Update on the initial therapy of multiple myeloma

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With the introduction of immunomodulatory drugs and proteasome inhibitors, major improvements have been achieved in the treatment and prognosis of multiple myeloma. Different treatment combinations are now in use and innovative therapies are being developed. This rapidly changing therapeutic landscape calls for an update on the Belgian myeloma guidelines, published in 2010.[1] Based on an extensive review of the recent literature, the myeloma study group of the Belgian Hematology Society has revised the consensus recommendations on myeloma care, to be used by haematologists as a reference for daily practice. When applicable, comments with regards to the Belgian reimbursement modalities are included. The full text with appendices can be downloaded from the Belgian Hematology Society website (www.bhs.be) and from the Belgium Journal of Hematology website (www.ariez.com).
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Introduction

After discussion on the diagnostic and prognostic work-up and the therapeutic options for multiple myeloma (MM), based on an extended review of the recent literature, a consensus recommendation was obtained by the members of the MM study group of the Belgian Hematology Society (BHS). Levels of evidence and grades of recommendations are based on previously published methods.[2] Guidelines on monoclonal gammopathies of undetermined significance (MGUS) have been reported elsewhere.[3,4] The group recommends participation in clinical trials to enhance progression in the rapidly evolving field of myeloma treatment.

Diagnosis

The diagnosis of MM requires 10% or more monoclonal plasma cells (PC) on bone marrow (BM) aspirate or a biopsy proven plasmacytoma, and the presence of M-protein in serum or urine except in patients with true non-secretory MM. MM can be symptomatic (active) or

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Table 1. Investigations required at diagnosis.

Screening tests	Blood count, urea, creatinine, calcium, phosphorus
	Proteins, electrophoresis of serum and urine, quantification of immunoglobulins
	X-rays of symptomatic areas
Tests to confirm diagnosis	Bone marrow aspirate and trephine biopsy, flow cytometry
	Immunofixation on serum and urine, characterization of the heavy and light chains
	Skeletal survey
Tests to estimate tumour burden	M-protein quantification in serum and urine (concentrate of 24h urine)
	Albumin, beta-2-microglobulin
	FISH analysis on selected or identified bone marrow plasma cells
Other	Measurement of FLC in oligosecretory, light chain and non-secretory MM
	MRI/CT scan
	PET-CT

Table 2. International Staging System.[13]

Stage	Criteria for ISS	Survival (months)
I	Serum beta-2-microglobulin <3.5 mg/l and serum albumin ≥3.5 g/l	62
II	Neither I or III	44
III	Serum beta-2-microglobulin >5.5 mg/l	29

asymptomatic (smoldering MM, SMM). Symptomatic disease is characterised by evidence of end-organ damage attributed to the underlying PC proliferative disorder, referred to CRAB features (C, increased calcium level; R, impaired renal function; A, anaemia; B, bone lesions).[5]

Investigations required at diagnosis are summarised in *Table 1*, and encompasses serum and urine protein electrophoresis (concentrate of 24h urine) to detect and evaluate the monoclonal component, quantification of IgG, IgA and IgM immunoglobulins, characterisation of the heavy and light chains by immunofixation, measurement of serum free light chain (FLC) for identifying and monitoring non-secretory and oligosecretory MM. Bone marrow studies should include fluorescence in situ hybridisation (FISH) analysis designed to detect t(11;14), t(4;14), hyperdiploidy, del(17p) and amp(1q) and preferentially be realised on purified myeloma cells. Conventional karyotyping to identify hyper-, hypodip-

Table 3. Mayo stratification for myeloma and risk-adapted therapy classification (mSMART) (adapted from Kumar, Cancer 2012).[14]

Standard risk	Intermediate risk	High risk
trisomies (hyperdiploidy)	t(4;14)	17p deletion
t(11;14)		t(14;16)
t(6;14)		t(14;20)

Table 4. Risk stratification for myeloma (adapted from Chng, Leukemia 2014).[15]

MM Patients	**Standard risk** 20%	**Intermediate risk** 60%	**High risk** 20%
Parameters	ISS I/II and absence of t(4;14), del(17p), del and +1q21, and age <55 years	others	ISS II/III and t(4;14) or del(17p)
Median OS	> 10 years	7 years	2 years

loidy and del(13q) also demonstrates some additional value in risk stratification.

