Melphalan, Prednisolone and Thalidomide (MPT)  
MMWOS001/01

Indication
Oral treatment for multiple myeloma

Eligibility criteria
Confirmed diagnosis of multiple myeloma
First line therapy in patients
- of 65 years or older
- any patient not eligible for high dose chemotherapy

Treatment intent
Palliative

Pre-treatment evaluation
Informed consent, provision of verbal and written information including specific information relating to the use of thalidomide and discussion of issues relating to contraception. Refer to local policy for prescribing of thalidomide and Thalidomide Pharmion™ Healthcare Professionals Educational Kit
Assessment of Performance Status
Height, weight and BSA
Baseline investigations
- as current Clinical Management Guideline for Myeloma
- FBC, U&E including creatinine clearance assessment and LFTs no longer than 7 days before first cycle
- pregnancy test as indicated
- Assessment and documentation of any neurological symptoms

Regimen
Thalidomide Pharmion™ is prescribed and dispensed according to the Thalidomide Pharmion™ Pregnancy Prevention Programme and local policy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan</td>
<td>7mg/m² daily</td>
<td>oral</td>
<td>Swallow whole on an empty stomach</td>
<td>1-4</td>
</tr>
<tr>
<td></td>
<td>to nearest 2mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>40mg daily</td>
<td>oral</td>
<td>With or after food</td>
<td>1-4</td>
</tr>
<tr>
<td>Thalidomide Pharmion™</td>
<td>50-200mg daily</td>
<td>oral</td>
<td>Take as a single dose at bedtime</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>Start at 50mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and increase at most weekly in 50mg increments.</td>
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</tr>
</tbody>
</table>

Dose Modifications at Initiation
- Neutrophils must be >1.0 x 10⁹ and platelets >75 x 10⁹ unless cytopenias are disease-related.
- If CrCl <50ml/min reduce melphalan dose to 75%. If CrCl <30ml/min discuss with consultant.
- Consider CTDa if CrCl <30ml/min

Cycle frequency – every 28 days
Planned number of cycles – continue until plateau phase achieved (minimum 6 cycles)

Supportive therapy
- Antiemetics as per local policy
- Gastroprotection according to local policy
- Allopurinol 300mg daily (100mg if <20ml/min) for cycles 1 & 2
- Encourage good oral fluid intake (2-3 litres/24 hours unless contraindicated)
- Thromboprophylaxis - low molecular weight heparin or aspirin, according to local policy.
- Laxatives as required

GSCF prophylaxis
Primary prophylaxis is not indicated.
Secondary prophylaxis may be considered after discussion with consultant and in line with WoSCAN GCSF guidelines

Emetogenic Risk
Low (10-30%)
Refer to local guideline for management

Adverse effects
Very common (≥ 1 in 10)
Neutropenia, leucopenia, lymphopenia, thrombocytopenia, nausea & vomiting, diarrhoea dyspepsia, constipation, fatigue, somnolence (thalidomide) insomnia (prednisolone) peripheral neuropathy, peripheral oedema.

Common (>1/100, <1 in 10)
Alopecia, impaired glucose control, arthralgia, cardiac failure, bradycardia, skin dryness/rashes, increased blood urea in patients with renal damage.

Teratogenic effects: Thalidomide is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects. Thalidomide must never be used by women who are pregnant or who are unable to comply with required contraceptive measures.

For more detailed information please refer to the current Summary of Product Characteristics for melphalan (Alkeran™), prednisolone (current supplier) and thalidomide(Thalidomide Pharmion™)

Precautions & contraindications
- hypersensitivity to melphalan, prednisolone, or thalidomide
- avoid immunisations with live vaccines
- avoid in pregnancy and breast feeding
- avoid concomitant use of NSAID if possible
- monitor blood glucose during steroid therapy
- Melphalan – use with caution in renal impairment & dose reduce as indicated
- Prednisolone – caution with tuberculosis, hypertension, congestive cardiac failure, liver failure, renal insufficiency, diabetes mellitus, osteoporosis, severe affective disorders, epilepsy and/or seizure disorders, peptic ulceration, thromboembolic disorders, chickenpox, measles
- Thalidomide Pharmion™ is currently the only brand of thalidomide licensed in the UK. The prescriber must ensure that the patient understands and complies with the conditions of the Thalidomide Pharmion® Pharmacy Prevention Programme. Thalidomide is contraindicated in patients unable to comply with the required contraceptive measures

Drug interactions
Prednisolone
- blood levels reduced by enzyme inducers eg rifampicin, phenytoin, carbamazepine
- coumarin anticoagulant response may be altered – closely monitor INR or PT
- effect may be increased by ciclosporin

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Melphalan
- increased risk of nephrotoxicity with ciclosporin

Thalidomide
- increased sedative effects of other medicines eg anxiolytics, analgesics
- increased bradycardic effects of other medicines eg beta-blockers
- combined hormonal contraceptives are not recommended due to increased risk of thromboembolic disease

For more detailed information please refer to the current Summary of Product Characteristics.

Investigations prior to subsequent cycles
- FBC, U&E, LFTs
- performance status
- assessment of toxicity, documented by CTCAE version 3.0
- consider nerve conduction tests in patients with grade 2 or greater symptoms of peripheral neuropathy
- Free light chains and paraprotein as appropriate every cycle
- Pregnancy testing as indicated

Dose modifications

Haematological

It is advised that neutrophil count should be at least $1 \times 10^9 /L$
platelet count should be at least $75 \times 10^9 /L$ before re-treatment.

If cytopenias are considered to be chemotherapy related, modification of the regimen may be indicated.

