LENALIDOMIDE, CYCLOPHOSPHAMIDE AND WEEKLY DEXAMETHASONE

INDICATIONS
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 TA171)

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. (Not funded by NHS England, individual funding required prior to initiation)

Note: Lenalidomide, cyclophosphamide and dexamethasone is the preferred option for younger and fit patients. If stem cells required after this regimen consider no more than 4 cycles prior to harvest. Lenalidomide, dexamethasone (low dose) is the preferred protocol for patients with poor performance status and generally frail (please see separate protocol).

TREATMENT INTENT
Disease modification

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 ratioElectrophoresis 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

This is a controlled document and therefore must not be changed
ADDITIONAL INVESTIGATIONS

- Plasma viscosity if hyper viscosity 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.
5. Counselling - all patients should receive verbal and written information on oral chemotherapy.
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. The manufacturer's risk management programme should be observed - see special warning below.
8. If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology
9. Treatment must be agreed at the relevant MDT.

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>Drug</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>The starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21. See dose reductions below.</td>
</tr>
<tr>
<td>Cyclophosphamide (Cycles 1-6)</td>
<td>Orally either 500 mg on days 1 and 8 or 50 mg continuously on days 1 to 21.</td>
</tr>
<tr>
<td>Dexamethasone (Cycles 1-6) or up to maximum response</td>
<td>40 mg PO daily on days 1, 8, 15 and 22 of each cycle. The dose may need to be reduced (prior to cycle 1 or at later cycles) in the elderly or if steroid-related side effects develop</td>
</tr>
</tbody>
</table>

---

**CYCLE FREQUENCY**

*Cycle length*: 28 days - i.e. 3 weeks on lenalidomide then 1 week off.

Response should be assessed every cycle. Suitable patients can continue to receive lenalidomide as per above schedule (with or without Dexamethasone. Or with or without Cyclophosphamide) until disease progression or unacceptable toxicity.
NB: PRESCRIBING REQUIREMENTS
A Prescription Authorisation Form must be completed at the same time as the lenalidomide prescription. Up to 3 cycles of lenalidomide can be dispensed at one time for male and female of non-child bearing age, but a blood count must be performed monthly. A negative pregnancy test result is required every 4 weeks within 3 days prior to the prescription date for all women of childbearing potential. Patients must be counselled about the teratogenic risk associated with lenalidomide.

DOSE MODIFICATIONS

Renal/Hepatic Impairment:

Lenalidomide:

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl 30 – 49 ml/min</td>
<td>10 mg OD</td>
</tr>
<tr>
<td>CrCl &lt; 30 ml/min, not requiring dialysis</td>
<td>7.5 mg once daily&lt;sup&gt;1&lt;/sup&gt;, or 15 mg every other day&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>CrCl &lt; 30 ml/min, requiring dialysis</td>
<td>5 mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
</tr>
</tbody>
</table>

<sup>1</sup> Dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment

<sup>2</sup> In countries where the 7.5 mg capsule is available

<sup>3</sup> The dose may be escalated to 10 mg once daily if the patient is tolerating the treatment

There are no specific dose recommendations in hepatic impairment.

Cyclophosphamide:

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &gt; 20 ml/min</td>
<td>100% dose</td>
</tr>
<tr>
<td>GFR 10 - 20 ml/min</td>
<td>75% dose</td>
</tr>
<tr>
<td>GFR &lt; 10 ml/min</td>
<td>50% dose</td>
</tr>
</tbody>
</table>

Exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision.

Myelosuppression: Lenalidomide treatment should not normally be given if the Absolute Neutrophil Counts (ANC) < 0.5 x 10^9/L, and/or platelet count < 30 x 10^9/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 restart of 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, provided that 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 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10⁹/L</td>
<td>Resume lenalidomide at 15 mg/day</td>
</tr>
<tr>
<td>For each subsequent drop below 30 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level (i.e. if on 15 mg, reduce to 10 mg - or if 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 10⁹/L</td>
<td>Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/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 10⁹/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 10⁹/L</td>
<td>Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10mg - or if was on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

Neuropathy: Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant toxicity is uncommon.

**CYCLOPHOSPHAMIDE**

**Myelosuppression:**
Dose reductions in cyclophosphamide may be necessary. It is preferable to reduce Cyclophosphamide prior to dose reducing Lenalidomide. If the neutrophil count falls below 0.5 x 10⁹/L or platelets below 50 x 10⁹/L, cyclophosphamide should be at least temporarily discontinued.
INVESTIGATIONS - Pre-treatment and during treatment:

- Ensure all staging investigations (as listed under the PRE-ASSESSMENT heading above) are done. Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC & U&E's – consider fortnightly for first cycle, then monthly.
- Ca++, LFTs – monthly.
- Ig's, paraprotein, urinary BJP and serum free light chain levels in patients with light chain disease - monthly.
- Random blood glucose/ blood sugar

CONCURRENT MEDICATIONS

- Consider prophylactic laxatives to be taken if needed
- Allopurinol 300mg daily for 7 days only for cycle 1 only. Aim to start day before chemotherapy
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Consider 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).

Refer to cyclophosphamide SPC for full details of its drug interactions.

EMETIC RISK

Moderate emetic risk on weekly cyclophosphamide days

ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

- **Teratogenic**: The manufacturer's risk management programme should be observed - see manufacturers data sheet. 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.
- **Diarrhoea**: Diarrhea was reported in 42% of patients requiring use of anti-diarrheal medication and supportive care. Bile salt malabsorption occurs in a small % of patients of lenalidomide, and consider addition of cholestyramine
- **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.
- **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.

- **Rash**: may require discontinuation of therapy, antihistamines or steroids but rechallenge with lenalidomide is reasonable in patients who do not have a severe rash and will often allow continued treatment.
- **Peripheral neuropathy**: Patients should be advised to report prickling, numbness and paraesthesia.
- **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 the increased risk of secondary malignancies in three large trials of lenalidomide treatment**. The MHRA recommend vigilance in reporting such events promptly. The quoted incidence is 3 to 4% per annum.

---

**TREATMENT RELATED MORTALITY**

<5%

---

**REFERENCES**

7. eMC UK Summary of Product Characteristics for cyclophosphamide 50 mg tablets, Pharmacia, Dec 2016.

---

REVIEW

<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>Pre assessment, dose modification, special warnings reviewed</td>
<td>May 2016</td>
<td>3.3</td>
<td>May 2018</td>
</tr>
<tr>
<td>Dr Jaimal Kothari Consultant</td>
<td>Regimen specific pre assessment included</td>
<td>May 2016</td>
<td>3.3</td>
<td>May 2018</td>
</tr>
<tr>
<td>Faouzi Djebbari (Haematology Pharmacist)</td>
<td>Updated drug regimen, concurrent medications and references</td>
<td>July 2017</td>
<td>3.4</td>
<td>June 2018</td>
</tr>
</tbody>
</table>