CARFILZOMIB/ LENALIDOMIDE / DEXAMETHASONE (Car/Len/Dex)

INDICATIONS
Relapsed 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:
   o FBC & film
   o Clotting screen
   o U&Es
   o LFTs
   o Calcium
   o Uric acid
   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 Hevylite analysis (if paraprotein level difficult to quantify)
   o Albumin & $\beta_2$ microglobulin for ISS staging
   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 Group and save
   o Imaging as per NICE/network guidance and clinical presentation
   o 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.
- Evaluate for presence of cardiac issues. This is usually done by clinical assessment although ECHO and ECG may be useful in occasional patients to document the extent of cardiac function prior to commencing therapy.
- Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1.

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. Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.

4. Counselling - all patients should receive verbal and written information on oral chemotherapy.

5. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures

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

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


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

#### CYCLES 1 to 18

<table>
<thead>
<tr>
<th>Pre- and Post Hydration</th>
<th>Cycle 1: pre- and post- hydration with 500mL sodium chloride 0.9% is recommended. Encourage 2-3L of oral fluids 48 hours before cycle 1 day 1. Subsequent cycles: pre- and post- hydration is recommended if lactate dehydrogenase (LDH) or uric acid is elevated and / or patients considered at risk for TLS. Encourage at least 1L oral fluids before and after each carfilzomib dose to maintain adequate hydration.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-medication</td>
<td>4 mg IV/PO dexamethasone (or the combination dexamethasone dose if due on that day) 30 minutes prior to all carfilzomib doses in the first cycle, and prior to all subsequent doses if any carfilzomib related rigors, chills, dyspnoea or other infusion reactions symptoms occur.</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td><strong>27 mg/m²</strong> (maximum dose 60 mg) intravenous infusion in 50mL glucose 5% over 10 minutes. For cycle 1 on Days 1 and 2 administer carfilzomib at <strong>20mg/m²</strong> (maximum dose 44 mg) in 50mL glucose 5% over 10 minutes. Doses capped at BSA 2.2m². Dose adjustments do not need to be made for weight changes ≤ 20% Cycles 1 to 12: Days 1, 2, 8, 9 and 15, 16 Cycles 13 to 18: Days 1, 2 and 15, 16 Patient must be monitored for 1 hour following carfilzomib infusions during cycle 1 and cycle 2 day 1.</td>
</tr>
<tr>
<td>WITH</td>
<td><strong>Dexamethasone</strong> 40 mg PO once a week On days 1, 8, 15 &amp; 22</td>
</tr>
<tr>
<td>WITH</td>
<td><strong>Lenalidomide</strong> 25mg PO once daily Days 1 to 21</td>
</tr>
</tbody>
</table>
**CYCLE 19- onwards (continuous therapy):**

Following 18 cycles, continue on Lenalidomide and dexamethasone therapy. Consider reduction of dexamethasone dose in elderly patients or in case of steroid side effects. Continue therapy provided no significant toxicity or disease progression.

<table>
<thead>
<tr>
<th>Lenalidomide (Continuous therapy)</th>
<th>25 mg orally once daily on days 1 to 21.</th>
</tr>
</thead>
<tbody>
<tr>
<td>WITH</td>
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<tr>
<td>Dexamethasone</td>
<td>40 mg PO on days 1, 8, 15 and 22.</td>
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<tr>
<td></td>
<td>NB: In case of elderly or if steroid-related side effects, consider using 20mg</td>
</tr>
</tbody>
</table>

**CYCLE FREQUENCY**

Repeat every 28 days, until signs of disease progression or unacceptable toxicity.

**DOSE MODIFICATIONS**

**HAEMATOLOGICAL TOXICITY**

Prior to initiating a new cycle of therapy:
- Platelets $\geq 50 \times 10^9/L$ and ANC $\geq 1.0 \times 10^9/L$
- Non-haem toxicities should resolve to G1 or baseline