Conventional radiography remains the gold standard for the evaluation of bone disease in MM patients. Magnetic resonance imaging (MRI) is indicated when symptomatic areas show no abnormality on routine x-rays. It should be part of the staging of solitary plasmacytoma to assess the extent of the lesion and detect occult lesions that are associated with the development of systemic disease. It should also be done in SMM as the presence of occult bone lesions increases the risk of progression to MM. Positron emission tomography (PET) detects small lesions, particularly extramedullary disease, but its use in MM must be better defined by further studies.[6,7]

Prognostic markers and risk stratification

Prognosis in MM depends on host factors (age, performance status, comorbidities), and tumour related factors (tumour biology, stage, disease aggressiveness, response to therapy). The most relevant host factor is age, while the most important tumour factors are genetic aberrations.[8,9] Up to 20% of MM present with adverse cytogenetic abnormalities. The adverse prognostic significance of del(13q) relates to its close association to t(4;14). Deletions 1p22 and 1p32, and amp(1q) have been recently associated with adverse prognosis.[10,11]

The Salmon-Durie classification and the International Staging System (ISS) (*Table 2*) provide information on prognosis but have limited value for treatment decisions.[12,13] The Mayo Clinic uses the mSMART prognostic score (stratification for myeloma and risk-adapted therapy) that classifies newly diagnosed MM into standard, intermediate or high-risk disease, based on cytogenetic findings (*Table 3*).[14] Patients with standard risk disease have a median overall survival (OS) of 6-7 years (y), whereas those with high-risk disease have a median OS of less than 2-3y, despite aggressive therapy. The presence of trisomies in intermediate or high-risk MM ameliorates the adverse impact of these markers. This score has not been validated by prospective trials. Combining cytogenetics with ISS, the International Myeloma Working Group (IMWG) segregates patients into three different risk groups (*Table 4*). Either ISS II or III and the presence of either t(4;14) and/or del(17p) detected by FISH define high-risk patients that have a median OS of about 2y, when low-risk MM can survive more than 10y.[15] This risk stratification system should be proposed as standard in future clinical trials.

Recommendations

- *Parameters to be assessed as part of routine examination at diagnosis are summarised in Table 1.*
- *All patients should undergo risk stratification using ISS (I,A) and cytogenetics (FISH) (II,B).*

Treatment

The aim of treatment in MM is to control disease, preserve quality of life and prolong survival. With few exceptions, only patients with symptomatic disease require treatment. Age, performance status and comorbidities are considered. The best sequence and combination of drugs are still a matter of debate. Therefore patients should be offered participation in clinical trials whenever possible. The main question remains whether a patient is eligible for autologous stem cell transplantation (ASCT) or not. Both in the transplant and non-transplant settings, studies have established a link between the maximal response after initial therapy and long-term outcome.[16,17] Improving depth of response is thus a major goal.

Smoldering myeloma (SMM)

High-risk SMM patients have a M-protein ≥30g/l, BM PCs ≥10% and an abnormal FLC ratio, but no organ damage. In this group, the median time to progression

Table 5. Risk factors in elderly patients (adapted from Palumbo, Blood 2011).[21]

	Risk factors
age	≥ 75 years
co-morbidities	cardiac, pulmonary, hepatic, renal, marrow dysfunction
frailty	weakness, poor endurance, weight loss, low physical activity, slow gait speed
disability	

Risk factors	Dose level adaptation
0	***0***
≥ 1	***-1***
≥ 1 and previous grade 3-4 non-hematologic toxicity	***-2***

