POCKET GUIDELINE

Hematology

Multiple Myeloma: Guidelines on treatment and management

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Index

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Hematology

Introduction

The landscape of treatment in multiple myeloma is rapidly changing.
Based on an extensive review of the recent literature, we propose an update of our recommendations on myeloma care, to be used by Belgian/European haematologists as a reference for daily practice. Levels of evidence and grades of recommendations are based on previously published methods. We recommend participation in clinical trials to gain knowledge in the fast evolving field of MM treatment.

DIAGNOSIS AND MONITORING OF MULTIPLE MYELOMA PATIENTS

Definition of active multiple myeloma

Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features and myeloma-defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
- Renal insufficiency: creatinine clearance < 40 mL per minute or serum creatinine > 177 μmol/L (> 2 mg/dL)
- Anaemia: haemoglobin value of > 2 g/dL below the lowest limit of normal, or a haemoglobin value < 10 g/dL
- Bone lesions: one or more osteolytic lesion on skeletal radiography, CT, or PET/CT. If bone marrow has < 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

Any one or more of the following biomarkers of malignancy (myeloma-defining events):

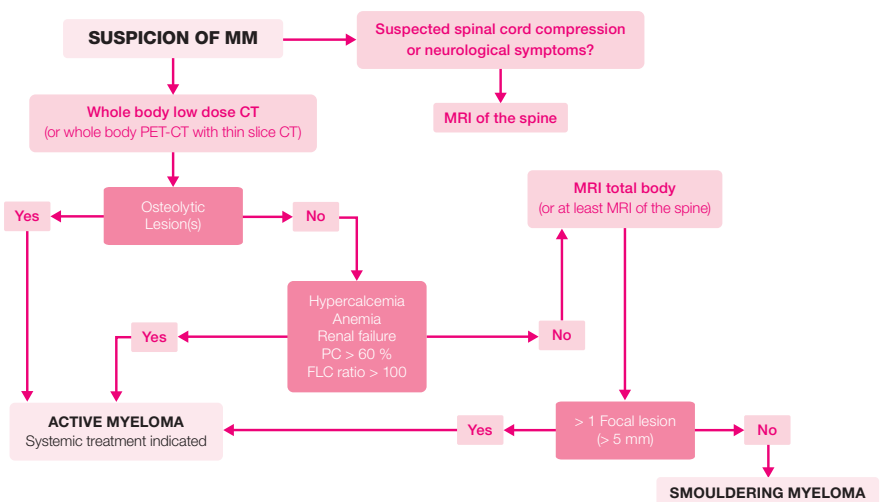
- ≥ 60% clonal plasma cells on bone marrow examination
- Serum involved/uninvolved free light chain ratio of ≥ 100, provided the absolute level of the involved light chain is at least 100 mg/L
- ≥ 1 focal lesion on MRI that is ≥ 5 mm

Initial work-up in case of clinical suspicion of MM

Biological tests	• Serum blood count, urea, creatinine, calcium, phosphorus • Proteins, electrophoresis of serum/urine, quantification of immunoglobulins • Immunofixation on serum/urine, characterization of heavy/light chains • M-protein quantification in serum/urine (24h urine concentrate) • Measurement of FLC in oligo- or non-secretory and light chain MM • Albumin, beta-2-microglobulin • CRP, LDH
Bone marrow aspirate	• Bone marrow aspirate and trephine biopsy, flow cytometry • iFISH analysis on selected or identified plasma cells (t(4;14), t(14;16), del 17p, chromosome 1 abnormalities)
Radiology (see *Figure 1*)	• WBLD-CT (standard) • Standard skeletal survey if WBLDCT not available • X-rays of symptomatic areas • MRI plus x-rays of the skull, humeri, femora and ribs or WBMRI • PET-CT

Abbreviations: FLC, free light chain; iFISH, interphasic fluorescence in situ hybridization; MM, multiple myeloma; MRI, magnetic resonance imaging; PET-CT, positron emitting tomography-CT scan; ULP, upper limit of normal; WBLDCT, whole body low dose CT scan; WBMRI, whole body magnetic resonance imaging

