Myeloma group

BORTEZOMIB LENALIDOMIDE AND DEXAMETHASONE (VRD)

INDICATION

Induction therapy for Multiple Myeloma

This combination is not funded by NHS England. Individual funding must be agreed prior to initiation.

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)
   - β₂ 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 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. Fertility - all patients should be offered fertility advice, as appropriate.

3. Hydration - fluid intake of at least 3 litres/day should be attempted.


5. Treatment must be agreed at the relevant MDT.

6. Document patient’s performance status

7. 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 risk Pregnancy Prevention Programme forms

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.

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

3. The conditions of the Lenalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the Celgene Pregnancy Prevention Programme.


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**DRUG REGIMEN**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Method</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² given SC bolus</td>
<td>Days 1, 4, 8 and 11.</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg PO (preferably nocte)</td>
<td>Days 1-14.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20 mg PO once daily</td>
<td>On the day of and day after each Bortezomib dose. This will be on days 1, 2, 4, 5, 8, 9, 11 &amp; 12</td>
</tr>
</tbody>
</table>

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

Bortezomib can also be administered weekly on days 1, 8 and 15 of a 21 days cycle.
**CYCLE FREQUENCY**

Repeat every 21 days, continue until maximal response plus two cycles or unacceptable toxicity up to a maximum of 6 - 8 treatment cycles. For patients eligible for transplant, interrupt treatment after 4 cycles to collect PBSC. Suitable patients can later continue on maintenance lenalidomide until disease progression or unacceptable toxicity.

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**DOSE MODIFICATIONS**

**Haematological toxicity:**

**BORTEZOMIB:** Thrombocytopenia due to Bortezomib is transient and very rarely causes significant bleeding. If baseline platelet count is > 70 x 10^9/L, then the risk of severe thrombocytopenia is very low.

In such patients, FBC should be checked only at the start of the cycle and does not need to be repeated before each dose.

In patients with plt < 70 x 10^9/L at the start of each cycle, the FBC should be checked before each dose, the drug should be withheld until FBC is through and the dose omitted if the platelets are < 25 x 10^9/L unless thrombocytopenia is thought to be mainly due to marrow infiltration by myeloma. In those circumstances, consider proceeding with treatment with platelet transfusion support.

In all other circumstances, if these levels are not reached, then treatment should be withheld and subsequent doses reduced by 25% (i.e. from 1.3 mg/m^2 to 1.0 mg/m^2 or from 1.0 mg/m^2 to 0.7 mg/m^2).

**LENALIDOMIDE:** Treatment should not normally be given if ANC < 0.5 x 10^9/L, and/or platelet count < 30 x 10^9/L. If low counts are thought to be due to myeloma per se, the use of G-CSF and platelet support should be considered.

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide. Dose reductions below are based on a starting dose of 25 mg/day. Please be aware that some patients can start a reduced dose from cycle 1.

**Thrombocytopenia:**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 30 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10^9/L</td>
<td>Resume lenalidomide at 15 mg once day</td>
</tr>
<tr>
<td>For each subsequent drop below 30 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg once daily). Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>
Neutropenia:

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to $&lt; 0.5 \times 10^9$/L</td>
<td>Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9$/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at 25 mg once daily</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9$/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at 15 mg once daily</td>
</tr>
<tr>
<td>For each subsequent drop below $&lt; 0.5 \times 10^9$/L</td>
<td>Interrupt lenalidomide treatment. Administer G-CSF for 3 days.</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9$/L</td>
<td>Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg once daily). Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

**Peripheral Neuropathy:**

**Bortezomib:** If there are symptoms of peripheral neuropathy, the dose reduction schedule must be invoked (see below). The drug should be stopped if symptoms or signs progress despite this.

<table>
<thead>
<tr>
<th>Grading of neuropathy</th>
<th>Bortezomib Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 with no pain or loss of function</td>
<td>None</td>
</tr>
<tr>
<td>G1 with pain or G2</td>
<td>Reduce to 1.0 mg/m² or change treatment schedule to 1.3 mg/m² once per week (if the current dose is twice per week)</td>
</tr>
<tr>
<td>G2 with pain or G3</td>
<td>Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m² once per week.</td>
</tr>
<tr>
<td>G4 and/or severe autonomic neuropathy</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

**Lenalidomide** is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant neurotoxicity is uncommon.
Renal & Hepatic Impairment:

### Bortezomib

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>For dialysis patients, bortezomib should be given after dialysis</td>
<td>Bili &gt; 1.5 x ULN: reduce to 0.7 mg/m² in the first treatment cycle. Consider dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.</td>
</tr>
<tr>
<td>No dose reduction necessary</td>
<td></td>
</tr>
</tbody>
</table>