(TTP) is 2.4y, with a 76% risk of progression at 5y.[18] Trials are now investigating the effect of novel drugs on suspending progression to symptomatic MM. In a recent prospective phase III study, early treatment in high-risk SMM with nine cycles of lenalidomide plus low dose dexamethasone (Rd) followed by lenalidomide maintenance for 2y, was found to delay disease progression and increase OS.[19] Further investigations are needed to confirm these promising data. Some authors suggest considering an anti-MM treatment for patients presenting an ultra high-risk of progression (within the following 24 months (m)), to avoid life-threatening complications at progression. These patients are identified by a BM PC infiltration >60%, a FLC ratio >100 and more than one focal lesion on MRI.[20] However, scientific justifications are currently lacking.

Recommendations

- *Patients with SMM should be followed-up every 3-4m and monitored for symptoms.*
- *There is no indication for treatment outside a clinical trial.*
- *Physicians should however, be aware that patients with >60% PCs in BM, high FLC ratio (>100) or more than one focal lesion on MRI, are at very high-risk of progression within a very short period of time.*

Symptomatic myeloma (MM)

Front-line treatment in the non-transplant setting

The aim of treatment in patients not eligible for ASCT is to achieve the maximal durable response with minimal treatment related toxicities. Increased risk of toxicity is a major problem in the elderly, especially in the presence of co-morbidities. Furthermore, early treatment discontinuation results in poorer outcomes. Risk factors are defined as age ≥75y, presence of co-morbidities, frailty or disability (*Table 5*).[21] Comorbidities, age, physical and mental capacities have recently been combined in a geriatric score of strong prognostic value, able to identify frail patients.[22]

The addition of novel agents thalidomide (MPT) or bortezomib (MPV) to the former standard melphalan plus prednisone (MP) induces superior responses and prolonged survival. There are no prospective trials comparing MPT with MPV. The most common regimens used in patients not eligible for ASCT are listed in *Appendix 1*.

i. Thalidomide-based regimens

MPT assessed in six randomised trials (RCT) reported higher overall response rates (ORR) and complete response (CR) as well as TTP, progression free survival (PFS) or event free survival (EFS) than MP alone.[23-28] Three trials reported higher OS rates.[23,24,28] An efficacy meta-analysis confirmed that MPT improves PFS and

Appendix 1. Common regimens for elderly patients with multiple myeloma.

Combination	Schedule	≥PR, %	≥VGPR, %	Median PFS months	3y-OS %	Ref
MPT	M : 0.25mg/kg days 1-4 P : 2mg/kg days 1-4 T : 400mg/day for twelve 6-week cycles	76	47	27.5	52	23
MPT	M : 0.25mg/kg days 1-4 P : 2mg/kg days 1-4 T : 100mg/day for twelve 6-week cycles	62	21	24.1	55	24
CTD	C : 500mg/week T : 50mg for 4 weeks to a maximum of 200mg/day D : 20mg/day, days 1-4 and 15-18 of each 28-day cycle	64	43	27	50	48
MPV	M : 9mg/m^2 days 1-4 P : 60mg/m^2 days 1-4 V : 1.3mg/m^2 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	71	30 (CR)	22	41	31
Rd	R : 25mg days 1-21 D : 40mg days 1,8,15,22 of each 4-week cycle	70	40	25.3	75	34
BP	B : 150mg/m^2 on days 1-2 P : 60mg/day on days 1-4	75	32 (CR)	14	32	38

Abbreviations: B, bendamustine; C, cyclophosphamide; D, dexamethasone; m, months; M, melphalan; P, prednisone; R, lenalidomide; Ref, references; T, thalidomide; V, bortezomib.