Figure 1. Imaging algorithm in suspected multiple myeloma



Practical guide to interpretation of cytogenetic abnormalities

Cytogenetic abnormality detected by FISH	Clinical setting in which abnormality is detected	
	SMM	MM
Trisomies	Intermediate risk of progression, median TTP of 3 years	Good prognosis, standard-risk MM, median OS 7–10 years. Most have myeloma bone disease at diagnosis. Excellent response to lenalidomide-based therapy
t(11;14) (q13;q32)	Standard risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(6;14) (p21;q32)		
t(4;14) (p16;q32)	High risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years. Needs bortezomib-based initial therapy and early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance.
t(14;16) (q32;q23)	Standard risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years. Associated with high levels of FLC and 25% present with acute renal failure as initial MDE.
t(14;20) (q32;q11)	Standard risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years
Gain(1q21)	High risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years
Del(17p)	High risk of progression, median TTP of 2 years	High-risk MM, median OS 3 years
Trisomies plus any one of the IgH translocations	Standard risk of progression, median TTP of 5 years	May ameliorate adverse prognosis conferred by high-risk IgH translocations and del 17p
Isolated monosomy 13 or isolated monosomy 14		Effect on prognosis is not clear
Normal	Low risk of progression, median TTP of 7–10 years	Good prognosis, probably reflecting low tumour burden, median OS > 7–10 years

Abbreviations: ASCT, autologous stem cell transplantation; FISH, fluorescent in situ *hybridization; FLC, free light chain; IgH, immunoglobulin heavy chain; MDE, myeloma-defining event; MM, multiple myeloma; OS, overall survival; SMM, smoldering multiple myeloma, TTP, time to progression.*

Staging by ISS and R-ISS

International Staging System (ISS)

Stage	Criteria for ISS	Survival (months)
I	Serum beta-2-microglobulin < 3.5 mg/l and serum albumin ≥ 3.5 g/l	62
II	Serum beta-2-microglobulin < 3.5 mg/l and serum albumin < 3.5 g/l or beta-2-microglobulin 3.5-5.5 mg/l, irrespective of serum albumin	44
III	Serum beta-2-microglobulin > 5.5 mg/l	29

Revised International Staging System (R-ISS)

R-ISS I
- Including ISS stage I (serum beta2 microglobulin < 3.5 mg/L and serum albumin level ≥ 3.5 g/dL)
- No high risk CA [del(17p) and/or t(4;14) and/or t(14;16)]
- Normal LDH level (less than the upper limit of normal range)

R-ISS III
- Including ISS stage III (serum beta2 microglobulin level > 5.5 mg/L)
- High-risk CA or high LDH level

R-ISS II
- Including all other possible combinations

	5-year OS*	Median OS	5-year PFS*	Median PFS
R-ISS I	82%	Not reached	55%	66 months
R-ISS II	62%	83 months	36%	42 months
R-ISS III	40%	43 months	24%	29 months

**At a median follow-up of 46 months*

IMWG Response criteria	
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow. In patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed
sCR	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed
Immuno-phenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analysed by multiparametric flow cytometry (with > four colours)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5})
PR	≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h. • If serum and urine M protein are not measurable, ≥ 50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria. • If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥ 30%. • In addition, if present at baseline, ≥ 50% reduction in size of soft tissue plasmacytomas is required. • Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed.
VGPR	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component < 100 mg/24 h. In patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed
MR for relapsed refractory myeloma only	≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89%. • In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required. • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
SD	Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed
PD	Increase of 25% from lowest response value in any of following: • Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or; • Urine M component (absolute increase must be ≥ 200 mg/24 h) and/or; • Only in patients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); • Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%). Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder Two consecutive assessments before new therapy are needed.