### Lenalidomide

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl 30 – 49 mL/min</td>
<td>10mg once daily*</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min, no dialysis</td>
<td>15 mg every other day**</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min, requiring dialysis</td>
<td>5 mg once daily***</td>
</tr>
<tr>
<td></td>
<td>No formal studies. No specific dose recommendations</td>
</tr>
</tbody>
</table>

*Can increase to 15mg OD if no response and patient tolerating
** Can increase to 10mg OD if no response and patient tolerating
*** On dialysis day, administer dose after dialysis

**INVESTIGATIONS (at the beginning of each cycle)**

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC U&E, Ca**
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib
- Ig’s, paraprotein, urinary BJP where present. Freelite assay may provide an early indication of response
- 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 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl)<10ml/min) for the duration of treatment and for 3 months after stopping bortezomib
- 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.
- Thromboprophylaxis/anticoagulation- see VTE section below.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Prescribe loperamide if needed for diarrhoea.
- Consider cholestyramine if suspicion of bile salt malabsorption with lenalidomide

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

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

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

- **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.

- **Diarrhoea**: was reported in 42% of patients requiring use of antidiarrheal medication (loperamide), supportive care and adequate hydration. Bile salt malabsorption occurs in a small proportion of patients on lenalidomide, consider dietary adjustments with low fat meal intake and prescribing bile acid sequestrants (colestyramine).

- **Rash**: can occur with lenalidomide. Antihistamines and topical corticosteroids can often be used to treat limited, localized, treatment-related rash, but lenalidomide interruption or discontinuation should be considered for grade 2/3 rash. Re-challenge with lenalidomide is reasonable in patients who do not have a severe rash and will often allow continued treatment. Lenalidomide must be discontinued for angioedema, grade 4 rash, and exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected, and should not be resumed after discontinuation for these reactions.

- **Venous thromboembolism (VTE)**: There is an increased risk of thrombosis with lenalidomide. 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, lenalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

- **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.

- **Drowsiness, somnolence and sedation:** can occur with lenalidomide. Take the dose at night time. Lenalidomide 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 lenalidomide.
- **There is an MHRA alert on an increased risk of secondary malignancies** in three large trials of Lenalidomide treatment. The MHRA recommend vigilance in reporting such events promptly. Quoted incidence is 3 to 4% per annum.

**TREATMENT RELATED MORTALITY**

<5%

**REFERENCES**

2. Velcade ® Borrzomib eMC UK Summary of Product Characteristics, Janssen, February 2019
7. Revlimid® (lenalidomide) 25mg capules. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, December 2018
<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadjoua Maouche Pharmacist</td>
<td>Formatting, adverse effects and pre assessment section</td>
<td>May 2016</td>
<td>1.3</td>
<td>May 2018</td>
</tr>
<tr>
<td>Faouzi Djebbari (Haematology Pharmacist)</td>
<td>Updated haematological toxicity, renal and hepatic impairment, concurrent medications and references</td>
<td>July 2017</td>
<td>1.4</td>
<td>June 2018</td>
</tr>
<tr>
<td>Nadjoua Maouche (Haematology pharmacist)</td>
<td>Standardisation of assessment, VTE information, investigations supports, adverse events.</td>
<td>June 2018</td>
<td>1.5</td>
<td>June 2019</td>
</tr>
<tr>
<td>Myeloma Protocol Review 2019</td>
<td>Update to: general pre-assessment, cycle frequency, extravasation risk, and references</td>
<td>June 2019</td>
<td>1.6</td>
<td>June 2020</td>
</tr>
<tr>
<td>Quality manager</td>
<td>Nursing care plan added</td>
<td>April 2021</td>
<td>1.7</td>
<td>June 2020</td>
</tr>
</tbody>
</table>
Nursing Care Plan: Bortezomib Lenalidomide Dexamethasone (VRD)

**Indication:** Relapsed or refractory myeloma.

**Frequency:** 6-8 cycles of 21 days.

**Alopecia:** No

**BORTEZOMIB (VELCADE):** Proteasome inhibitor

Administered subcutaneously on days 1, 4, 8, 11 (can also be given on days 1, 8 and 15 of a 21 day cycle). 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.

**LENALIDOMIDE (REVLIMID):** Immunomodulator and angiogenesis inhibitor.

Administered orally on days 1-14.

**Emetic risk:** minimal.

**Side effects:** neutropenia, peripheral neuropathy, diarrhoea, constipation, flu like syndrome, infections, fatigue, muscle cramps, rash/itching, venous thromboembolism, bone marrow depression, drowsiness/sedation (recommended taking at night time).

**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 (due to the teratogenic effect of lenalidomide).
- Lenalidomide can cause a rash (may be paused if rash is grade 2-3).
- 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.**