BENDAMUSTINE, BORTEZOMIB & DEXAMETHASONE (BVD)

INDICATIONS

Relapsed multiple myeloma in bortezomib naïve patients where other treatments are contraindicated or inappropriate.
Bendamustine Funding from Cancer Drugs Fund. Requires **Blueteq** application.
Bortezomib Funding from Cancer Drugs Fund. Requires **Blueteq** application.

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)
   - 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.
   - **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions**. Ensure irradiation card is attached to the patient's notes.
   - Imaging as per NICE/network guidance and clinical presentation
   - Bone marrow aspirate and trephine (and immunophenotype if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict 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. Hydration - fluid intake of at least 3 litres/ day should be attempted
3. Fertility - all patients should be offered fertility advice, asappropriate.
4. 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. Obtain written consent for the treatment.
5. Document patient's height and weight
6. Document patient's performance status.
7. Treatment must be agreed at the relevant MDT**.**

REGIMEN SPECIFIC PRE- ASSESMENT

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.
2. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1.

DRUG REGIMEN

Dexamethasone	20 mg PO once daily	On the days of and day after bortezomib days 1,2, 8,9 15,16 and 22, 23
Bortezomib	1.3 mg/m^2 given as S/C bolus	Days 1, 8, 15 and 22.
Bendamustine	70 mg/m^2 IV infusion in 500 ml sodium chloride 0.9% over 30 - 60 min.	Days 1, 8.

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

CYCLE FREQUENCY

The cycle is repeated every 28 days for a minimum of 6 cycles and a maximum of 8 cycles depending on response.

DOSE MODIFICATIONS

Haematological toxicity:

Bendamustine: Dose reductions in bendamustine may be necessary. Treatment related fall in neutrophil count below 1.0 x 10^9/L or platelets below 75 x 10^9/L, bendamustine should be temporarily withheld until counts recover with G-CSF therapy + transfusions. If the cytopaenias are **disease related, please use G-CSF cover and platelet support.**

Bortezomib: Withhold at G3 non-haem or G4 haem toxicities. Once resolved, re-initiate at 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless benefit outweighs risk.

Peripheral neuropathy

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

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 or change treatment schedule to 1.3 mg/m^2 once per week
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

Hepatic /renal Impairment:

Bortezomib

Renal	Hepatic
For dialysis patients, bortezomib should be given after dialysis No dose reduction necessary	Bili > 1.5 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.

Bendamustine

Renal	Hepatic		
> 10 ml/min – no dose adjustment	Mild:	Bili <20 micromol/L	Give 100%
≤ 10 ml/min – limited data	Moderate:	Bili 20 – 51micromol/L	Give 70% dose
	Severe:	Bili > 51micromol/L	Contraindicated

INVESTIGATIONS – during treatment

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&Es, LFTS, Ca^{++}, glucose – every 3 - 4 weeks.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib.
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 6 days, from day 2 – 7 of first cycle only. Skin rash has been reported in patients taking concomitant Allopurinol and Bendamustine It is suggested that allopurinol is omitted on the days of Bendamustine administration.
- Prophylactic fluconazole 50mg OD
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min)
- 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.
- Bone protection as per NSSG Bone Protection protocol MM3.

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.

EMETIC RISK

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

EXTRAVASATION RISK

Bendamustine- vesicant/irritant

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.

- **Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis** have been reported in patients who received bendamustine and allopurinol simultaneously. If patients experience any skin reactions during treatment, they should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious muco-cutaneous reaction, treatment with bendamustine should be withheld until complete resolution of the event or discontinued. Other potential causes of skin toxicity should be evaluated and suspected agents discontinued accordingly.

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

- **Bendamustine MHRA Alert** (20 July 2017): Hepatitis B virus (HBV) reactivation has been reported; monitor known carriers of HBV for signs and symptoms of active HBV infection. Increased mortality mainly due to opportunistic infections was observed in recent clinical studies when bendamustine was used in combination treatment outside the approved indications. Infections include bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia, varicella zoster virus, and cytomegalovirus infection. Some fatal cardiac, neurological, and respiratory toxicities were also reported.

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REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, adverse effects and pre assessment section	May 2016	1.3	May 2018
Dr Jaimal Kothari Consultant	Regiment specific section included	May 2016	1.3	May 2018
Manuela Sultanova Service Coordinator	Formatting, standardisation of pre-assessment section	July 2017	1.4	May 2018
Network Protocol Review	Funding. Dosing. Extravasation risk. MHRA alert. Standardisation of supports, dose modifications and investigations	June 2018	2.0	June 2020
Quality manager	Addition of nursing care plan	April 2021	2.1	June 2020

Nursing Care Plan
Bendamustine Bortezomib Dexamethasone (BVD)

Indication: Relapsed Myeloma.
Frequency: 6-8 cycles of 28 days.
Alopecia: Possible thinning of hair.
Send a group and save sample to blood transfusion and inform patient and laboratory that they will require irradiated blood products for all future transfusions due to Bendamustine treatment. Give patient an irradiated blood product booklet and card

BENDAMUSTINE: **Alkylating agent.**

Administered as intravenous infusion over 30-60 minutes on days 1 and 8.
Classification of extravasation: vesicant/irritant.
Emetic risk: moderate.
Side effects: infusion reactions: fever, chills, itchy skin, nausea and vomiting, anorexia, bone marrow depression, diarrhoea, constipation, mucositis, fatigue, raised LFT's, hypokalaemia, cardiac impairment, hypo/hypertension, insomnia, skin disorders.

BORTEZOMIB (VELCADE): **Proteasome inhibitor**

Administered subcutaneously on days 1, 8, 15, 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 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.
- Risk of skin reactions (Steven-Johnson Syndrome) when Allopurinol is given concomitantly with Bendamustine. For patients with a low risk of tumour lysis syndrome Allopurinol to be started on day 2. Check prescription on Aria for start dates of Allopurinol.
- Bloods are required at the start of each cycle. Patients with unstable blood counts may require more frequent monitoring.

- 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.