Thames Valley
Strategic Clinical Network

BENDAMUSTINE, THALIDOMIDE & DEXAMETHASONE (BTD)

INDICATIONS

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

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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 microglobulinll
   - 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, as appropriate.
4. Counselling- all patients should receive verbal and written information on oral chemotherapy. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.
5. 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 including signing Celgene Pregnancy Prevention Programme forms
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. The conditions of the Thalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the Celgene Pregnancy Prevention Programme.
2. Clinical Assessment of thrombo-embolic risk.
3. Evaluate for and document 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 thalidomide.

DRUG REGIMEN

Thalidomide	100 mg po (preferably nocte) Start with 50 mg and escalate if tolerated	Daily
Bendamustine	60 mg/m^2 intravenous infusion in 500 ml 0.9% sodium chloride over 30 – 60 min	Days 1, 8
Dexamethasone	20 mg po OD	Days 1, 8, 15 and 22

CYCLE FREQUENCY

The cycle is repeated every 28 days for a minimum of 6 cycles and a maximum of 9 cycles depending on response.

DOSE MODIFICATIONS

Myelosuppression: 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 cytopenias are disease related, please use G-CSF cover and platelet support.

Neuropathy: Thalidomide should be stopped or dose reduced if there are symptoms of progressive peripheral neuropathy causing functional disability (grade 2 and above). Consider cautious re-introduction of thalidomide at a dose of 50mg daily if symptoms resolve to grade 1 or better after a two-week gap. Subsequent cautious dose escalation should be considered if symptoms permit.

Renal/Hepatic Impairment
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

Thalidomide

Renal	Hepatic
No dose adjustment necessary	No dose adjustment necessary

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.
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle
- 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.
- Thromboprophylaxis/anticoagulation – see VTE section below.
- Bone protection as per NSSG Bone Protection protocol MM.3

EMETIC RISK

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

EXTRAVASATION RISK

Bendamustine- vesicant/irritant

ADVERSE EVENTS/ REGIMEN SPECIFIC COMPLICATIONS

- **Teratogenic**: the Celgene Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention programme.

- **Peripheral neuropathy**: Patients should be advised to report prickling, numbness and paraesthesia.

- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with thalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

    1. Prophylactic low-molecular weight heparin OR
    2. Prophylactic NOAC e.g. apixaban 2.5mg bd (check product specific information)

  Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors

  If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

- **Drowsiness, somnolence and sedation**: Take thalidomide dose at night time. Thalidomide may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking thalidomide.

- **Dizziness and orthostatic hypotension**: Patients should be advised that thalidomide may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position.

- **Skin toxicity**: in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.

- **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.

- **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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8. Bendamustine Levact® eMC UK Summary of Product Characteristics for, Napp Pharmaceuticals ltd, March 2018.
9. MHRA Safety Alert: Bendamustine (Levact): increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections, hepatitis B reactivation. 20th July 2017

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, adverse effects and pre assessment section, dose modification, contraindication section removed	May 2016	2.3	May 2018
Dr J. Kothari Consultant	VTE reviewed and regimen specific pre assessment section included	May 2016	2.3	May 2018
Manuela Sultanova Service Coordinator	Formatting, standardisation of some sentences across all protocols e.g pre assessment section, VTE etc.	July 2017	2.4	May 2018
Network Protocol Review	Add Blueteq. Treatment intent. Pre-assessment. Dexamethasone dosing schedule. VTE information. Renal/hepatic modification. Concurrent medication dosing. Extravasation risk. Adverse events section. MHRA alert.	June 2018	3.0	June 2020
Quality manager	Addition of nursing care plan	April 2021	3.1	June 2020

Thames Valley
Strategic Clinical Network

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.