

MELPHALAN, PREDNISOLONE AND THALIDOMIDE (MPT)

INDICATION

As initial therapy or at relapse in transplant ineligible patients.

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
 - FBC & film
 - Clotting screen
 - U&Es
 - LFTs
 - Calcium
 - Albumin
 - Uric acid
 - CRP
 - Baseline random blood glucose level
 - 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)
 - β_2 microglobulin
 - LDH
 - 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 i appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ

Additional Investigations

- 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. Document patient’s height and weight, dose on actual body weight.
- 5. Document patient’s performance status.
- 6. Treatment must be agreed at the relevant MDT.
- 7. Counselling - all patients should receive verbal and written information on oral chemotherapy. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
- 8. 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 Pregnancy Prevention Programme forms.

REGIMEN SPECIFIC PRE- ASSESSMENT

- 1. The conditions of the Thalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the Celgene Pregnancy Prevention Programme.
- 2. Clinical Assessment of thrombo-embolic risk.
- 3. Evaluate for and document presence of neuropathy. This is usually done by clinical assessment although nerve conduction studies may be useful in occasional patients to document the extent of neurological damage prior to treatment with thalidomide.

DRUG REGIMEN

Thalidomide	100 mg/day orally. Usually start with 50 mg/day for first cycle.	Nocte
Melphalan	7 mg/m ² PO daily (tablets are 2 mg in strength)	Days 1 to 4
Prednisolone	40 mg/m ² PO daily NB: Dose of prednisolone may be reduced in the very elderly or if significant toxicity occurs	Days 1 to 7

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.

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.

Hepatic/Renal Impairment

Melphalan

Renal	Hepatic
Currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering melphalan tablets to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established. In myeloma patients with renal damage, temporary but significant increases in blood urea levels have been observed during melphalan therapy.	No recommendations. If excess toxicity, consider dose reduction on subsequent cycles

Thalidomide

Renal	Hepatic
No dose reduction necessary	No dose reduction necessary

INVESTIGATIONS – prior to each cycle of treatment

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC - monthly.
- U&E, LFTs, Ca⁺⁺ - monthly.
- Ig's, paraprotein, or Freelite assay if appropriate, usually monthly after first 2 months.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl)<10ml/min)
- Consider Prophylactic fluconazole 50mg OD if appropriate.
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Thromboprophylaxis/anticoagulation – see VTE section below.
- Bone protection as per NMSG Bone Protection protocol MM.3

EMETIC RISK

Low emetic risk. Low-moderate on Melphalan days.

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

- **Teratogenic:** The Celgene Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention programme
- **Peripheral neuropathy:** Patients should be advised to report prickling, numbness and paraesthesia.
- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with thalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:
 1. Prophylactic low-molecular weight heparin OR
 2. Prophylactic NOAC e.g. apixaban 2.5mg bd (check product specific information)

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors

If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

- **Drowsiness, somnolence and sedation:** Prescribe thalidomide as night time dose. 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
- **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.
- **Melphalan related toxicities** include: Myelosuppression, nausea, vomiting and diarrhea, stomatitis, alopecia. Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.
- **Steroid related toxicities include:** mood changes, restlessness, withdrawal effects, glucose intolerance
- **Skin toxicity:** in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.

REFERENCES

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2. Cavenagh JD, Oakervee H; UK Myeloma Forum and the BCSH Haematology/Oncology Task Forces. Thalidomide in multiple myeloma: current status and future prospects. *Br J Haematol.* 2003 Jan;120(1):18-26.
3. Thalidomide, Celgene ® eMC UK Summary of Product Characteristics for, last updated March 2018
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6. Palumbo A et al. A Phase III Study of Enoxaparin vs Aspirin vs Low-Dose Warfarin as Thromboprophylaxis for Newly Diagnosed Myeloma Patients Treated with Thalidomide Based-Regimens. *Blood (ASH Annual Meeting Abstracts)* 2009 114: Abstract 492.
7. Melphalan 2mg tabs eMC UK Summary of Product Characteristics , Aspen, March 2014

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, adverse effects and pre assessment section , dose modification, renal section	May 2016	4.3	May 2018
Dr Jaimal Kothari Consultant	VTE, regimen specific pre assessment included	May 2016	4.3	May 2018
Manuela Sultanova Service Coordinator	Formatting, correct Wessex address, Standardisation of General pre-assessment and VTE	August 2017	4.4	May 2018
Network Protocol Review	Emetic risk Standardisation of assessment, investigations, concurrent medication, formatting, VTE information, Melphalan renal dosing. Adverse events	June 2018	4.5	June 2020