CYCLOPHOSPHAMIDE / BORTEZOMIB/DEXAMETHASONE (CycloBorDex) AMYLOIDOSIS PROTOCOL

INDICATION

Bortezomib is routinely commissioned by NHS England (baseline commissioning) for the 1st line treatment of patients with multi-system amyloidosis following National Amyloidosis Centre review

Note: Mayo-stage III patients have an overall mortality risk of 50% in the first year.

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 Uric acid
   o CRP
   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 Albumin & $\beta_2$ microglobulin for ISS staging
   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
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

- 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.
- Echocardiogram/ cardiac MRI as appropriate
- Patients with suspected/proven cardiac amyloid should be managed as an inpatient on a cardiology ward for at least the first cycle, joint care with cardiologist. Admit patients for chemotherapy if systolic BP <100mmHg, NT-pro BNP >1800pg/mL, or Mayo stage III or IV

Refer for a specialist review at the national amyloidosis centre.

DRUG REGIMEN

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib</strong></td>
<td>1.3 mg/m² given as SC bolus as standard. In certain situations, in the first cycle, bortezomib can be administered intravenously in patients with impaired sub-cut absorption</td>
<td>Days 1, 8, 15 and 22.</td>
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<tr>
<td>WITH</td>
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<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>10 mg PO once daily increased to 20mg once daily if tolerated</td>
<td>On days of bortezomib only.</td>
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<td>WITH</td>
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<thead>
<tr>
<th>Treatment</th>
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<th>Days</th>
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<tbody>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>500 mg PO or IV weekly</td>
<td>Days 1, 8, 15, 22 and 29 for weekly dosing</td>
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<tr>
<td>OR 50 mg daily PO</td>
<td>Days 1-35</td>
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In patients with suspected/proven cardiac amyloid, add Doxycycline 100mg BD
CYCLE FREQUENCY

Repeat every 35 days, for typically between 4-6 cycles. Consider reduction of dexamethasone dose in elderly patients and watch fluid balance closely.

DOSE MODIFICATIONS

Haematological toxicity:

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Posology modification or delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological toxicity during a 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 x 10^9/L and platelets &lt; 50 x 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 50mg daily omit for a week and consider reduced frequency.</td>
</tr>
<tr>
<td>• If prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>• If several bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 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 ≥ 3 non-haematological toxicities (see above for neuropathic pain and/or peripheral neuropathy)</td>
<td>Withhold bortezomib until symptoms resolved to G1 or baseline then reinitiate treatment at 0.7 mg/m^2 once per week.</td>
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</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>
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<tr>
<td>G4 and/or severe autonomic neuropathy</td>
<td>Discontinue</td>
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</table>
Renal/Hepatic Impairment:

Bortezomib:

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

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
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<tbody>
<tr>
<td>Clinical decision</td>
<td>Exposure to active metabolites may not be increased,</td>
</tr>
<tr>
<td>GFR &gt; 20ml/min</td>
<td>suggesting that dose reduction may not be necessary.</td>
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<tr>
<td>GFR 10 – 20ml/min</td>
<td>Clinical decision.</td>
</tr>
<tr>
<td>GFR &lt; 10ml/min</td>
<td></td>
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<tr>
<td>100% dose</td>
<td></td>
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<tr>
<td>75% dose</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.

INVESTIGATIONS (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 bone marrow assessment after four cycles for non-secretory Myeloma.
- Random blood glucose/ blood sugar

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 Bone protection as per NSSG Bone Protection protocol MM.3
- Proton Pump Inhibitor or H2 antagonist at clinician’s discretion.
- Consider prophylactic fluconazole 50mg od.
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.

- Prescribe loperamide if needed for diarrhoea.
Myeloma group

- In patients with suspected/proven cardiac amyloid, add Doxycycline 100mg BD, and monitor/counsel patients regarding photosensitivity.

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, carbamazepine, 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.

Refer to cyclophosphamide SPC for full details of drug interactions.

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**Extravasation risk:** bortezomib-irritant

**EMETIC RISK**

Moderate emetic risk on weekly cyclophosphamide days, otherwise low risk.

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**ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS**

**Sudden Cardiac Death:** patients with proven/suspected cardiac amyloid have a risk of fatal arrhythmias in the early days/weeks of treatment. Patients should be counselled appropriately for this.

- **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. 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, amenorrhea, haemorrhagic cystitis, 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)

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**TREATMENT RELATED MORTALITY**

Patients with Mayo Stage III amyloid have an approximate 50% mortality in the first year. Patients should be carefully counselled about this very high risk.

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**REFERENCES**

6. eMC UK Summary of Product Characteristics for Velcade, Janssen, February 2019
10. eMC UK Summary of Product Characteristics for cyclophosphamide 50 mg tablets, Pharmacia, Dec 2016.

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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, drug regime, contraindication section removed</td>
<td>May 2016</td>
<td>1.2</td>
<td>May 2018</td>
</tr>
<tr>
<td>Faouzi Djebbari (Haematology Pharmacist)</td>
<td>Updated indication, drug regimen, haematological toxicity, renal and hepatic impairment, concurrent medications, adverse effects and references</td>
<td>July 2017</td>
<td>1.3</td>
<td>June 2018</td>
</tr>
<tr>
<td>Cheuk-kie Jackie Cheung (Haematology Pharmacist)</td>
<td>Addition of prophylactic fluconazole</td>
<td>July 2017</td>
<td>1.4</td>
<td>June 2018</td>
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