Chemotherapy Protocol

MULTIPLE MYELOMA

MPT-MELPHALAN (PO)-PREDNISOLONE-THALIDOMIDE

Regimen

- Multiple Myeloma – MPT-Melphalan (PO)-Prednisolone-Thalidomide

Indication

- First line treatment of multiple myeloma in patients who or are unsuitable for bone marrow transplantation

- Second line or subsequent treatment of relapsed or progressive multiple myeloma in those with renal impairment who are not eligible for a transplant

Toxicity

Drug	Adverse Effect
Melphalan	Gastro-intestinal disturbances, stomatitis, nausea, vomiting, alopecia, myalgia, muscle atrophy and fibrosis
Prednisolone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Thalidomide	Drowsiness, constipation, dizziness, increased risk of thromboembolic events, dry skin/rash, peripheral neuropathy, teratogenicity, syncope, bradycardia

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, LFTs and U&Es every 4 weeks

- Paraprotein or light chains every 4 weeks

- Pregnancy testing in women of childbearing potential. A negative pregnancy test must be obtained within 3 days of starting thalidomide the test must be repeated every 4 weeks (every 2 weeks in women with irregular menstrual cycles) with the final test 4 weeks after the last dose of thalidomide.

- Regular monitoring of blood glucose is considered good practice

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Dose modifications based on haematological parameters apply to melphalan only.

Neutrophils ($x10^9$/L)	**Dose Modifications (melphalan)**
1 or greater	100%
less than 1	Delay treatment for up to 2 weeks until the neutrophils are $1x10^9$/L or above and then continue with full dose and growth factor support and/or dose reduction. If recovery takes longer than 2 weeks consider stopping treatment.
Platelets ($x10^9$/L)	**Dose Modifications (melphalan)**
75 or above	100%
less than 75	Delay treatment for up to 2 weeks until the platelets are $75x10^9$/L or above and then continue with reduced dose. If recovery takes longer than 2 weeks consider stopping treatment.

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	**Bilirubin µmol/L**		**AST/ALT units/L**	**Dose (% of original dose)**
Melphalan	N/A		N/A	No dose adjustment necessary
Thalidomide	N/A		N/A	No dose modification required

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Melphalan	30 or greater	100%
	less than 30	Initiate treatment at 75%, increase at subsequent cycles if tolerated
Thalidomide	N/A	No dose modification required

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Thalidomide

Peripheral Neuropathy

If NCI-CTC grade 1 neurological toxicity occurs treatment may be continued, if symptoms worsen consider dose reduction or interruption. Treatment may be reintroduced at a reduced dose if symptoms resolve. If NCI-CTC grade 2 neurological toxicity occurs suspend treatment or reduce the dose by at least 50%. Treatment may be reintroduced at a reduced dose if symptoms resolve to grade 1 or below. For NCI-CTC neurological toxicity grade 3 or above or toxicity that does not resolve despite treatment interruption / dose reduction thalidomide treatment should be stopped.

Thromboembolism

The thrombotic risk for patients commencing on thalidomide must be assessed. Appropriate thromboprophylaxis must be prescribed according to local policies. Thromboprophylaxis is generally recommended for at least the first 5 months of thalidomide treatment, especially in patients with additional thrombotic risk factors. Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.

The occurrence of a thromboembolic event such as a DVT or thromboembolism, notably pulmonary embolism, is an indication for full anticoagulation following standard treatment guidelines. Thalidomide may be stopped, but can be re-introduced, initially at 50mg daily with escalation at subsequent cycles to 100mg, assuming good anticoagulant control and no other untoward side effects.

All patients should be initially prescribed a low molecular weight heparin at the appropriate prophylactic dose. Therapeutic warfarin is an alternative to low molecular heparin. Aspirin 75mg each morning is an alternative in very low risk patients once a response has been obtained.

Teratogenicity

Thalidomide is highly teratogenic.

All prescribers, patients and pharmacy staff must comply with the manufacturer's Pregnancy Prevention Programme.

Women of child-bearing potential taking thalidomide must use one agreed effective method of contraception for at least 4 weeks before starting thalidomide, while on thalidomide and for one month after. They must have a negative pregnancy test within 3 days prior to starting treatment. Pregnancy testing should be repeated monthly thereafter until one month after stopping thalidomide (or every 2 weeks in women with irregular menstrual cycles).
If a woman taking thalidomide thinks she may be pregnant she must stop the drug immediately and seek medical advice.

Men taking thalidomide must use a barrier method of contraception throughout treatment and for one week after stopping, if their partner is capable of bearing children.

Other

For other thalidomide related toxicities of NCI-CTC grade 3 or above. Stop thalidomide until recovery to NCI-CTC grade 1 or below. Cautious reintroduction of thalidomide at a dose of 50mg a day may be considered with dose escalation if tolerated.

Prednisolone

For patients who are unable to tolerate the standard dose of prednisolone the dose may be reduced or omitted as appropriate.

Regimen

28 day cycle continued until plateau plus two cycles (6 cycles will be set in ARIA)

There are different versions of this protocol in use. Check you have the intended version.