extends OS by 20% (6.6m).[29] A safety meta-analysis showed that MPT induces more grade 3-4 non-hematologic toxicities (39% versus 17%), with a higher risk of both peripheral neuropathy (PN) (6-23%) and venous thromboembolic events (VTE) (3-12%), particularly in patients with a poor performance status.[30] Dose adjustments have been proposed in patients over 75y and frail individuals (*Table 6*).[21]

ii. Bortezomib-based regimens

In the VISTA phase III trial, MPV demonstrated a substantial superiority over MP in terms of ORR, with longer TTP (24 versus 16.6m), better OS (56.4 versus 43.1m) and a 31% reduced risk of death. Comparable response rates were seen in both adverse and favourable cytogenetics. MPV was well tolerated despite more grade 3-4 toxicities, particularly PN (14%), infections (10%), neutropenia (40%) and thrombocytopenia (37%).[31] Incidence and severity of PN related to bortezomib can be reduced by weekly dosing as well as by subcutaneous administration, with no impact on OS.[32] Addition of thalidomide to MPV (MPVT) suggested a superior PFS and OS.[33] However, since patients with MPVT received VT maintenance while those treated with MPV received no maintenance, it is impossible to determine what caused the survival benefit.

iii. Lenalidomide-based regimens

Lenalidomide plus low-dose dexamethasone (Rd) (dexamethasone 160mg per cycle, 40mg on days 1, 8, 15, 22), widely used in the United States (US), induces responses in approximately 70% of patients with a median PFS of 2y and little toxicity.[34] In patients over 70y, the 3y OS rate of 73% seems comparable to MPT and MPV.[35] The FIRST phase III RCT randomised 1.623 newly diagnosed MM patients over 65y between MPT versus Rd for 18m versus Rd until progression. Continuous Rd significantly improved PFS compared with MPT, with a 28% reduction in risk of progression, better ORR (≥PR, 75% versus 62%) and duration of response. The OS interim analysis showed a 22% reduction in risk of death in favour of continuous Rd over MPT. The safety

Table 6. Suggested dose adjustment in elderly patients (adapted from Palumbo, Blood 2011).[21]

Drug	Schedule	Initial/standard dose *Dose level 0*	Reduced dose *Dose level -1*	Further reduction if needed *Dose level -2*
Dexamethasone	days 1,8,15,22, every 4 weeks	40 mg/d	20 mg/d	10 mg/d
Prednisone	3x/week	50 mg/d	25 mg/d	12,5 mg/d
Melphalan	days 1-4, every 4-6 weeks	0.25 mg/kg/d	0.18 mg/kg/d	0.13 mg/kg/d
Cyclophosphamide	days 1-21	100 mg/d	50 mg/d	50 mg qod
Thalidomide	continued	100 mg/d	50 mg/d	50 mg qod
Lenalidomide in RD/Rd	days 1-21 every 4 weeks	25 mg/d	15 mg/d	10 mg/d
Lenalidomide in MPR	days 1-21 every 4 weeks	10 mg/d	5 mg/d	5 mg qod
Bortezomib	days 1,4,8,11 every 3 weeks days 1,8,15,22 every 5 weeks	1.3 mg/m^2/d twice weekly	1.3 mg/m^2/d once weekly	1 mg/m^2/d once weekly

Table 7. Dose adjustment for melphalan in renal impairment (adapted from Dimopoulos, J Clin Oncol 2010).[88]

Creatinine clearance	Dose reduction	Dose adjustment of melphalan (given for 4-7 days)
≥ 60 ml/min	0%	0.15 – 0.25 mg/kg/d
15-60 ml/min	25%	0.11 – 0.19 mg/kg/d
< 15 ml/min and/or dialysis	50%	0.075 – 0.125 mg/kg/d

profile of Rd was manageable, with reduced hematologic secondary primary malignancies (SPM) compared to MPT.[36]

In the MM-015 trial, the addition of lenalidomide to MP followed by lenalidomide maintenance until progression (MPR-R) or no maintenance (MPR) was compared to MP without maintenance. MPR-R and MPR showed superior ORR compared to MP (77% and 68% versus 50% respectively), but only MPR-R produced a significantly longer PFS (31m versus 14m and 13m), with no benefit on OS.[37] Three RCT are ongoing, the ECOG trial comparing MPR to MPT, the SWOG trial comparing Rd to bortezomib-lenalidomide-dexamethasone (VRD), and the HOVON-87 study comparing MPT followed by thalidomide maintenance, with MPR followed by lenalidomide maintenance.

