

Supplementary materials to: de Mel S, Tso ACY, Soekojo CY, et al. Singapore Myeloma Study Group consensus guidelines for the management of patients with newly diagnosed multiple myeloma. Ann Acad Med Singap 2025;54:561-84.
DOI: <https://doi.org/10.47102/annals-acadmedsg.202532>.

Appendix S1.

Drug Toxicity and Dose Adjustments for Induction and maintenance therapy in multiple myeloma

This section provides guidance on the dosages and administration of drugs commonly used in induction therapy for MM. Recommendations for dose adjustments in renal and hepatic impairment as well as information on common toxicities are also provided. The source of this information is the manufacturers' package insert as well as recent publications in the field. We recommend that an oncology trained pharmacist is assigned for dispensing these agents.

1. Bortezomib

Bortezomib is indicated in the induction regimens for both transplant eligible and ineligible patients.

We recommend the following prior to initiating a new cycle of therapy:

- Platelet count should be $> 70 \times 10^9/L$
- Absolute Neutrophil Count (ANC) should be $> 1.0 \times 10^9/L$
- Non-hematological toxicities should have resolved to Grade 1 or baseline

See Table 9.

2. Thalidomide

Thalidomide is used in induction regimens for transplant eligible MM patients(112). Peripheral neuropathy, constipation, sedation and hypothyroidism are the significant toxicities.

See Table 10.

3. **Lenalidomide**

Lenalidomide based regimens are used in both the induction and maintenance settings for both transplant eligible and ineligible patients. The recommended starting dose of lenalidomide is 25mg once daily on days 1-21 of a 28-day cycle. The recommended dose of dexamethasone is 20-40mg orally once daily on day 1,8,15 and 22(182). In the maintenance setting, the recommended dose is 10mg daily for 21 days of a 28 day cycle(183).

Prior to initiating a new cycle of therapy:

- Platelet count should be $>75 \times 10^9/L$
- ANC should be $> 1.0 \times 10^9/L$
- OR dependent on bone marrow infiltration by plasma cells, platelet count should be $> 30 \times 10^9/L$

See Table 11.

4. **Daratumumab**

Daratumumab is used in induction regimens for both transplant eligible and ineligible patients. Its dosing schedule differs by regimen but consists primarily of weekly dosing at initiation followed by transitioning to bi-weekly and then monthly dosing.

It requires premedication with a corticosteroid, paracetamol and an IV or oral antihistamine at least during the first two cycles. Daratumumab can also be administered as a subcutaneous (Sc) injection and the Sc route has been shown to have a lower incidence of infusion-related reactions(184).

See Table 12.

Tables

Bortezomib

<u>Bortezomib Dosage Adjustment Based on Organ Dysfunction</u>				
Renal Impairment	- Dose adjustments not necessary in renal impairment - Administer bortezomib after dialysis. Dialysis may reduce drug concentrations			
Hepatic Impairment	Liver Dysfunction	Bilirubin Level	AST Levels	Modification of starting dose
	Mild	$\leq 1.0 \times \text{ULN}$	$> \text{ULN}$	None
		$> 1.0 \times - 1.5 \times \text{ULN}$	Any	
	Moderate	$> 1.5 \times - 3 \times \text{ULN}$	Any	Reduce to 0.7mg/m^2 in cycle 1. Consider dose escalation to 1.0mg/m^2 or further dose reduction to 0.5mg/m^2 in
	Severe	$> 3 \times \text{ULN}$	Any	

