Regimen Monograph

A - Regimen Name

MPT Regimen

Melphalan-Prednisone-Thalidomide

Disease Site Hematologic - Multiple Myeloma

Intent Palliative

Regimen Category **Evidence-Informed :**

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses For previously untreated multiple myeloma patients who are unsuitable for stem cell transplantation.

Supplementary Public Funding

melphalan
ODB - General Benefit (melphalan - oral tablets) (ODB Formulary)

prednisone
ODB - General Benefit (prednisone) (ODB Formulary)

thalidomide
Exceptional Access Program (thalidomide - Multiple myeloma in patients ≥65 years of age in combination with melphalan and prednisone, with specific criteria) (EAP Website)

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B - Drug Regimen

Standard schedule*:

melphalan	4 mg /m²	PO	Days 1 to 7
(Outpatient prescription in multiples of 2mg tablets)			
prednisone	40 mg	PO	Days 1 to 7
(Outpatient prescription in multiples of 5mg tablets)			
thalidomide	100 mg	PO	Days 1 to 28
(Outpatient prescription in 50 or 100 mg capsules)			

Q 28 Days

*Refer to section E (dose modifications) and consider the table below

Alternative schedule:**

melphalan 9 mg/m^2 PO Days 1 to 4

prednisone 100 mg PO Days 1 to 4

thalidomide 200 mg PO Daily

Q 42 Days

****Starting dose based on age and blood counts:**

Age (years)	Blood counts x 10^9/L	Melphalan# (mg/kg daily)	Prednisone (mg/kg daily)	Thalidomide (mg daily)
≤ 75	ANC ≥ 1.5 AND platelets ≥ 100	0.25	2	200
>75	ANC ≥ 1.5 AND platelets ≥ 100	0.20	2	100

≤ 75	ANC < 1.5 but ≥ 1 OR Platelets < 100, but ≥ 50	0.125	2	200
>75	ANC < 1.5, but ≥ 1 OR Platelets < 100, but ≥ 50	0.10	2	100

#max daily dose 24 mg (patients ≤ 75 years); 20 mg (patients > 75 years)

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C - Cycle Frequency

Standard schedule: REPEAT EVERY 4 WEEKS for up to 6 cycles

Alternative schedule: REPEAT EVERY 6 WEEKS for up to 12 cycles

Unless disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

- Thalidomide may only be prescribed and dispensed by physicians and pharmacists registered with RevAid®. Patients must also be registered and meet all conditions of the RevAid® program. Call 1-888-RevAid1 or log onto www.RevAid.ca.
- Prophylactic anticoagulants should be used, especially in patients with other risk factors and for at least the first five months of treatment.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Thalidomide dose level (Q 42 day schedule)	Age ≤ 75 years	Age > 75 years
0	200 mg daily	100 mg daily
-1	100 mg daily	50 mg daily
-2	50 mg daily	50 mg every other day
-3	50 mg every other day	Discontinue

Hematologic conditions to be met before starting a new cycle of MPT:

Baseline counts (x 10^9/L)	Conditions met: Start a new cycle if non-heme toxicity ≤ grade 2 and:	Conditions NOT met: HOLD x 1 week*, then start new cycle if:
ANC ≥ 1.5 and platelets ≥ 100	ANC ≥ 1.5 and platelets ≥ 100	ANC < 1.5, but ≥ 1 and platelets < 100, but ≥ 50; and ↓ melphalan 50%**
ANC ≥ 1.5 and platelets < 100, but ≥ 50	ANC ≥ 1.5 and platelets ≥ 50	ANC < 1.5, but ≥ 1 and platelets ≥ 50; and ↓ melphalan 50%**
ANC < 1.5, but ≥ 1 and platelets ≥ 100	ANC ≥ 1 and platelets ≥ 100	ANC ≥ 1 and platelets < 100, but ≥ 50; and ↓ melphalan 50%**

ANC < 1.5, but ≥ 100 and platelets < 100, but ≥ 50	ANC ≥ 1 and platelets ≥ 50	ANC ≥ 1, but < 1.5 and platelets ≥ 50; and ↓ melphalan 50%**

*If ANC < 1 and platelets < 50, omit melphalan for that cycle

**No dosage adjustment suggested for thalidomide

Non-hematologic toxicity:

Toxicity	Thalidomide Dose and Action	Melphalan/Prednisone Dose and Action
Grade 3 or 4 thromboembolism	Hold, ensure adequately anticoagulated. Maintain dose level unless occurred despite adequate anticoagulation; if so, discontinue	No change
Grade 3 neurotoxicity	Hold until resolves to ≤ grade 1, then decrease by 1 dose level	No change
Grade 4 neurotoxicity	Discontinue	Discontinue
Grade 3 rash or mild hypersensitivity	Hold until rash resolves to ≤ grade 1, then decrease by 1 dose level	No change
Grade 4 rash or severe hypersensitivity	Discontinue	Discontinue
Grade 3 or 4 constipation	Initiate bowel regimen and hold until resolves to ≤ grade 2, then decrease by 1 dose level	No change
Over sedation	Consider short drug holiday or ↓ dose; may restart at the same or lower dose when recovered	No change
Severe syncope/bradycardia	Consider ↓ dose or discontinue	No change
Other grade 3 toxicity	Hold until resolves to ≤ grade 2 then decrease by 1 dose level	No change

Other grade 4 toxicity	Discontinue

Hepatic Impairment

Melphalan: No adjustment required.

Thalidomide: Not specifically studied in patients with hepatic impairment.

Renal Impairment

Melphalan: Increased incidence of severe myelosuppression has been observed in patients with BUN ≥ 10.7 mmol/L. Dose reduction should be considered in patients with renal insufficiency receiving melphalan.