Types of response

Types of response	Response criteria Based on flow cytometry or NGF (such as Euroflow operation procedure for MRD detection in MM or validated equivalent method) or NGS (LymphoSIGHT or other validated equivalent method)
MRD-negativity	Absence of aberrant clonal PC in BM, ruled out by an assay with minimum sensitivity of 1 in 10^{-5} nucleated cells of higher
Imaging and MRD-negativity	MRD-negativity as defined by flow or NGS, plus disappearance of every area of increased tracer uptake found at baseline or preceding PET/CT, or decrease to < mediastinal blood pool SUV, or decrease to less than that of surrounding normal tissue
Sustained MRD-negativity	MRD negativity in BM (as defined by flow or NGS or both) and by imaging (as defined), confirmed minimum 1 year apart; subsequent evaluations can be used to further specify the duration of negativity

Abbreviations: BM, bone marrow; MM, multiple myeloma; MRD, minimal residual disease; NGF, next-generation flow cytometry; NGS, next-generation sequencing; PC, plasma cells; PET-CT, positron-emitting tomography-computed tomography

FIRST-LINE TREATMENT OF TRANSPLANT-ELIGIBLE PATIENTS

Indication of therapy

- Therapy is indicated in all patients with a diagnosis of MM as defined by the IMWG 2014 criteria.
- Treatment choice depends of patient eligibility for ASCT based on age, performance status and comorbidities.
- In asymptomatic MM, treatment can only be recommended in the context of a clinical trial.
- Patients should be monitored for symptoms and followed every 1-3 months.

Goal of therapy

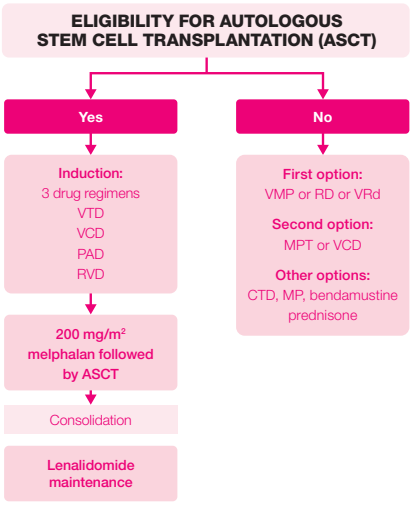
- Achieving complete response, since it is associated with improved progression-free and overall survival.
- Be aware that the true value of complete response relies on the minimal residual status.

Check-list before starting therapy for symptomatic MM

Patient	Criteria of transplant eligibility	comorbidities, medical history echocardiography pulmonary functional assessment
	In the elderly	geriatric assessment
Disease	Risk assessment	ISS (see page 9) R-ISS (see page 10)
	Pain	consider adequate analgesia
Therapy	Prevention of ONJ	dental check-up before bisphosphonates education of patient and dentist
	Bone disease	calcium and vitamin D supplementation
	Prevention of infection	acyclovir (herpes, zoster) vaccination (flu, pneumococcus)
	Assessment of thromboembolic risk	aspirin or LMWH (see page 24)
	Assessment of polyneuropathy	avoid neurotoxic drugs assess symptoms before each administration of MM drugs related to the occurrence of polyneuropathy

Abbreviations: ISS, international staging system; LMWH, low molecular weight heparin; OJN, osteonecrosis of the jaw; R-ISS, revised international staging system

Figure 2. Front-line therapy in MM patients



Induction followed by HDM with ASCT remains the standard of care in patients in good clinical condition.

Abbreviations:
ASCT, autologous stem cell transplantation;
CTD, cyclophosphamide-thalidomide-dexamethasone;
MP, melphalan-prednisone;
MPT, melphalan-thalidomide-dexamethasone;
PAD, bortezomib-adriamycin-dexamethasone;
Rd, lenalidomide-dexamethasone;
RVD, bortezomib-lenalidomide-dexamethasone
VCD, bortezomib-cyclophosphamide-dexamethasone;
VMP, bortezomib-melphalan-prednisone;
VTD, bortezomib-thalidomide-dexamethasone;

Induction therapy in transplant eligible MM patients

- Induction consists of 4-6 cycles of therapy in order to achieve rapid disease control, improve symptoms and allow for subsequent stem cell collection.
- Three-drug combinations including at least bortezomib and dexamethasone are considered the standard of care before ASCT.
- VTD is superior to VCD in terms of response rate, with lower incidence of haematological toxicities but at the cost of more peripheral polyneuropathy.
- vtD is an alternative proposed to reduce the incidence of polyneuropathy, at the expense of lower response rates.
- VRD induces higher CR rates before (77% > VGPR) and after ASCT (88% ≥ VGPR), but is not reimbursed in Belgium at the moment.
- Switching therapy is recommended in case of progressive disease after 2 cycles or less than partial response after 4 cycles.

