CYCLOPHOSPHAMIDE / BORTEZOMIB / DEXAMETHASONE (VCD)

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

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)
   - β_2 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 Disctrict Hospital
Salisbury
Wiltshire
SP2 8BJ

Additional Investigations

1 Plasma viscosity if hyperviscosity suspected.
2 If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology.
3 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.
4 Fertility - all patients should be offered fertility advice, as appropriate.
5 Hydration - fluid intake of at least 3 litres /day should be attempted.
6 Document patient's height and weight, dose on actual body weight.
7 Document patient's performance status.
8 Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE-ASSESSMENT

1. Evaluate for presence of neuropathy prior to starting bortezomib. 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

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1, 8 and 15	Subcutaneous bolus over 3 to 5 minutes
Dexamethasone	20mg OD	1, 2, 8, 9, 15 and 16 (on the day of and day after each Bortezomib dose)	Oral
Cyclophosphamide	500mg OD	1, 8 and 15	Oral or Intravenous
	OR		
	50mg OD	Once daily from days 1 to 21	Oral

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 for the maximum number of allowed bortezomib doses, until signs of disease progression or unacceptable toxicity. Allowable number of doses is as follows

- 51 doses for transplant ineligible patients (first line therapy)

DOSE MODIFICATIONS

Prior to initiating a new cycle of therapy:

- Platelets 70 x 10^9/L
- Absolute Neutrophil Count (ANC) ≥ 1.0 x 10^9/L
- Non-haematological toxicities should resolve to grade 1 or baseline

Haematological Toxicity:

Bortezomib	
If on a bortezomib dosing day (other than day 1): Platelet ≤ 30 x 10^9/L or ANC ≤ 0.75 x 10^9/l	Withhold bortezomib
If several bortezomib doses in a cycle are withheld: ≥ 2 doses during weekly administration	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)
Cyclophosphamide	
If prolonged grade 3 neutropenia or thrombocytopenia, or if thrombocytopenia with bleeding is observed in the previous cycle	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 x 10^9/L and platelets < 50 x 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 a reduced frequency.

Non-haematological Toxicity:

Bortezomib	
Any ≥ grade 3 non-haem toxicities (except neuropathic pain and/or peripheral neuropathy)	Withhold bortezomib until symptoms resolved to grade 1 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)
Cyclophosphamide	
Grade 2 or higher urinary tract or bladder toxicity.	Withhold Cyclophosphamide. Resume once toxicity resolves to grade 1 or lower.
Any other grade 3 or 4 non-haematological toxicities	
Treatment doses may be withheld at the clinician's discretion.	

Peripheral neuropathy:

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

	Severity (CTCAE Grade)	**Recommendation**
Bortezomib	Grade 1 with no pain or loss of function	No adjustment.
	Grade 1 with pain or Grade 2	Reduce to 1.0 mg/m2
	Grade 2 with pain or Grade 3	Withhold treatment until symptoms of toxicity have resolved. On resolution - Restart at 0.7 mg/m^2.
	Grade 4 and/or severe autonomic neuropathy	Discontinue

Renal and Hepatic impairment:

Bortezomib	
Renal*	**Hepatic**
No dose reduction necessary. For dialysis patients, bortezomib should be given after dialysis. It is unclear whether baseline kidney dysfunction influences the risk of bortezomib-related renal adverse events.	Bilirubin 1.0 - 1.5 x ULN: No dose reduction required. Bilirubin > 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.

***Renal adverse events (i.e., AKI, thrombotic microangiopathy), although infrequent, have been reported with bortezomib treatment.

Cyclophosphamide	
Renal	**Hepatic**
Clinical decision GFR ≥ 30ml/min 100% dose GFR 10 – 29ml/min 75% dose GFR < 10ml/min 50% dose or omit For dialysis patients: 50% dose, give before dialysis and at a minimum interval of 12 hours prior to dialysis	Exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision. Not recommended in severe liver disease, due to the risk of reduced efficacy.

INVESTIGATIONS

Repeat at the start of each cycle, unless otherwise noted

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&E, LFTs, Ca^{2+}
- 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, serum free light chains by Freelite assay.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance.

CONCURRENT MEDICATIONS

- ***Cycle 1 only*** - Allopurinol 300 mg daily for 7 days (TLS prophylaxis)
- 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 throughout treatment.
- Consider Co-trimoxazole 960mg OD on M/W/F if PJP risk is deemed to be high.
- **For patients newly diagnosed and deemed at very high risk of infections only:** Consider prophylactic levofloxacin 500mg OD for 12 weeks (cycles 1-4). Beware that the **MHRA discourages prophylactic use of fluoroquinolones** since levofloxacin and other fluoroquinolones can cause disabling and potentially long-lasting or irreversible side effects. **The risk/benefit ratio should be carefully considered before use.** See MHRA warning here. Adjust dose for renal function.
- Proton Pump Inhibitor or H2 antagonist at clinician's discretion.
- Consider loperamide if required for the management of transient diarrhoea.
- Bone protection as per NSSG Bone Protection protocol MM.3

INTERACTIONS

The following information may not be fully inclusive, please refer to the individual medicines' summary of product characteristics (medicines.org.uk) or alternative information sources where necessary.

