MELPHALAN, PREDNISOLONE AND THALIDOMIDE (MPT)

INDICATION

As initial therapy or at relapse in transplant ineligible patients.

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:

   • FBC & film
   • Clotting screen
   • U&Es
   • LFTs
   • Calcium
   • Albumin
   • Uric acid
   • 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)
   • $\beta_2$ 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 investigation:

   • 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 including signing Celgene risk management programme forms (see web page for links).

REGIMEN SPECIFIC PRE-ASSESSMENT

The conditions of the Thalidomide 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>Dosage</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Thalidomide</td>
<td>100 mg/day orally. Usually start with 50 mg/day for first cycle. Nocte</td>
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<tr>
<td>Melphalan</td>
<td>7 mg/m² PO daily (tablets are 2 mg in strength) Days 1 to 4</td>
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<tr>
<td>Prednisolone</td>
<td>40 mg/m² PO daily (5 mg and 25 mg in strength) NB: Dose of prednisolone may be reduced in the very elderly or if significant toxicity occurs Days 1 to 7</td>
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CYCLE FREQUENCY

Every 4 weeks until plateau phase (paraprotein level stable for 3 months) and then stop.

DOSE MODIFICATIONS

Haematological toxicity
- Neutrophil count should be > 1.0 x 10⁹/L and platelet count should be > 75 x 10⁹/L before melphalan treatment, unless low counts are thought to be due to myeloma per se.
- The melphalan dose should be reduced if severe myelotoxicity occurs, consider alternative regimen
- If the nadir neutrophil count is > 1.5 and nadir platelets > 100, consideration may be given to a cautious increase in melphalan dose for subsequent cycles.

Hepatic/Renal Impairment

<table>
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<tr>
<th>Melphalan</th>
<th>Renal</th>
<th>Hepatic</th>
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<tbody>
<tr>
<td>GFR 30 – 50 ml/min</td>
<td>75% dose clinical decision</td>
<td>No recommendations. If excess toxicity, consider dose reduction on subsequent cycles</td>
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<tr>
<td>GFR &lt; 30 ml/min</td>
<td>clinical decision</td>
<td></td>
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</table>
Thalidomide

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose reduction necessary</td>
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</tbody>
</table>

**Neuropathy:**
Thalidomide should be stopped or reduced if there are symptoms of progressive peripheral neuropathy causing functional disability (grade 2 or above). Consider cautious re-introduction of thalidomide at a dose of 50mg daily if symptoms resolve to grade 1 or better after a two-week gap. Subsequent cautious dose escalation should be considered if symptoms permit.

**INVESTIGATIONS – prior to each cycle of treatment**

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC - monthly.
- U&Es, LFTs, Ca++ - monthly.
- Ig’s, paraprotein, or Freelite assay if appropriate, usually monthly after first 2 months.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Random blood glucose/blood sugar

**CONCURRENT MEDICATIONS**

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prescribe prophylactic laxatives to be taken if needed.
- 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, see 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**
Low emetic risk

**ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS**

- **Teratogenic:** A risk management programme should be observed. The concomitant use of 2 effective methods 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 thalidomide must be in line with the pregnancy prevention programme.
• **Drowsiness, somnolence and sedation:** Take the dose at night time. Thalidomide 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 thalidomide.

• **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

      Additionally:
      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.

• **Peripheral neuropathy:** Patients should be advised to report prickling, numbness and paraesthesia.

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

• **Skin toxicity:** in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.

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


3. eMC UK Summary of Product Characteristics for Thalidomide, Celgene, December 2016


7. eMC UK Summary of Product Characteristics for Melphalan 2mg tabs, Aspen, March 2014

8. eMC UK Summary of Product Characteristics for Prednisolone 1mg and 5 mg tablets, Wockhardt UK Ltd, November 2015

REVIEW

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
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<tr>
<td>Nadjoua Maouche Pharmacist</td>
<td>Formatting, adverse effects and pre assessment section, dose modification, renal section</td>
<td>May 2016</td>
<td>4.3</td>
<td>May 2018</td>
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<tr>
<td>Dr Jaimal Kothari Consultant</td>
<td>VTE, regimen specific pre assessment included</td>
<td>May 2016</td>
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<td>May 2018</td>
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<tr>
<td>Manuela Sultanova Service Coordinator</td>
<td>Formatting, correct Wessex address, Standardisation of General pre-assessment and VTE</td>
<td>August 2017</td>
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<td>May 2018</td>
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