**Indication**
First line or relapsed multiple myeloma in patients who are not eligible for stem cell transplantation.

**ICD-10 codes**
Codes with a pre-fix C90

**Regimen details**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Melphalan</td>
<td>7mg/m²</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>Prednisolone</td>
<td>40mg/m² OM*</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>1-28 (continuously)</td>
<td>Thalidomide</td>
<td>50mg ON **</td>
<td>PO</td>
<td></td>
</tr>
</tbody>
</table>

* Dose may be reduced in elderly and/or frail patients.
**Thalidomide may be increased to 100mg ON during cycle 1 if tolerated and to 200mg ON for subsequent cycles.

**Cycle frequency**
28 days

**Number of cycles**
Maximum of 6-9 cycles

**Administration**

Melphalan is available as 2mg tablets. Melphalan tablets are cytotoxic. Tablets should be swallowed whole with a glass of water and should not be broken, crushed or chewed.

Prednisolone is available as 5mg and 25mg tablets. The dose should be taken once a day in the morning, with or after food.

Thalidomide is available as 50mg capsules. The capsules should be swallowed whole in the evening.

Women of child bearing potential must have a **NEGATIVE PREGNANCY TEST** within 72 hours before starting thalidomide therapy, and then once a month during treatment continuing until one month after stopping treatment (every 2 weeks if irregular periods). If a woman thinks she may be pregnant she must stop taking thalidomide immediately. Thalidomide must be prescribed and dispensed according to the Pregnancy Prevention Programme.

**Pre-medication**
Nil

**Emetogenicity**
This regimen has low emetogenic potential.
**Additional supportive medication**

H₂ antagonist or proton pump inhibitor

Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden, for the first cycle only

Bisphosphonates as per local policy

Antifungal, antiviral and PCP prophylaxis as per local policy.

Laxatives if required

Thromboprophylaxis is required – risk assess patient and consider prophylactic LMWH as per local policy (unless platelet count < 30 x 10⁹/L, then withhold until recovered). If patient is already taking warfarin consider switch to treatment dose LMWH or DOAC (as applicable within NICE guidance).

**Extravasation**

N/A

**Investigations – pre first cycle**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC and film</td>
<td>7 days</td>
</tr>
<tr>
<td>Clotting screen</td>
<td>7 days</td>
</tr>
<tr>
<td>U+Es (including creatinine)</td>
<td>7 days</td>
</tr>
<tr>
<td>LFTs</td>
<td>7 days</td>
</tr>
<tr>
<td>Calcium</td>
<td>7 days</td>
</tr>
<tr>
<td>Pregnancy test (women of child bearing potential)</td>
<td>72 hours</td>
</tr>
<tr>
<td>HIV, hepatitis B and C status</td>
<td>7 days</td>
</tr>
</tbody>
</table>

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)

Bone marrow aspirate and trephine, including FISH.

Assessment of venous thromboembolic risk.

**Investigations – pre subsequent cycles**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>72 hours</td>
</tr>
<tr>
<td>U+Es (including creatinine)</td>
<td>7 days</td>
</tr>
<tr>
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<td>Calcium</td>
<td>7 days</td>
</tr>
<tr>
<td>Pregnancy test (women of child bearing potential)</td>
<td>72 hours</td>
</tr>
</tbody>
</table>

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)

**Standard limits for administration to go ahead**

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>≥ 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 75 x 10⁹/L</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>≥ 50mL/min</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt; ULN</td>
</tr>
</tbody>
</table>

**Dose modifications**

- **Haematological toxicity**

  Treatment on day 1 should only be initiated if neutrophils ≥ 1.0 x 10⁹/L and platelets ≥ 75 x 10⁹/L.

  If prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding, reduce melphalan dose to 75% for subsequent cycles.
- **Renal impairment**

  **Melphalan:**

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Melphalan dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>100%</td>
</tr>
<tr>
<td>10-50</td>
<td>75%</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>50%</td>
</tr>
</tbody>
</table>

- **Hepatic impairment**

  There are no dose modification recommendations for melphalan in hepatic impairment, however, if excess toxicity experienced, consider dose reduction for subsequent cycles.

- **Other toxicities**

  **Thalidomide:**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Definition</th>
<th>Thalidomide dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>Grade 1-2</td>
<td>Reduce thalidomide dose by 50% and consider discontinuing.</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4</td>
<td>Stop thalidomide (usually permanently). If symptoms resolve consider starting at 50mg for subsequent cycles (dose may be escalated in 50mg increments).</td>
</tr>
<tr>
<td>Sedation, constipation, rash,</td>
<td>Grade 3-4</td>
<td>Stop thalidomide for remainder of cycle. Consider restarting at 50mg for subsequent cycles (dose may be escalated in 50mg increments).</td>
</tr>
<tr>
<td>fatigue, tremor, oedema</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

  Thalidomide – MHRA alert: viral reactivation and pulmonary hypertension:
  - Cases of viral reactivation have been reported in patients previously infected with varicella-zoster and Hepatitis B. Previously infected patients should be closely monitored for signs and symptoms or reactivation throughout treatment.
  - Cases of pulmonary hypertension have been reported following thalidomide treatment. Patients should be closely monitored for signs and symptoms of cardiopulmonary disease.

  **Adverse effects** - for full details consult product literature/ reference texts

  - **Serious side effects**
    - Myelosuppression
    - Thrombotic events
    - Neuropathy
    - Tumour lysis syndrome
    - Cardiac failure
    - Teratogenicity
    - Pulmonary fibrosis

  - **Frequently occurring side effects**
    - Myelosuppression
    - Constipation
    - Sedation
    - Nausea and vomiting
    - Fatigue
    - Peripheral neuropathy
    - Headache
    - Rash
• Other side effects
  Altered LFTs
  Decreased appetite
  Confusion
  Depression

**Significant drug interactions** – for full details consult product literature/ reference texts

**Warfarin/coumarin anticoagulants:** increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral vitamin K antagonist monitor the INR at least once a week and adjust dose accordingly.

**Thalidomide**
May increase **sedative** and **bradycardic** effects of other medication.

May increase **peripheral neuropathy** associated with other medication.

**Combined oral contraceptive pill:** increased risk of venous thrombo-embolic events - avoid concurrent use.

**Additional comments**
Women of child bearing potential and males must use contraception as outlined by a MHRA approved Risk Management Program.
Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

**References**

- Summary of Product Characteristics: Thalidomide (Celgene) accessed 3 August 2016 via [www.medicines.org.uk](http://www.medicines.org.uk)

Written/reviewed by: Becky Bagnall (Haematology Pharmacist, North Bristol NHS Trust) Agreed at myeloma SSG meeting August 2016

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Date: January 2017