BORTEZOMIB (VELCADE), LENALIDOMIDE AND DEXAMETHASONE (VRD)

INDICATION

Induction therapy for Multiple Myeloma

This combination is unlicensed and 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
   - 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)
   - β2 microglobulin
   - 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.


6. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE-ASSESMENT

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.

The conditions of the Lenalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients.

Clinical assessment of thrombo-embolic risk.

DRUG REGIMEN

<table>
<thead>
<tr>
<th>Drug</th>
<th>dose</th>
<th>Schedule</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. Suitable patients can later continue on maintenance lenalidomide until disease progression or unacceptable toxicity.
DOSE MODIFICATIONS

Haematological toxicity:

**BORTEZOMIB:** Thrombocytopenia due to Bortezomib is transient and very rarely causes significant bleeding. If baseline platelet count is > 70, then the risk of severe thrombocytopenia is very low.\(^2\)

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 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 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/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 x 10^9/L</td>
<td>Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 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 ≥ 0.5 x 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 x 10^9/L</td>
<td>Interrupt lenalidomide treatment. Administer G-CSF for 3 days.</td>
</tr>
<tr>
<td>Return to ≥ 0.5 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>
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</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/m^2 or Change treatment schedule to 1.3 mg/m^2 once 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/m^2 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 toxicity 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 No dose reduction necessary</td>
<td>Bili &gt; 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.</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>15mg every other day**</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min, requiring dialysis</td>
<td>5mg 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/

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

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC U&E, Ca**
- 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.

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**CONCURRENT MEDICATIONS**

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Prophylactic aciclovir 200 mg bd to tid (depending on renal function) for the duration of treatment and 3 months post therapy.
- Bone protection as per NSSG Bone Protection protocol MM.3 Prophylactic fluconazole.
- Proton Pump Inhibitor or H2 antagonist at clinician’s discretion.
- Consider prophylactic co-trimoxazole, particularly if heavily pre-treated or previous autograft.
- Thrombophrophylaxis/anticoagulation as below
- Prescribe loperamide if needed for diarrhoea.
- Consider cholestyramine if suspicion of bile salt malabsorption

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, antivirals, isoniazid, nitrofurantoin or statins), or with a decrease in blood pressure.

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.

Patients on oral hypoglycaemic may require close monitoring of blood sugar levels.

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**EMETIC RISK**

Low
ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

- **Painful 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:** Diarrhea was reported in 42% of patients requiring use of antidiarrheal medication and supportive care. Bile salt malabsorption occurs in a small % of patients of lenalidomide, and consider addition of cholestyramine.

- **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.

- **Venous thromboembolism (VTE):**
  
  There is an increased risk of thrombosis, and some form of prophylaxis is recommended as follows:

  1. Aspirin can be appropriate for patients with no additional risk factors for thrombosis
  2. If additional risk factors consider:
     - Prophylactic low-molecular weight heparin, OR
     - Vitamin K antagonists at a therapeutic dose, to maintain an international normalised ratio (INR) of 2–3, OR
     - Direct oral anticoagulant e.g. apixaban for thromboprophylaxis or treatment dose as indicated.

  **Aspirin is generally not preferred for higher risk patients with additional risk factors such as immobility. If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.**

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

- **Teratogenic:** A risk management programme should be observed. The concomitant use of 2 effective methods of contraception is mandatory in all female patients of child bearing potential. Male patients should also use a condom when having sexual intercourse with women of child bearing potential. Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme.

- **Other warnings:** Patients should be informed not to donate blood or semen during or within 8 weeks of stopping Lenalidomide treatment.

- **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. eMC UK Summary of Product Characteristics for Velcade, Janssen, March 2017


REVIEW

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<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>
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