LENALIDOMIDE WITH DEXAMETHASONE

INDICATION

1- Relapsed or refractory multiple myeloma in patients who have received two or more prior lines of therapy. The drug cost for people remaining on the treatment for more than 26 cycles of 28 days will be met by the manufacturer. (NICE 2009)

2- Clinically appropriate as 2nd line treatment for multiple myeloma patients who have a contraindication to bortezomib or previously received bortezomib in the first line setting.

This will require individual funding.

Note: Lenalidomide with dexamethasone (low dose) is the preferred protocol for patients with poor performance status and generally frail. Lenalidomide, cyclophosphamide and dexamethasone is the preferred option for younger and fit patients (please see separate protocol).

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   o FBC & film
   o Clotting screen
   o U&Es, LFTs, Calcium
   o Albumin
   o Uric acid
   o ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
   o Virology: HIV, Hepatitis B (including core antibody), and Hepatitis C
   o Calculated creatinine clearance (CrCl), urine protein/creatinine ratio
   o Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   o Serum free light chain assay (Freelite)
   o β2 microglobulin
   o 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).
   o Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
   o Imaging as per NICE/network guidance and clinical presentation

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ

Additional investigations:
   Plasma viscosity if hyperviscosity suspected

2. Fertility - all patients should be offered fertility advice, as appropriate.
3. Hydration - fluid intake of at least 3 litres /day should be attempted.
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. The manufacturer's risk management programme should be observed - see special warning below.

REGIMEN SPECIFIC PRE-ASSESSMENT

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>Lenalidomide (Continuous therapy)</th>
<th>The starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21. See below for dose reductions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>WITH Dexamethasone (Cycles 1-6) or to maximum response</td>
<td>40 mg po on days 1, 8, 15 and 22. NB: The dose may need to be reduced in the elderly or if steroid-related side effects develop³.</td>
</tr>
</tbody>
</table>

**CYCLE FREQUENCY:**

**Cycle length:** 28 days – i.e. 3 weeks on lenalidomide then 1 week off. Consider switching to lenalidomide/cyclophosphamide/dexamethasone if no response observed after 4 cycles⁴.

Response should be assessed after 4 courses. Suitable patients can continue on maintenance lenalidomide until disease progression or unacceptable toxicity.

**DOSE MODIFICATIONS**

**Myelosuppression:**
Lenalidomide treatment should not normally be given if the Absolute Neutrophil Counts (ANC) < 0.5 x 10⁹/L, and/or platelet count < 30 x 10⁹/L. If the low counts are thought to be due to myeloma per se, the use of G-CSF and platelet support should be considered.

**Recommended dose adjustments during treatment and to restart treatment:**
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.
Note: Consider re-escalating lenalidomide dose provide toxicities have completely resolved.
Starting dose = 25 mg/day.

### 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>
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<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>
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### Renal/Hepatic Impairment:

<table>
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<th>Hepatic</th>
</tr>
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<tbody>
<tr>
<td>CrCl  30- 50 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>
</tbody>
</table>

*Can increase to15mg 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/
CONCURRENT MEDICATIONS

- Consider prophylactic laxatives to be taken if needed.
- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Prophylactic fluconazole.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Thromboprophylaxis/anticoagulation as above.
- Consider prophylactic co-trimoxazole if heavily pre-treated or previous autograft.
- Prophylactic acyclovir 200 mg bd to tid (depending on renal function).

EMETIC RISK
Minimal emetic risk.

ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

Teratogenic: The risk management programme should be observed - see link to manufacturers data sheet on website. The concomitant use of an effective method of contraception is mandatory in all female patients of childbearing potential. Male patients should also use a condom when having sexual intercourse with women of childbearing potential. **Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme.**

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

If additional risk factors consider:

2. Prophylactic low-molecular weight heparin OR
3. Vitamin K antagonists at a therapeutic dose, to maintain an international normalised ratio (INR) of 2–3
   Alternatively:
4. Can consider use of a direct oral anticoagulant eg 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.

- **Drowsiness, somnolence and sedation:** 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.
• **Peripheral neuropathy**: Patients should be advised to report pricking, numbness and paraesthesia. Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant toxicity is uncommon.

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

• **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.

**REFERENCES**


5. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, August 2015

**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, renal section, reference, pre assessment section</td>
<td>May 2016</td>
<td>4.3</td>
<td>May 2018</td>
</tr>
<tr>
<td>Dr Jaimal Kothari Consultant</td>
<td>Regimen specific pre assessment section included</td>
<td>May 2016</td>
<td>4.3</td>
<td>May 2018</td>
</tr>
<tr>
<td>Manuela Sultanova Service Coordinator</td>
<td>Formatting, Standardisation of wording in pre-assessment section, Wessex lab address and VTE</td>
<td>August 2017</td>
<td>4.4</td>
<td>May 2018</td>
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