Front-line therapy in transplant-eligible MM-patients

Front-line regimens	Schedule	≥PR	≥VGPR	Median PFS	3y-OS	References
VTD	Bortezomib 1.3 mg/m² sq days 1,8,15,22 Thalidomide 100 mg orally days 1-21 Dexamethasone 40 mg orally days 1,8,15,22 28-day cycles	93%	63%	NR	90%	Cavo, Lancet 2010
vTD	Bortezomib 1 mg/m² orally sq days 1,8,15,22 Thalidomide 100 mg J1-28 Dexamethasone 40 mg orally days 1-4,9-11 on cycles 1-2, days 1-4 on cycles 3-4 21-day cycles	89%	51%	26m	NA	Moreau, Blood 2011
VCD	Bortezomib 1.3 mg/m² IV or sq days 1,8,15,22 Cyclophosphamide 300 mg/m² orally days 1,8,15 Dexamethasone 40 mg orally days 1,8,15,22 28-day cycles	88%	71%	NA	NA	Reeder, Blood 2010
PAD	Bortezomib 1.3 mg/m² sq days 1,8,15,22 Adriamycin, 9 mg/m² days 1-4 Dexamethasone 40 mg orally days 1-4,9-12,17-20 28-day cycles	90%	42%	35m	61%	Sonneveld, JCO 2012
VRD	Bortezomib 1.3 mg/m² sq days 1,4,8,11 Lenalidomide 25 mg orally days 1-14 Dexamethasone 20 mg orally days 1,2,4,5,8,9,11,12 28 days cycles		CR, 59%	50m	81% at 4y	Attal, NEJM 2017

Abbreviations: A, doxorubicin; C, cyclophosphamide; D, dexamethasone; m, months; M, melphalan; P, prednisone; NA, not available; NR, not reached; OS, overall survival; PAD, bortezomib, doxorubicin, dexamethasone; PFS, progression-free survival; PR, partial response; R, lenalidomide; t, low-dose thalidomide; T, thalidomide; v, low dose bortezomib; V, bortezomib; VGPR, very good partial response; y, years.

Management of polyneuropathy induced by bortezomib or thalidomide

Grade of neuropathy	Bortezomib	Thalidomide
grade 1 (paraesthesia, weakness and/or loss of reflexes without pain of loss of function)	no action	no action
grade 1 with pain or grade 2 (interfering with function but not with daily activities)	reduce the dose to 1 mg/m^2	reduce the dose to 50% or suspend the drug until disappearance of symptoms, then re-initiate at 50% dose
grade 2 with pain or grade 3 (interfering with daily activities)	suspend the drug until disappearance of symptoms then re-initiate at 0.7 mg/m^2 and administer once weekly	suspend the drug until disappearance of symptoms, then re-initiate at low dose if PN grade 1
grade 4 (permanent sensory loss interfering with function)	discontinue the drug	discontinue the drug

Stem cell collection

- Collection of peripheral blood progenitor cells for usually more than one ASCT (at least 2.5 x10^6 CD34+ cells/kg per graft).
- Lenalidomide can impair stem cell collection, when used, apheresis should be performed after 3-4 cycles, eventually after cyclophosphamide or plerixafor.

Conditioning and transplantation

- Melphalan 200 mg/m^2 is the standard conditioning regimen prior to ASCT.
- Dose reduction (100 to 140 mg/m^2) is recommended in case of renal impairment (estimated GFR < 60ml/min).
- There is no additional benefit to add bortezomib in the conditioning

Consolidation

- Short term therapy given for a limited period of time, in order to improve disease control by deepening response.
- VTD consolidation increases the CR rate by 30%.
- Bortezomib-based consolidation should be considered in patients not achieving at least VGPR or nCR/CR after ASCT.
- Second transplant is recommended in patients with adverse cytogenetics at diagnosis.
- Second ASCT should also be considered in patients not achieving VGPR after first transplant and unable to received bortezomib-based consolidation.