iv. Bendamustine-based regimens

Compared to MP, bendamustine with prednisolone (BP) provides higher CR rates (32% versus 13%), shorter time to response (6.8 versus 8.6 cycles) and extended TTP (14 versus 10m), but no advantage in OS (32m). Common adverse reactions are cytopenias, nausea and vomiting.[38]

Table 8. Dose adjustment for lenalidomide in renal impairment (adapted from Dimopoulos, J Clin Oncol 2010).[88]

Creatinine clearance	Dose adjustment of lenalidomide	Remarks
≥ 50 ml/min	25 mg once daily	full dose
30-50 ml/min	10 mg once daily	
< 30 ml/min, not requiring dialysis	15 mg every other day	
< 30 ml/min, requiring dialysis	5 mg once daily	following dialysis on dialysis days

Recommendations

- *Elderly patients should be assessed for risk factors defined as age ≥75y, presence of co-morbidities, frailty (weakness, poor endurance, weight loss, low physical activity, slow gait speed), or disability.*
- *Geriatric scales may be helpful in identifying frail patients. In the presence of ≥1 risk factor, dose reductions are mandatory.*
- *Outside clinical trials, patients not eligible for ASCT should receive either MPT (I,A) or MPV (I,A) as standard first-line therapy, both reimbursed in Belgium.*
- *There is no evidence of the superiority of one regimen over the other in the absence of RCTs. The choice between MPV and MPT should be made on an individualised basis and determined by anticipated (based on risk factors) and observed toxicities.*
- *Recommended treatment duration is nine cycles for MPV and 18m for MPT.*
- *Treatment duration can however be shorter because of therapy-related toxicities.*
- *MPT requires prophylactic anticoagulation, while MPV requires antiviral prophylaxis against herpes zoster.*
- *Due to its excellent tolerability and lesser induction of PN, bortezomib-based regimens using subcutaneous administration on a weekly basis are preferred, especially in elderly, less fit or frail patients (II,B).*
- *MPV is also preferred in patients with a major risk for VTE, pre-existing PN or renal impairment.*
- *Rd may offer an alternative treatment (II,B), but is not reimbursed for front-line therapy in Belgium.*
- *Bendamustine-prednisone is an effective regimen, approved in Belgium for MM patients over 65y presenting with PN, ineligible for ASCT.*

Front-line treatment in patients eligible for ASCT

High-dose melphalan (HDM) followed by ASCT remains the first-line standard of care in patients up to 65y in good physical condition. Induction with novel agents has improved disease outcome by increasing the number of patients achieving at least a VGPR after ASCT.[16,17]

Induction therapy

The goal of induction is to reduce tumour burden before stem cell collection. With novel agents, the majority of patients achieve a maximal response after 4-6 cycles. Although CR prior to ASCT is a good prognostic factor, there is no evidence that prolongation of induction beyond six cycles to achieve CR improves outcome. We recommend switching to an alternative regimen in case of progressive disease (PD) after two cycles. The most common regimens used in this setting are listed in *Appendix 2*.

Two phase III trials showed the efficacy of bortezomib-based induction regimens before ASCT. Compared to VAD, the use of bortezomib in the VD or the PAD (bortezomib-doxorubicin-dexamethasone) regimens significantly increased the CR/nCR rates post-ASCT.[39,40] Responses were maintained in patients with adverse cytogenetic features. Bortezomib is reimbursed in this setting since September 2014.