Creatinine clearance (mL/min)	**Melphalan (% usual dose)**
10-50	50% and monitor
<10	50% and monitor

Thalidomide:
Not specifically studied in patients with renal impairment. Monitor patients with severe renal impairment as metabolites are eliminated via urine. Some data suggested that no dose modification is needed in renal impairment (including patients on dialysis); however monitor closely as there have been reports of fatal hyperkalemia in renally impaired patients.

Dosage in the Elderly

For patients > 75 years old, the recommended starting dose is 100 mg/day.

The frequency of serious adverse effects, such as atrial fibrillation, back pain and fall, including fatal reactions was higher in patients > 75 years old compared to younger patients.

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F - Adverse Effects

Refer to melphalan, prednisone, thalidomide drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
	• Myelosuppression +/- infection, bleeding (may be severe) • Nausea, vomiting	• Venous thromboembolism • Constipation • Somnolence • Peripheral neuropathy (may be severe) • Dizziness • Fatigue • Confusion	• Arterial thromboembolism • Arrhythmia • Cardiotoxicity • GI obstruction / perforation • Hepatotoxicity • Pancreatitis • Hypersensitivity • Secondary malignancy • Seizure • Renal failure • Pneumonitis • Hemolysis • Vasculitis • Tumour lysis syndrome • Hypotension • Rash

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G - Interactions

Refer to melphalan, prednisone, thalidomide drug monograph(s) for additional details

- Use with caution when combined with other neurotoxins and sedatives given increased risk of neurotoxicity and sedation
- Use beta-blockers with caution given increased risk of bradycardia
- Use with caution and consider thromboembolism prophylaxis when used with hormonal therapy, contraceptives, erythropoietic agents and corticosteroids
- H2 receptor antagonists may reduce absorption of melphalan; avoid or monitor if used together
- Use with caution and monitor renal function when given with cyclosporine or cisplatin
- Avoid concurrent treatment with nalidixic acid
- Use with caution with BCNU and interferon

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H - Drug Administration and Special Precautions

Refer to melphalan, prednisone, thalidomide drug monograph(s) for additional details

Administration

Melphalan:

- Oral self-administration; drug available by outpatient prescription.
- Keep refrigerated.
- Take on an empty stomach.

Thalidomide:

- Oral self-administration; taken usually once daily preferably with a glass of water, with or without food at about the same time each day.
- Swallow capsules whole; they should not be broken, chewed, or opened.
- Thalidomide should be administered at bedtime to minimize adverse effects such as dizziness and somnolence.
- Avoid use of alcohol since this may potentiate sedation.
- Do not extensively handle the capsules. Females who may become or plan to become pregnant can handle thalidomide if they are using latex gloves.
- Remove capsule from the original packaging only at administration time. Do not put the capsule on the counter or dish/container before taking it; give the capsule directly from the packaging and place into the mouth.
- If a dose is missed, take it if it is within 12 hours from the missed dose, otherwise skip this and give the next dose as scheduled. Do not double the dose to make up for the forgotten one.

Warnings/precautions (melphalan)

- Melphalan is contraindicated in patients whose disease has demonstrated a prior resistance to this agent, or have demonstrated hypersensitivity to melphalan or to any of its excipients. There is cross-sensitivity between melphalan and chlorambucil, which is manifested as a rash.

- Avoid the use of live vaccines.
- Melphalan should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior radiation or chemotherapy, or whose marrow function is recovering from previous chemotherapy. Melphalan should not be administered concurrently with radiotherapy.

Warnings/precautions (thalidomide)

- Thalidomide is contraindicated in patients with peripheral neuropathy, or with known hypersensitivity to thalidomide, lenalidomide, or pomalidomide, women who are pregnant or breastfeeding and patients unable to follow or comply with the required contraceptive measures of the RevAid program (see pregnancy lactation section below).
- Patients should be warned of the risk of drowsiness, dizziness or orthostatic hypotension. Caution in patients using sedatives or alcohol.
- May increase viral load if used in patients with HIV.
- Use with caution in patients with risk factors for VTE or ATE, or using thrombogenic agents. Oral contraceptives should be avoided due to the increased risk of VTE.
- Use with caution in combination with corticosteroids in myeloma due to the risk of thromboembolism - consider prophylactic anticoagulation.
- Use with caution in patients with risk factors for peripheral neuropathy, taking neurotoxic drugs, or taking drugs that may cause severe skin reactions.

Pregnancy and Lactation

- Thalidomide is contraindicated in pregnant women and in females of childbearing potential and in males who do not comply with the contraception conditions of the RevAid® program. Refer to the thalidomide drug monograph for details.
- Breastfeeding is contraindicated.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- RevAid requirements regarding pregnancy tests for women of childbearing potential; before starting and as indicated per RevAid
- Neurological exams; baseline and periodic (ie: monthly for the first 3 months, and periodically thereafter); consider using electrophysiologic testing at baseline and every 6 months.
- Liver and renal function tests; baseline and periodic, especially in patients with pre-existing liver disorders or concurrent use of hepatotoxic or nephrotoxic drugs
- ECG as clinically indicated

- Clinical toxicity assessment for bleeding, infection, pulmonary, GI (including constipation), rash, CNS effects (including seizures), arterial and venous thromboembolism, syncope/bradycardia, at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Uric acid levels; baseline and periodic

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 2009;27(22):3664-70.

Melphalan and thalidomide drug monographs, Cancer Care Ontario.

Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367(9513):825-31.

Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010 Sep 2;116(9):1405-12.

PEBC Advice Documents or Guidelines

- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

June 2019 Updated emetic risk category; added PEBC guideline link

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

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Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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