

# 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.

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## TREATMENT INTENT

Disease modification

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## GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:

- FBC & film
- Clotting screen
- 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 &  $\beta_2$  microglobulin for ISS staging
- 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**

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**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.
  5. Document patient's height and weight, dose on actual body weight.
  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**

<b>Bortezomib</b>	1.3 mg/m <sup>2</sup> 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	Days 1, 8, 15 and 22.
WITH		
<b>Dexamethasone</b>	10 mg PO once daily increased to 20mg once daily if tolerated	On days of bortezomib only.
WITH		
<b>Cyclophosphamide</b>	500 mg PO or IV weekly	Days 1, 8, 15, 22 and 29 for weekly dosing
	OR 50 mg daily PO	Days 1-35

**In patients with suspected/proven cardiac amyloid, add Doxycycline 100mg BD**

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## 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  $\geq 70 \times 10^9/L$  and ANC  $\geq 1.0 \times 10^9/L$
- Non-haem toxicities should resolve to G1 or baseline

Toxicity	Posology modification or delay
<b>Haematological toxicity during a cycle</b>	
<ul style="list-style-type: none"> <li>• If prolonged grade4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle</li> </ul>	Omit cyclophosphamide 1 week (continue dexamethasone). Restart at same dose when neutrophils and platelets recovered as above. If recurrent, i.e. if neutrophils $< 1.0 \times 10^9/L$ and platelets $< 50 \times 10^9/L$ on day 1 of subsequent cycles (when previously $>$ 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.
<ul style="list-style-type: none"> <li>• If platelet <math>\leq 30 \times 10^9/L</math> or ANC <math>\leq 0.75 \times 10^9/l</math> on a bortezomib dosing day (other than Day 1)</li> </ul>	Withhold bortezomib
<ul style="list-style-type: none"> <li>• If several bortezomib doses in a cycle are withheld (<math>\geq 3</math> doses during twice weekly administration or <math>\geq 2</math> doses during weekly administration)</li> </ul>	Reduce bortezomib by 1 dose level (from 1.3 mg/m <sup>2</sup> to 1 mg/m <sup>2</sup> , or from 1 mg/m <sup>2</sup> to 0.7 mg/m <sup>2</sup> )
G $\geq 3$ non-haem toxicities  (see above for neuropathic pain and/or peripheral neuropathy)	Withhold bortezomib until symptoms resolved to G1 or baseline then reinitiate with one dose level reduction (from 1.3 mg/m <sup>2</sup> to 1 mg/m <sup>2</sup> , or from 1 mg/m <sup>2</sup> to 0.7 mg/m <sup>2</sup> )

### Bortezomib-related neuropathy:

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

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**Renal/Hepatic Impairment:**

**Bortezomib:**

Renal	Hepatic
For dialysis patients, bortezomib should be given after dialysis No dose reduction necessary	Bil 1.0-1.5 x ULN: no dose reduction required  Bili > 1.5x ULN: reduce to 0.7 mg/m <sup>2</sup> in the first treatment cycle. Consider dose escalation to 1.0 mg/m <sup>2</sup> or further dose reduction to 0.5 mg/m <sup>2</sup> in subsequent cycles based on patient tolerability.

**Cyclophosphamide:**

Renal	Hepatic
Clinical decision GFR > 20ml/min 100% dose GFR 10 – 20ml/min 75% dose GFR < 10ml/min 50% dose	Exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision.

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<sup>++</sup>
- 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.

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- 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.

**Extravasation risk:** bortezomib-irritant

#### EMETIC RISK

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

#### 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, amenorrhoea, 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)

## 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.

## REFERENCES

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## REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, drug regime, contraindication section removed	May 2016	1.2	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated indication, drug regimen, haematological toxicity, renal and hepatic impairment, concurrent medications, adverse effects and references	July 2017	1.3	June 2018
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Addition of prophylactic fluconazole	July 2017	1.4	June 2018
Myeloma Protocol Review 2019	Update of general pre- assessment, clarification of dosing in hepatic impairment, update of concurrent medications, extravasation risk, update of references	June 2019	1.5	June 2020
Quality manager	Nursing Care plan added	April 2021	1.6	June 2020

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## Nursing Care Plan

### Cyclophosphamide Bortezomib Dexamethasone for Amyloidosis

**Indication:** First line treatment of patients with multi-system amyloidosis following National Amyloidosis Centre review

**Frequency:** Each cycle lasts 35 and typically 4-6 cycles are given.

**Alopecia:** Potential for hair thinning/loss with cyclophosphamide.

**CYCLOPHOSPHAMIDE:** Alkylating agent.

Administered as orally on **days 1, 8, 15, 22 and 29 if having weekly dosing. Some patients may have a lower dose of cyclophosphamide, which is given on days 1-35 of each cycle.**

**Emetic risk:** moderate.

**Side effects:** nausea/vomiting, diarrhoea, myelosuppression, taste changes, minimal alopecia, bone marrow suppression, low risk haemorrhagic cystitis.

**BORTEZOMIB (VELCADE):** Proteasome inhibitor

Administered subcutaneously on **days 1, 8, 15 and 22.** Minimum of 72 hours required between doses.

**Emetic risk:** Low.

**Classification of extravasation:** irritant

**Side effects:** tachycardia, diarrhoea, constipation, anorexia, nausea/vomiting, thrombocytopenia, neutropenia, peripheral neuropathy (sensory and motor), headache, rash, fatigue, postural hypotension, dizziness, shingles, inflammation at injection site, infections, bone marrow depression.

**DEXAMETHASONE:** corticosteroid tablets

Administered orally on the day of each bortezomib dose only. Taken with or after food preferably at breakfast

**Side effects:** restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

#### Regime Specific Considerations

- Lying and standing Blood pressure to be recorded pre cycle 1, advise patients that velcade can cause orthostatic hypotension and counsel them to sit upright for a moment before standing from a sitting/lying position.
- Bloods are required at the start of each cycle. Patients with unstable blood counts (specifically low platelets, see protocol) may require more frequent monitoring.
- Pregnancy test for pre-menopausal women under the age of 55 before the start of each cycle.
- Advise patients to maintain a fluid intake of 2-3 litres and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.

Assess for presence of peripheral neuropathy before starting treatment and **prior to the start of each cycle.**