Initially delay re-treatment by 1-2 weeks.
If counts have not recovered as above after 2 weeks, consider G-CSF and/or switching to CTDa

Renal

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCI</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan</td>
<td>30-50ml/min</td>
<td>75%</td>
<td>Discuss with consultant</td>
</tr>
<tr>
<td></td>
<td>&lt;30ml/min</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>No dose adjustment required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>No dose adjustment required but monitor in patients with severe impairment</td>
<td></td>
<td></td>
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</tbody>
</table>

Hepatic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bil</th>
<th>AST/ALT</th>
<th>% of full dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan</td>
<td></td>
<td></td>
<td></td>
<td>No dose reduction required. If excessive toxicity consider dose reduction on subsequent cycles</td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
<td></td>
<td>No dose reduction required</td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
<td></td>
<td>No dose reduction required but monitor in patients with severe impairment</td>
</tr>
</tbody>
</table>
### Others

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>1 or above</td>
<td>Increase/change antiemetics. No dose reduction.</td>
</tr>
<tr>
<td>Neuropathy (thalidomide)</td>
<td>1</td>
<td>Continue to monitor the patient with clinical examination. Consider reducing dose if symptoms worsen. Refer to consultant.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Reduce dose) or interrupt treatment. If no improvement, or continued worsening, discontinue. If resolves to grade 1 or better, treatment may be restarted - refer to consultant.</td>
</tr>
<tr>
<td>Any other toxicity</td>
<td>3 resolving</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Problems tolerating withdrawal from steroid</td>
<td>3 resolving</td>
<td>Consider prescribing a reducing dose of steroid if withdrawal poorly tolerated</td>
</tr>
</tbody>
</table>

#### Evaluation of response to treatment
- review by haematologist every cycle
- for response criteria, see Appendix 1
- If PR not achieved after 3 cycles, refer to consultant

#### References
- Scottish Medicines Consortium, Drug Advice No. (525/08) Published 12.01.2009
- The North London Cancer Network, Dosage adjustments for Cytotoxics in Renal Impairment November 2003
- Medical Research Council Myeloma IX Study Version 3 14 March 2006
- Medical Research Council Myeloma VII Study September 1993

#### Document Control

<table>
<thead>
<tr>
<th>Prepared by</th>
<th>Sally McKendrick, Craig Richardson, Kelly Baillie</th>
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<tbody>
<tr>
<td>Checked by</td>
<td>Dr Grant McQuaker, Dr Richard Soutar</td>
</tr>
<tr>
<td>Approved by</td>
<td>RCAG Prescribing Advisory Subgroup</td>
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<tr>
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<td>MMWOS001/01</td>
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<tr>
<td>Replaces</td>
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Appendix 1

EBMT/IMBTR Definitions of Response and Progression (Blade et al, 1998)

Complete Response (CR)
1) Absence of the original monoclonal paraprotein in serum/urine by routine electrophoresis and immunofixation maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
2) <5% plasma cells in a bone marrow aspirate and on trephine biopsy.
3) No increase in size or number of lytic bone lesions on radiological investigations, if performed, (development of a compression fracture does not exclude response)
4) Disappearance of soft tissue plasmacytomas.

Patients in whom some but not all of the criteria for CR are fulfilled are classified as PR. This includes patients in whom electrophoresis is negative but in whom immunofixation has not been performed.

Partial Response (PR)
1) >50% reduction in the serum monoclonal paraprotein level, maintained for a minimum of 6 weeks.
2) Reduction in 24-hour urinary light chain excretion either by >90% or to <200mg/24 hours, maintained for a minimum of 6 weeks.
3) For patients with non-secretory myeloma only, 50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, maintained for a minimum of 6 weeks.
4) >50% reduction in the size of soft tissue plasmacytoma.
5) No increase in size or number of lytic bone lesions on radiological investigations, if performed.

Patients in whom some but not all, of the criteria for PR are fulfilled are classified as MR

Minimal Response (MR)
1) 25-49% reduction in the serum monoclonal paraprotein level, maintained for a minimum of 6 weeks.
2) 50-89% reduction in 24-hour urinary light chain excretion which still exceeds <200mg/24 hours, maintained for a minimum of 6 weeks.
3) For patients with non-secretory myeloma only, 25-49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, maintained for a minimum of 6 weeks.
4) 25-49% reduction in the size of soft tissue plasmacytoma.
5) No increase in size or number of lytic bone lesions on radiological investigations, if performed.

MR also includes patients in whom some, but not all, of the criteria for PR are fulfilled.

No Change (NC)
Not meeting the criteria of either minimal response or progressive disease.

Progressive Disease
1) >25% increase in the serum monoclonal paraprotein level which must also be an absolute increase of at least 5g/l and confirmed by at least one repeated investigation.
2) >25% increase in 24-hour urinary light chain excretion which must also be an absolute increase of at least 200mg/24 hours and confirmed by at least one repeated investigation.
3) >25% plasma cells in a bone marrow aspirate or trephine biopsy which must also be an absolute increase of at least 10%.
4) Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas.
5) Development of new lytic bone lesions or soft tissue plasmacytomas. Development of a compression fracture does not exclude continued response.
6) Development of hypercalcaemia (corrected >2.8mmol/l) not attributable to any other cause.

Plateau
Stable values (within 25% above or below value at time response is assessed) maintained for at least 3 months.

Relapse from CR
1) Reappearance of serum or urinary paraprotein on routine electrophoresis or on immunofixation confirmed by at least one further investigation excluding oligoclonal immune reconstitution.
2) >5% plasma cells in a bone marrow aspirate or trephine biopsy.
3) Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions. Development of a compression fracture does not exclude continued response.
4) Development of hypercalcaemia (corrected >2.8mmol/l) not attributable to any other cause.