Bortezomib + strong CYP3A inhibitors (ketoconazole, clarithromycin, erythromycin, -azole anti-fungals (excluding low dose fluconazole))**:** Bortezomib serum levels may be increased and may increase toxicities. Concurrent use should be avoided.

Bortezomib + strong CYP3A inducers (rifampicin, carbamazepine, phenytoin, St John's Wort etc.): Bortezomib serum levels may be reduced, this has an unknown effect on overall treatment efficacy, concurrent use is not recommended and should be avoided.

Bortezomib + medicines causing hypotension: Use caution as concurrent medicines may worsen symptoms of hypotension e.g., diuretics, blood pressure medication etc. Closely monitor blood pressure.

Cyclophosphamide + amiodarone: Possible early onset pulmonary toxicity – use with caution.

Cyclophosphamide + digoxin: Possible reduced absorption of Digoxin in tablet form, short lived effect reversible within 7 days of stopping treatment – use with caution.

Cyclophosphamide + grapefruit: Ingestion of grapefruit can decrease or delay activation of cyclophosphamide and should be avoided during treatment, or at a minimum avoided within the 48-hour period preceding treatment and on the day of treatment.

Cyclophosphamide + warfarin/coumarin anticoagulants: Increased or fluctuating anticoagulant effects. Avoid where possible – consider switch to LMWH or DOAC. If continuing treatment, liaise with anticoagulant team (or GP where relevant) to increase INR monitoring frequency and adjust dose.

VCD + anti-hyperglycaemic agents: Use of this regimen can upset control of blood sugar, through direct effects on blood sugar and potentiation of drug-related hypoglycaemic effects. In clinical trials, hypoglycaemia was uncommonly reported while hyperglycaemia was commonly seen. Hyperglycaemia is frequently observed alongside corticosteroid use. Patients with diabetes must be advised to monitor blood glucose at least 4 times a day (with meals and before bedtime) and liaise with their specialist diabetic nurse in primary care to adjust therapy as needed.

Extravasation risk:
Irritant: bortezomib

EMETIC RISK

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

ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

Risk of reactivation of hepatitis B virus (MHRA alert 2019)

Hepatitis B virus reactivation has been reported in patients treated with immunosuppressive agents for myeloma, including several fatal cases worldwide.
All patients must be screened for hepatitis B virus before initiation of VCD; patients with unknown serology who are already on treatment should also be screened.

Guidance on Hepatitis B reactivation during immunosuppressive SACT can be found from the following bodies:

- National Institute for Health and Care Excellence (Clinical guidelines [CG165])
- European Association for the Study of the Liver (EASL HBV guideline 2017)
- American Society of Clinical Oncology (Huang et al, Journal of Clinical Oncology 2020) (Huang et al, Journal of Clinical Oncology 2020)
- UK Chemotherapy board

Local Hepatitis B reactivation policy should be followed. Consider consulting the local Viral Hepatitis team for advice.

- **Peripheral neuropathy:** Patients should be advised to report pain, hypersensitivity prickling, numbness and paraesthesia, if these occur consider dose reduction, as per above recommendations. Consider use of amitriptyline, gabapentin/pregabalin and pain team referral. Local neuropathy assessment tools should be utilised. Use 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. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

  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 fludrocortisone and/or sympathomimetics. 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, insomnia, gastritis, fluid retention, weight gain, hyperglycaemia, glucose intolerance.

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

TREATMENT RELATED MORTALITY

<5%

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REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, drug regimen, contraindications removed	May 2016	1.6	May 2018
Dr Jaimal Kothari Consultant	Regimen specific pre assessment section included	May 2016	1.6	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated haematological toxicity, renal and hepatic impairment, concurrent medications, adverse effects and references	July 2017	1.7	June 2018
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Addition of prophylactic fluconazole	July 2017	1.8	June 2018
Nadjoua Maouche (Haematology pharmacist)	Indications. Standardisation of assessment, formatting.	June 2018	1.9	June 2019
Myeloma Protocol Review 2019	Clarification of bortezomib hepatic impairment section, update of concurrent medications, extravasation risk, update of references	June 2019	2.0	June 2020
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	2.1	June 2021
Quality manager	Nursing care plan added	April 2021	2.2	June 2021
NSSG Myeloma Group	2021 Annual myeloma protocol review	June 2021	2.3	June 2022
NSSG Myeloma Group	Updated concurrent medication section	Nov 2022	2.4	June 2023
NSSG Myeloma Group	Indications, renal and hepatic dose recommendations, concurrent medications, interactions, side effects and references all updated. Reformat.	Sep 2024	3.0	Sep 2026

Nursing Care Plan
Cyclophosphamide Bortezomib Dexamethasone

Indication: First line treatment for Myeloma and for use in relapsed/refractory disease.
Frequency: Each cycle lasts 21 days – given until disease progression or unacceptable toxicity.
Alopecia: Potential for hair thinning/loss with cyclophosphamide.

CYCLOPHOSPHAMIDE: Alkylating agent.
Administered as orally on **days 1, 8, 15.**
Emetic risk: moderate.
Side effects: nausea/vomiting, diarrhoea, myelosupression, taste changes, minimal alopecia, bone marrow suppression, low risk haemorrhagic cystitis.

BORTEZOMIB (VELCADE): Proteasome inhibitor
Administered subcutaneously on **days 1, 8 and 15**. 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 and the day after. 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 bortezomib 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.**