Melphalan, Prednisolone and Thalidomide (MPT)

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

Day	Drug	Dose	Route
1-4	Melphalan	7mg/m^2	PO
1-4	Prednisolone	40mg/m^2 OM*	PO
1-28 (continuously)	Thalidomide	50mg ON **	PO

* 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

H_2 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
Thromoboprophylaxis is required – risk assess patient and consider prophylactic LMWH as per local policy (unless platelet count < 30 x 10^9/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

Investigation	Validity period
FBC and film	7 days
Clotting screen	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Pregnancy test (women of child bearing potential)	72 hours
HIV, hepatitis B and C status	7 days

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

Investigation	Validity period
FBC	72 hours
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Pregnancy test (women of child bearing potential)	72 hours

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

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance	≥ 50mL/min
Bilirubin	< ULN

Dose modifications

- **Haematological toxicity**

Treatment on day 1 should only be initiated if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L.

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

- **Renal impairment**

Melphalan:

CrCl (mL/min)	**Melphalan dose**
> 50	100%
10-50	75%
< 10	50%

- **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:

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

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
- Summary of Product Characteristics: Melphalan (Aspen) accessed 3 August 2016 via www.medicines.org.uk
- MHRA alert accessed 3 August 2016 via https://www.gov.uk/drug-safety-update/letters-sent-to-healthcare-professionals-in-june-2016
- Palumbo A, Bringhen S, Caravita T, et al; Italian Multiple Myeloma Network, GIMEMA. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet. 2006 Mar 11;367(9513):825-31.
- Facon T, Mary JY, Hulin C, et al; Intergroupe Francophone du Myélome. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007 Oct 6;370(9594):1209-18.

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Date: January 2017