**Carfilzomib Dose Adjustments**

<table>
<thead>
<tr>
<th>Current dose</th>
<th>Reduce dose to</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 mg/m$^2$</td>
<td>20 mg/m$^2$</td>
</tr>
<tr>
<td>20 mg/m$^2$</td>
<td>15 mg/m$^2$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematological toxicity during a cycle</th>
<th>Carfilzomib dose modification or delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If Absolute neutrophil count $&lt; 0.5 \times 10^9 /L$</td>
<td>Withhold Carfilzomib dose, if recovered to $\geq 0.5 \times 10^9/L$, continue at the same dose level. For subsequent drops to $&lt; 0.5 \times 10^9/L$, follow the same recommendations as above and consider further dose level reduction when restarting Carfilzomib</td>
</tr>
<tr>
<td>• If platelet $\leq 10 \times 10^9/L$ or evidence of bleeding with thrombocytopenia</td>
<td>Withhold Carfilzomib dose. if recovered to $\geq 10 \times 10^9/L$ and/or bleeding is controlled, continue at the same dose level For subsequent drops to $&lt; 10\times10^9 /L$, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilzomib</td>
</tr>
</tbody>
</table>
Lenalidomide Dose Adjustments
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.

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.

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>
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<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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</tbody>
</table>

RENAL/HEPATIC IMPAIRMENT:

Carfilzomib

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine≥ 2 x baseline, or CrCl&lt;15 mL/min, or CrCl ≤ 50% of baseline, or if dialysis: <strong>withhold Carfilzomib</strong></td>
<td>No dedicated pharmacokinetic studies have been completed in patients with hepatic impairment</td>
</tr>
<tr>
<td>Resume carfilzomib when renal function has recovered to within 25% of baseline: consider resuming at 1 dose level reduction.</td>
<td></td>
</tr>
</tbody>
</table>
Lenalidomide

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl 30- &lt;50 mL/min</td>
<td>10 mg 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 to 15 mg OD if no response and patient tolerating
**Can increase to 10 mg OD if no response and patient tolerating
***On dialysis day, administer dose after dialysis/

No formal studies. No specific dose recommendations

INVESTIGATIONS (at the beginning of each cycle unless otherwise noted)

- FBC
- U&E, LFTs, Ca**
- Blood pressure
- Ig’s, paraprotein, Freelite assay.
- Consider repeat BM aspirate and trephine after 3 cycles in non-secretory myeloma and check result prior to starting cycle #5.
- Random blood glucose/ blood sugar

EMETIC RISK

Low-Moderate emetic risk

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 50 mg OD
- Bone protection as per NSSG Bone Protection protocol MM.3
- Thromboprophylaxis/anticoagulation as below.
- Consider prophylactic co-trimoxazole if heavily pre-treated or previous autograft.
- Consider cholestyramine if suspicion of bile salt malabsorption
- Prophylactic acyclovir 200 mg bd to tid (depending on renal function).

Patients on oral hypoglycaemic may require close monitoring of blood sugar levels.
ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

Carfilzomib:

- The most common adverse events occurring in at least 20% of patients treated with Carfilzomib in the combination therapy trial: upper respiratory tract infection, neutropenia, thrombocytopenia, diarrhoea, fatigue, pyrexia decreased lymphocytes, dyspnoea, hypertensions, decreased phosphate, anaemia, muscle spasm, cough, and hypokalemia.

- **Infusion reactions**: Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration. Dexamethasone should be administered prior to carfilzomib to reduce the incidence and severity of reactions.

- **Cardiac and pulmonary** toxicities have been reported. Cardiac toxicity may occur in up to 5 percent of patients.

- **Others**: Tumour lysis syndrome, acute renal failure, pulmonary hypertension, Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, Posterior reversible encephalopathy syndrome (PRES)

Lenalidomide:

- **Teratogenicity**: The manufacturer's pregnancy prevention programme must be observed. Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme.

- **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.

- **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.

- **Myelosuppression**
- **Drowsiness, somnolence and sedation**: Dose best taken at night time.
- **Peripheral neuropathy**: Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant toxicity is uncommon. Patients should be advised to report prickling, numbness and paraesthesia.
• **Dizziness and orthostatic hypotension**
• 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.

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**TREATMENT RELATED MORTALITY**

2-3%

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**REFERENCES**


4. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, May 2017

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**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>Dr Ramasamy Consultant</td>
<td>New document</td>
<td>May 2016</td>
<td>1.0</td>
<td>May 2018</td>
</tr>
<tr>
<td>Faouzi Djebbari (Haematology Pharmacist)</td>
<td>Updated concurrent medication and references</td>
<td>July 2017</td>
<td>1.1</td>
<td>June 2018</td>
</tr>
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