				subsequent cycles based on tolerability

Bortezomib Dosage Adjustment Based on Drug Induced Toxicity

Hematological Toxicity	• If platelet counts $<30 \times 10^9/\text{L}$ or ANC $<0.75 \times 10^9/\text{L}$ on a dosing day (other than Day 1), bortezomib therapy should be withheld • If several doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration) the dose of bortezomib should be reduced by one dose level (from $1.3\text{mg}/\text{m}^2$ à $1\text{mg}/\text{m}^2$, or from $1\text{mg}/\text{m}^2$ à $0.7\text{mg}/\text{m}^2$)								
Neuropathy (Neuropathic pain and/or peripheral sensory or motor neuropathy)	<table><tr><th>Severity of Neuropathy</th><th>Modification of dose & regime</th></tr><tr><td>Grade 1</td><td>No modification</td></tr><tr><td>Grade 2</td><td>Change to weekly dosing. If administered IV, change to SC. If already on weekly SC, reduce dose by one dose level (from $1.3\text{mg}/\text{m}^2$ à $1\text{mg}/\text{m}^2$, or from $1\text{mg}/\text{m}^2$ à $0.7\text{mg}/\text{m}^2$)</td></tr><tr><td>Grade 3</td><td>Hold dose until resolution of toxicity, then restart at one dose level down or $0.7\text{mg}/\text{m}^2$</td></tr></table>	Severity of Neuropathy	Modification of dose & regime	Grade 1	No modification	Grade 2	Change to weekly dosing. If administered IV, change to SC. If already on weekly SC, reduce dose by one dose level (from $1.3\text{mg}/\text{m}^2$ à $1\text{mg}/\text{m}^2$, or from $1\text{mg}/\text{m}^2$ à $0.7\text{mg}/\text{m}^2$)	Grade 3	Hold dose until resolution of toxicity, then restart at one dose level down or $0.7\text{mg}/\text{m}^2$
Severity of Neuropathy	Modification of dose & regime								
Grade 1	No modification								
Grade 2	Change to weekly dosing. If administered IV, change to SC. If already on weekly SC, reduce dose by one dose level (from $1.3\text{mg}/\text{m}^2$ à $1\text{mg}/\text{m}^2$, or from $1\text{mg}/\text{m}^2$ à $0.7\text{mg}/\text{m}^2$)								
Grade 3	Hold dose until resolution of toxicity, then restart at one dose level down or $0.7\text{mg}/\text{m}^2$								

	Grade 4	Discontinue treatment	
--	---------	-----------------------	--

Table 9. Dose adjustment and toxicity of bortezomib. (*VELCADE[®] (bortezomib) for Injection Package Insert*)

Thalidomide

<u>Thalidomide Dosage Adjustment Based on Organ Dysfunction</u>	
Renal Impairment	No dose adjustment required No supplemental dose required if on haemodialysis
Hepatic Impairment	No recommendations for dosage adjustments in manufacturer's labeling

<u>Management of Drug Induced Toxicities</u>		
Peripheral Neuropathy	- Monitor for PN especially in first few months of therapy - Thalidomide-induced neuropathy can be irreversible; thus, patient should be informed to stop treatment if significant numbness or paraesthesia occurs	
	Severity of Neuropathy	Modification of dose
	Grade 1	No modification

	Grade 2	Reduce dose by 50% OR Hold therapy till resolution of toxicity then restart at 50% of dose
	Grade 3	Stop till resolution of toxicity, restart at low dose when PN grade 1
	Grade 4	Discontinue treatment
Sedation	- Decreases with continued administration of constant dose 'Hangover effect' can be minimized by administering in the evening, approximately 3 – 4 hours before bedtime	
Constipation	- Significant at higher doses - Can be overcome by extra dietary fibre and laxatives	
Hypothyroidism	Monitor thyroid function and manage hypothyroidism accordingly	

Table 10. Dose adjustment and toxicity of thalidomide.

Lenalidomide

Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT)

- Lenalidomide should be initiated only when ANC $>1.0 \times 10^9/L$, and/or platelet counts $> 75 \times 10^9/L$
- Recommended starting dose is 10mg OD continuously (on days 1-21 of repeated 28-day cycles) until disease progression or intolerance.

	Starting dose (10mg)	If dose increased (15mg)*
Dose level -1	5mg	10mg
Dose level -2	5mg (days 1-21 every 28 days)	5mg
Dose level -3	Not applicable	5mg (days 1-21 every 28 days)
	Do not dose below 5mg (days 1-21 every 28 days)	

* After 3 cycles of lenalidomide maintenance, dose can be increased to 15mg OD if tolerated

<u>Lenalidomide Dosage Adjustment Based on Drug Induced Toxicity</u>		
Thrombocytopenia	When Platelets	Recommended Course
	First falls to $< 30 \times 10^9/L$	Interrupt treatment
	Return to $\geq 30 \times 10^9/L$	Resume at Dose Level -1
	For each subsequent drop $< 30 \times 10^9/L$ Return to $\geq 30 \times 10^9/L$	Interrupt treatment Resume at next dose level lower
Neutropenia	When Neutrophils	Recommended Course*
	Falls to $< 0.5 \times 10^9/L$	Interrupt treatment
	Return to $\geq 1.0 \times 10^9/L$	Resume at Dose Level -1
	For each subsequent drop $< 0.5 \times 10^9/L$ Return to $\geq 0.5 \times 10^9/L$	Interrupt treatment Resume at next dose level lower

	*May consider adding GCSF and maintain dose level at physician's discretion
--	---

Lenalidomide in combination with dexamethasone until disease progression for transplant-ineligible patients