Maintenance

- Less intensive treatment given over a prolonged period of time, in order to suppress any MRD and prolong response duration, PFS and OS.
- Lenalidomide 10-15 mg daily is associated with a 23% reduction in risk of death and a 2 years increase in median OS. There is a benefit in all subgroups except in high risk cytogenetics and ISS3. However, lenalidomide maintenance in the Myeloma XI trial was associated with an improved PFS, irrespective of cytogenetic risk.
- Proposed duration of therapy is 2 years with a 3 weeks on/ 1 week off schedule.
- There is a concern with a higher incidence of secondary primitive cancers, but the OS benefit of lenalidomide maintenance largely outweigh the risk of developing a SMP.
- Bortezomib given at the dose of 1.3 mg/m^2 overcomes the adverse prognosis of del(17p) but is not reimbursed in this setting.

Allogeneic stem cell transplantation

- Curative option for MM, but no routine indication in the front-line setting because of high treatment-related mortality, risk of graft-versus-host disease even with reduced intensity conditioning and occurrence of long-term post-transplant relapses.
- To be performed in the context of a clinical trial.

Renal impairment

- Renal failure (creatinine > 2 mg/dl) is seen in around 20% newly diagnosed MM at diagnosis.
- Prompt rehydration and treatment of precipitating events (hypercalcemia, acidosis, infection and discontinuation of nephrotoxic drugs).
- Bortezomib is safely used without dose modification, even in patients under dialysis.
- It acts rapidly (responses in 0.7-1.6 months) and can be used in association with dexamethasone (40 mg, days 1-4) ± thalidomide, doxorubicin or cyclophosphamide.
- Thalidomide does not require dose reduction, but may induce severe hyperkalaemia, particularly in patients under dialysis.
- Lenalidomide requires appropriate dose reductions.
- Plasma exchanges are theoretically useful in cast nephropathy, but remove FLC only from the intravascular compartment (17% of total body FLC).
- Use of extended high-cut-off haemodialysis does not offer any advantage in terms of haemodialysis independence at 3 months.

Plasma cell leukaemia

- Most aggressive form of plasma cell dyscrasia with a median OS around 1 year.
- Defined by the presence of plasma cell consisting of more than 20% of the differential white cell count in the peripheral blood, or an absolute plasma cell peripheral blood count of greater than 2.0 x 10^9 cells/l.
- In transplant eligible patients, induction with triplets (VRd or KRd) or 4 alternating cycles of PAD and VCD (IFM), followed by double ASCT.
- In case of extensive disease burden or no response to initial therapy, VTD-PACE or VRD-PACE.
- In transplant ineligible patients, induction with VCD or PAD up to 8-10 cycles, followed by indefinite maintenance therapy to keep the disease under control.

Risk assessment and prevention of thromboembolic disease

Patient or disease risk factors	
• Newly diagnosed MM • Hyperviscosity • Personal or family history of VTE • Obesity (BMI ≥ 30) • Co-morbidities (cardiac, diabetes, renal disease) • Immobility • Thrombophilia • Myeloproliferative disease • Hemoglobinopathies • Recent surgery (< 6 weeks), trauma, neurologic disability • Medications (erythropoietin, hormone replacement therapy, tamoxifen)	0-1 risk factor, consider prophylactic aspirin (75-325 mg) ≥ 2 risk factors, consider either LMWH (equivalent of enoxaparin 40 mg once daily) or warfarin (target INR 2-3)
Therapy-related risk factors	
• Chemotherapy using antracyclines • High-dose steroid (≥ 480 mg/m dexamethasone) • Multi-drug regimens	LMWH (equivalent of enoxaparin 40 mg once daily) or warfarin (target INR 2-3)

FIRST-LINE TREATMENT OF NON-TRANSPLANT ELIGIBLE PATIENTS

Frailty scores and associated dose modifications

Elderly patients are more vulnerable and frailty results in more treatment related adverse effects, which often leads to reduced treatment efficacy and discontinuation. Frailty scores can help to tailor the intensity of therapy, with reduced doses but more durable responses, minimal related toxicities and better quality of life.

