

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- 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]:
- 5- Relapsed or refractory multiple myeloma in patients who are at second or subsequent relapses and who have not received prior bortezomib based therapy.

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

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- 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.
 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

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

Bortezomib	1.3 mg/m ² given as SC bolus	Days 1, 8 and 15
WITH		
Dexamethasone	20 mg PO once daily	Days 1, 2, 8, 9, 15 and 16 i.e. on the day of and day after each bortezomib dose. This will usually be days 1, 2, 8, 9, 15 & 16

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WITH		
Cyclophosphamide	500 mg PO or IV weekly	Days 1, 8 and 15 for weekly dosing
	OR	
	50 mg daily PO	Days 1 to 21 for daily dosing

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 doses, until signs of disease progression or unacceptable toxicity. Allowable number of doses is as follows

- 24 doses for transplant eligible patients (first line therapy)
- 51 doses for transplant ineligible patients (first line therapy)
- 32 doses at first relapse

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
• If prolonged G4 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 $< 1.0 \times 10^9/L$ 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 a reduced frequency.
• 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)	Withhold bortezomib
• If several bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 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)
$G \geq 3$ non-haem toxicities <i>(see above for neuropathic pain and/or peripheral neuropathy)</i>	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)

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^2
G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate treatment at 0.7 mg/m^2 once per week.
G4 and/or severe autonomic neuropathy	Discontinue

Renal/Hepatic Impairment:

Bortezomib:

Renal	Hepatic
Clinical decision if GFR $< 20\text{ml/min}$ In dialysis patients, give after dialysis	Bili $> 1.5\text{x ULN}$: 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.

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Cyclophosphamide:

Renal	Hepatic
Clinical decision GFR > 20ml/min 100% dose GFR 10 – 20ml/min 75% dose GFR < 10ml/min 50% dose For dialysis patients, 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.

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 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.
- Consider levofloxacin prophylaxis at 500mg od for 12 weeks (i.e. cycles 1-4) for all newly diagnosed myeloma patients. If this regimen is used in the relapsed setting, consider levofloxacin at clinician discretion, only in patients deemed at high risk of infections. Adjust dose for renal function
- 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,

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carbamazepine, phenytoin, phenobarbital, and St John's wort) is not recommended as efficacy may be reduced.

Extravasation risk:

Irritant: bortezomib

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

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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

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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

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, myelosuppression, 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 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**.