phenobarbital, and St John’s wort) is not recommended as efficacy may be reduced.

**Extravasation risk:** bortezomib-irritant
EMETIC RISK

Moderate emetic risk on weekly cyclophosphamide days, otherwise low 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 (> Grade 2).

- **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.

- **Cyclophosphamide related toxicities include:** leucopenia, amenorrhoea, haematuria, hair loss, mucosal ulceration, anorexia, nausea and vomiting, pigmentation (typically affecting the palms and nails of the palms and the soles of the feet), pneumonitis and interstitial pulmonary fibrosis.

- **Dexamethasone related toxicities include:** mood changes, restlessness, withdrawal effects, glucose intolerance.

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

TREATMENT RELATED MORTALITY

<5%

REFERENCES
