MELPHALAN, BORTEZOMIB, PREDNISOLONE (MelBorPred)

INDICATION

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- 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]

3- 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 approval**

Note: MelBorPred may be particularly suitable for patients over the age of 75 or those with marked pre-existing neuropathy. As it uses weekly Bortezomib for 4 weeks over a 35 day cycle, the incidence of serious neuropathy is likely to be less than with twice weekly administration. This protocol has been modified from the VISTA trial. In this study a maximum of 51 doses of Bortezomib were given.

TREATMENT INTENT

Disease Modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - PT and APTT or Coagulation profile
   - 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 Investigation

- 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 SC bolus	Days 1, 8, 15, 22
WITH		
Melphalan	7 mg/m^2 PO daily (tablets are 2 mg in strength)	Days 1 - 4
Prednisolone	60 mg/m^2 PO daily NB: Dose of prednisolone may be reduced in the very elderly or if significant toxicity occurs	Days 1 - 4

At least 72 hours should elapse between consecutive doses of bortezomib.

CYCLE FREQUENCY

Repeat every 35 days, continue until signs of disease progression or unacceptable toxicity. It is recommended that patients receive up of 12 treatment cycles particularly in a newly diagnosed patient to ensure optimal Bortezomib exposure. In a relapsed setting in patients with a confirmed maximal response receive 2 additional cycles of treatment to a total of 8 cycles.

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

DOSE MODIFICATIONS

Haematological toxicity:
Dose adjustments during treatment and re-initiation of treatment for combination therapy
Prior to initiating a new cycle of therapy:
- Platelets ≥ 70 x 10^9/L and ANC ≥ 1.0 x 10^9/L
- Non-haem toxicities should resolve to G1 or baseline

Toxicity	Posology modification or delay
Haematological toxicity during a cycle	
• If prolonged G4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Reduce melphalan dose by 25% in the next cycle.
• If platelet ≤ 30 x 10^9/L or ANC ≤ 0.75 x 10^9/l on a Bortezomib dosing day (other than Day 1)	Withhold Bortezomib
• If several Bortezomib doses in a cycle are withheld ≥ 2 doses during weekly administration	Bortezomib reduced 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 ≥ 3 non-haem toxicities *(see below for* neuropathic pain and/or peripheral neuropathy)	Bortezomib withheld until symptoms resolved to G1 or baseline. Bortezomib reinitiated 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/Hepatin 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^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.

Melphalan:

Renal	Hepatic
Currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering melphalan tablets to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established. In myeloma patients with renal damage, temporary but significant increases in blood urea levels have been observed during melphalan therapy.	No recommendations. If excess toxicity, consider dose reduction on subsequent cycles

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INVESTIGATIONS (at the beginning of each cycle unless otherwise noted)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC (prior to each Bortezomib dose if known thrombocytopenia)
- 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)
- Igs, Paraprotein, Freelite assay
- Serum free light chain
- Consider repeat BM aspirate and trephine after 3 courses 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

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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

Low emetic 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 500 mL intravenous 0.9% sodium chloride with each bortezomib dose.

- **Gastrointestinal**: Nausea, diarrhoea, vomiting and constipation are very common and ileus has been reported.

- **Steroid 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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10. Melphalan 2mg tabs eMC UK Summary of Product Characteristics , Aspen, March 2014

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, adverse effects and pre assessment section , dose regimen contraindication section removed	May 2016	1.7	May 2018
Dr J. Kothari Consultant	Regimen specific pre assessment section included	May 2016	1.7	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated renal and hepatic impairment, concurrent medication, adverse effects and references	July 2017	1.8	June 2018
Nadjoua Maouche (Haematology pharmacist)	Indications. Standardisation of assessment, investigations, supports, formatting, Melphalan renal dosing.	June 2018	1.9	June 2019
Myeloma Protocol Review 2019	Addition of allowable number of doses per treatment line, clarification of dosing in hepatic impairment, extravasation risk, update of references	June 2019	2.0	June 2020
Quality Manager	Nursing care plan added	April 2021	2.1	June 2020

Nursing Care Plan
Melphalan Bortezomib Prednisolone

Indication: First line or relapsed/refractory Myeloma (suitable for patients with pre-existing peripheral neuropathy).
Frequency: 35 day cycles continue until signs of disease progression or unacceptable toxicity. Usually up to 12 cycles for newly diagnosed patients and up to 8 cycles in relapsed disease.
Alopecia: Potential hair loss/thinning with Melphalan.

MELPHALAN: Alkylating agent
Administered orally on **days 1-4.**
Emetic risk: Low.
Side effects: Bone marrow depression, risk on infection, anaemia, fatigue, diarrhoea, mucositis.

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.

PREDNISOLONE: corticosteroid tablets
Administered orally with food (ideally in the moring) on **days 1-4.**
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.
- 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.**
- 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