- Lenalidomide should be initiated only when ANC $>1.0 \times 10^9/L$, and/or platelet counts $> 50 \times 10^9/L$
- Recommended starting dose is 25mg OD (on days 1-21 of repeated 28-day cycles) until disease progression or intolerance.
- Dexamethasone is given at 40mg orally OD on days 1, 8, 15 and 22 every 28 days
- Dose reductions for each drug can be managed independently

	Lenalidomide	Dexamethasone [^]
Starting Dose	25mg	40mg
Dose Level -1	20mg	20mg
Dose Level -2	15mg	12mg
Dose Level -3	10mg	8mg
Dose Level -4	5mg	4mg
Dose Level -5	5mg every other day	NA

[^]Starting dose of dexamethasone for patients over than 75 years of age is 20mg OD

Lenalidomide Dosage Adjustment Based on Drug Induced Toxicity

Thrombocytopenia	When Platelets	Recommended Course
	Falls to $< 25 \times 10^9/L$ Return to $\geq 50 \times 10^9/L$	Stop lenalidomide for remainder of cycle Resume at Dose Level -1
Neutropenia	When Neutrophils	Recommended Course*
	First falls $< 0.5 \times 10^9/L$ Return to $\geq 1.0 \times 10^9/L$, when neutropenia is only observed toxicity	Interrupt treatment Resume at Starting Dose
	Returns to $\geq 0.5 \times 10^9/L$, when dose dependent hematological toxicities other than neutropenia are observed	Resume at Dose Level -1
	For each subsequent drop $< 0.5 \times 10^9/L$ Return to $\geq 0.5 \times 10^9/L$	Interrupt treatment Resume at next dose level lower
	*May consider adding GCSF and maintain dose level at physician's discretion	

For haematological toxicity, the dose of lenalidomide may be re-introduced at the next higher dose level (up to the starting dose) upon improvement of bone marrow function. (ANC $\geq 1.5 \times 10^9/L$ and platelet $\geq 100 \times 10^9/L$ at beginning of new cycle)

For other Grade 3 or 4 toxicities related to lenalidomide, treatment should be stopped and only restarted at the next lower dose level when toxicity has resolved to $\leq$ Grade 2 based on physician's discretion.

Lenalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, anaphylactic reaction, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected and should not be resumed following discontinuation from these reactions.

Lenalidomide Dosage Adjustment Based on Organ Dysfunction

Renal Impairment	- Mild renal impairment: No dose adjustment required - Recommended starting dose in moderate or severe impairment or end stage renal failure (ESRF) are as follows:		
	Renal Impairment	CrCl (mL/min)	Dose Adjustment (Day 1-21 of a 28-day cycle)
	Moderate	30 – 50	10mg once daily*
	Severe	< 30, not requiring dialysis	15mg every other day
	ESRF	< 30, requiring dialysis	5mg once daily Dose should be administered post dialysis
	* Dose may be escalated to 15mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment		

	After initiation of lenalidomide, subsequent dose modifications in renally impaired patients should be based on individual patient treatment tolerance.
Hepatic Impairment	No recommendations for dosage adjustments in manufacturer's labeling

REVLIMID[®] (Lenalidomide) Package Insert

Table 11. Dose adjustment and toxicity of lenalidomide.

Daratumumab

The recommended dose of IV daratumumab is 16mg/kg per dose. Subcutaneous daratumumab can be given as an alternative at 1800mg per dose (preferred option).

The tables below describe the dosing schedule of daratumumab, given either as an intravenous infusion or as an injection administered subcutaneously.

When used as a monotherapy or given in combination with 4-week cycle dosing regimens:

Weeks	Schedule
Weeks 1 – 8	Weekly (total of 8 doses)
Weeks 9 – 24	Every 2 weeks (total of 8 doses)
Weeks 25 onwards till disease progression	Every 4 weeks

When used in combination with 3-week cycle regimens (e.g. bortezomib):

Weeks	Schedule
-------	----------

Weeks 1 – 9	Weekly (total of 9 doses)
Weeks 10 – 24	Every 3 weeks (total of 5 doses)
Weeks 25 onwards till disease progression	Every 4 weeks

<u>Daratumumab (IV/SC) Dosage Adjustment Based on Organ Dysfunction</u>	
Renal Impairment	No dosage adjustments are necessary
Hepatic Impairment	No dosage adjustments are necessary

<u>Management of Drug Induced Toxicities</u>	
Haematological toxicities	- No dose adjustments are recommended. Dose delay may be required to allow recovery of blood counts - May consider supportive care with transfusions or growth factors

DARZALEX[®] (Daratumumab) Package Insert

Table 12. Dosing schedules, dose adjustment and toxicity of daratumumab.