Frailty score and associated dose modifications for tailored therapy in newly diagnosed MM patients aged 65 years or more.

International Myeloma Working Group Frailty Score Age < 75y: 0; 75-80y: 1; > 80y: 2 CCI-score ≤ 1: 0; ≥ 2: 1 ADL > 4: 0; ≤ 4: 1 IADL > 5: 0; ≤ 5: 1	**Frailty scores**		
	Fit (total score = 0)	**Intermediate fitness (total score = 1)**	**Frail (total score ≥ 2)**
Recommended therapy • Other options	Standard (twice-weekly) VMP, Rd • VTD, VRD, VCD (up to 8 cy) • Stem cell transplantation for selected patients	Once-weekly VMP, Rd, Vd	Rd • MP, CP • Palliative care
Dose modifications: • Dexamethasone (d) • Melphalan (M) • Thalidomide (T) • Lenalidomide (R) • Bortezomib (V) • Prednisone (P) • Cyclophosphamide (C)	 40 mg 0.25 mg/kg on day 1-4 q4-6 wks 100 mg/day 25 mg, days 1-21 q4 wks 1.3 mg/m² twice weekly 60 mg/m² days 1-4 300 mg/m² days, 1, 8, 15 q4w	 20 mg per week 0.18 mg/kg on days 1-4 q4-6 wks 50 mg/day 25 or 15 mg days 1-21 q4 wks 1.3 mg/m² once weekly 30 mg/m² days 1-4 150 mg/m²	 10 mg per week 0.13 mg/kg on days 1-4 q4-6 wks 50 mg qod 10 mg days 1-21 q4 wks 1.0 mg/m² once weekly 15 mg/m² days 1-4 75 mg/m²

Common induction regimens

Based on the characteristics of the patient and of the myeloma, reimbursed regimens in Belgium are:

- Lenalidomide-low dose dexamethasone, given till progression: all oral regimen, thrombosis prophylaxis mandatory
- Subcutaneously bortezomib based triplets, mainly VMP. No need for thrombosis prophylaxis

New combinations as VRD, daratumumab-VMP, and daratumumab-Rd are promising, but not yet reimbursed.

Common induction regimens for transplant-ineligible MM patients

Combination	Schedule	≥PR	≥VGPR	Median PFS	3y-OS
VMP	Bortezomib: 1.3 mg/m² sq days 1, 4, 8, 11, 22, 25, 29, 32 for first four 6-week cycles, then days 1, 8, 15, 22 for subsequent five 6-week cycles Melphalan: 9 mg/m² orally days 1-4 Prednisone: 60 mg/m² orally days 1-4	71%	30% (CR)	18.3 months	41%
Once-weekly VMP	Bortezomib: 1.3 mg/m² sq days 1, 8, 15, 22 for 5-week cycles Melphalan: 9 mg/m² orally days 1-4 Prednisone: 60 mg/m² orally days 1-4	85%	55%	24.8 months	88%
VCD	Bortezomib 1.3 mg/m² IV or sq days 1,8,15,22 Cyclophosphamide 300 mg/m² orally days 1,8,15 Dexamethasone 40 mg orally days 1,8,15,22 28-day cycles	88%	71%	NA	NA
Continuous Rd	Lenalidomide 25 mg days 1-21 Dexamethasone 40 mg days 1,8,15,22 of each 4-week cycle	81%	48%	26.0 months	70%
VRd	Bortezomib 1.3 mg/m² sq days 1,8,15 Lenalidomide 25 mg orally days 1-21 Dexamethasone 20 mg days 1,2,8,9,15,16 every 3 weeks	90.2% (ORR)	74.9%	41 months	Median OS: not reached

C: cyclophosphamide; CR: complete response; d: low-dose dexamethasone; D: high-dose dexamethasone; m: months; M: melphalan; ORR: objective response rate; OS: overall survival; P: prednisone; PFS: progression-free survival; PR: partial response; R: lenalidomide; T: thalidomide; V: bortezomib; VGPR: very good partial response

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