Cycle 1

Drug	Dose	Days	Administration
Melphalan	7mg/m^2	1, 2, 3, 4	Oral
Prednisolone	40mg/m^2	1, 2, 3, 4	Oral
Thalidomide	50mg	1-28 incl.	Oral

Cycle 2 onwards

Drug	Dose	Days	Administration
Melphalan	7mg/m^2	1, 2, 3, 4	Oral
Prednisolone	40mg/m^2	1, 2, 3, 4	Oral
Thalidomide	100mg	1-28 incl.	Oral

Dose Information

- Melphalan dose will be rounded to the nearest 2mg (up if halfway)
- Melphalan is available as 2mg tablets
- Prednisolone dose will be rounded to the nearest 5mg (up if halfway)
- Prednisolone is available as 5mg and 25mg tablets
- Thalidomide is available as 50mg capsules.

Administration Information

- Melphalan tablets should be stored in the fridge
- Prednisolone should be taken in the morning, with or after food
- Thalidomide should be taken at night to avoid daytime drowsiness

Additional Therapy

- Anti-emetics

  As take home medication

  - metoclopramide 10mg three times a day oral when required

- Thromboprophylaxis according to local formulary choice. For example;

  - dalteparin 5000units once a day subcutaneous injection
  - enoxaparin 40mg once a day subcutaneous injection
  - heparin 5000units twice a day subcutaneous injection

- Allopurinol 300mg once a day oral for 7 days on cycle one only
- Consider anti-infective prophylaxis in high risk patients, including:

  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only

- Laxatives as required for thalidomide-induced constipation.
- Bisphosphonates in accordance with local policies
- Mouthwashes according to local or national policy on the treatment of mucositis.
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.
- For all patients taking thalidomide; the patient, prescriber, and supplying pharmacy must comply with an appropriate pregnancy prevention programme.
- Every thalidomide prescription must be accompanied by a complete Prescription Authorisation Form.

Coding

- Procurement – X70.4
- Delivery – X73.1

References
1. Palumbo A, Bringhen S, Liberati AM et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood (2008);112:3107–3114.

REGIMEN SUMMARY

MPT-Melphalan (PO)-Prednisolone-Thalidomide

Cycle 1

Take Home Medicines

1. Warning – Pregnancy Prevention Programme
   Administration Instructions
   Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

2. Melphalan 7mg/m^2 once a day for 4 days oral
   Administration Instructions
   Tablets should be stored in a refrigerator. Oral chemotherapy.

3. Prednisolone 40mg/m^2 once a day in the morning for 4 days oral
   Administration Instructions
   Take in the morning with or after food.

4. Thalidomide 50mg once a day for 28 days oral
   Administration Instructions
   Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg.
   Take at night to avoid daytime drowsiness.

5. Metoclopramide 10mg up to three times a day when required oral
   Administration Instructions
   When required for the relief of nausea. Please supply 28 tablets or nearest original pack size

6. Allopurinol 300mg once a day for 7 days oral
   Administration Instructions
   Take with or after food with plenty of water. Please supply 7 days.

7. Aciclovir 400mg twice a day for 28 days oral
   Administration Instructions
   Please supply 28 days or an original pack if appropriate.

8. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
   Administration Instructions
   Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
   This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

9. Thromboprophylaxis according to local formulary choice. For example;

   Administration Instructions
   The choice of thromboprophylaxis is dependent on local formulary choice and may include;

   - dalteparin 5000units once a day subcutaneous injection
   - enoxaparin 40mg once a day subcutaneous injection
   - heparin 5000units twice a day subcutaneous injection

   Please supply 28 days or nearest original pack size.

10. Gastric Protection

Administration Instructions

The choice of gastric protection is dependent on local formulary choice and may include;

- esomeprazole 20mg once a day oral
- omeprazole 20mg once a day oral
- lansoprazole 15mg once a day oral
- pantoprazole 20mg once a day oral
- rabeprazole 20mg once a day oral
- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral
- ranitidine 150mg twice a day oral

Please dispense 28 days or nearest original pack size.

Cycle 2 onwards

Take Home Medicines

11. Warning – Pregnancy Prevention Programme

Administration Instructions

Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

12. Melphalan 7mg/m^2 once a day for 4 days oral

Administration Instructions

Tablets should be stored in a refrigerator. Oral chemotherapy

13. Prednisolone 40mg/m^2 once a day in the morning for 4 days oral

Administration Instructions

Take in the morning with or after food.

14. Thalidomide 100mg once a day at night for 28 nights oral

Administration Instructions

Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg.
Take at night to avoid daytime drowsiness.

15. Metoclopramide 10mg up to three times a day when required oral

Administration Instructions

Please supply 28 tablets or equivalent original pack size

16. Aciclovir 400mg twice a day for 28 days oral

Administration Instructions

Please supply 28 days or an original pack if appropriate.

17. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral

Administration Instructions

Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

18. Thromboprophylaxis

Administration Instructions

The choice of thromboprophylaxis is dependent on local formulary choice and may include;

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

Please supply 28 days or nearest original pack size.

19. Gastric Protection

Administration Instructions

The choice of gastric protection is dependent on local formulary choice and may include;

- esomeprazole 20mg once a day oral
- omeprazole 20mg once a day oral
- lansoprazole 15mg once a day oral
- pantoprazole 20mg once a day oral
- rabeprazole 20mg once a day oral
- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral
- ranitidine 150mg twice a day oral

Please dispense 28 days or nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	May 2016	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Mathew Jenner Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.