The neurotoxicity of bortezomib can be greatly diminished by subcutaneous administration. Twice weekly intravenous administration should, however, be considered when there is a need for rapid disease control and in extramedullary disease, since optimal plasma concentrations are reached in a shorter time.[41]

Three trials have investigated the combination of bortezomib with thalidomide and steroids (VTD) as induction therapy.[42-44] Compared to TD, VTD followed by

tandem ASCT and maintenance with the same regimen provided significantly better ORR and PFS but more toxicity, particularly PN (10% versus 3%), with no OS advantage. VTD was, however, able to overcome the poor prognostic effect of t(4;14).[42] Compared to TD or the VMPCB/VBAD combination, VTD followed by bortezomib maintenance induced higher pre- and post-transplant CRs.[43] To reduce the incidence of PN, the IFM proposed dose reductions of bortezomib and thalidomide in the vtD regimen with good ORR and lower grade 3-4 PN (14% versus 34%).[44]

Other 3-drug induction regimens have been reported in phase II trials, with no clear superiority of one particular regimen. The most promising 3-drug induction regimen may be the VRD combination. In a phase I-II trial, VRD showed very high ORR and CR rates, with only 2% grade 3 PN and 6% thrombosis. After a medium follow-up of 21m, PFS and OS were 75% and 97%, respectively.[45] VRD followed by early transplantation is currently compared with VRD alone in the ongoing IFM 2009-DFCI phase III trial. VCD represents an excellent alternative based on efficacy, safety, cost and convenience, with similar activity compared to VRD.[46] The addition of lenalidomide to VCD (VCDR) does not provide any significant advantage over the 3-drug combination.[47] In case of unavailability of bortezomib, the combination of cyclophosphamide-thalidomide-dexamethasone (CTD) is also an adequate alternative.[48] Rd appears a good option prior to ASCT, resulting in a 94% 2y post-transplant OS, supporting this combination as a standard induction option for MM patients in the US.[34] There are no data comparing bortezomib-based combinations with Rd.

In patients with adverse cytogenetic MM, induction with VD partially overcomes the poor prognosis of the t(4;14), but has no impact on del(17p).[49] In del(17p) MM, long-term administration of bortezomib (PAD induction, bortezomib maintenance) significantly reduces its adverse impact on PFS and OS.[50] Iterative reinductions with VRD appears promising for patients with del(17p) and t(4;14), but 13% of them still escape to this strategy.[51]

Newer and potentially more potent proteasome inhibitors such as carfilzomib and ixazomib (MLN 9708) as well as the new IMiD pomalidomide are currently evaluated in newly diagnosed MM patients, with very promising results.[52,53]

Autologous stem cell transplantation

i. Stem cell collection

Guidelines for stem cell collection were published in 2009.[54] Collection of ≥4 million CD34+ cells/kg is recommended when possible. If not, patients can be safely transplanted with ≥2.5 million CD34+ cells/kg. Collection of 8-10 million CD34+ allows for two autografts. There is generally no problem for stem cell collection with G-CSF alone after TD or bortezomib containing induction regimens, but prolonged treatment with lenalidomide may reduce mobilisation efficiency.[55] In this setting, stem cell collection should be performed after 3-4 courses of lenalidomide therapy, and may require the use of cyclophosphamide.[56] The combined use of plerixafor with G-CSF may considerably improve mobilisation efficiency. Plerixafor is reimbursed in Belgium for MM patients with poor stem cell mobilisation.

ii. Conditioning

HDM (200mg/m^2) (mel200) remains the standard conditioning regimen prior to ASCT in patients under 65y. Increased doses of melphalan or total body irradiation both increase toxicity without improvement in ORR or PFS.[57] The addition of four injections of bortezomib (1mg/m^2 on days -6,-3,+1,+4) to HDM showed a synergistic effect without increasing toxicity in a phase II study, but the impact of this regimen is unknown in the absence of RCT.[58]

iii. Age

Although most RCT select patients ≤65, in selected patients ≥65, outcomes after ASCT are similar.[59-61] Over 70, however, treatment-related mortality (TRM) increases to >15%.[60] In patients aged 65-75, intermediate dose melphalan (100mg/m^2) (mel100) has shown contradictory results.[23,62] Used in a sequential approach with novel agents, mel100 and ASCT showed good responses without significant toxicities.[63]

iv. Timing of transplantation

Retrospective studies evaluating early ASCT versus ASCT upon relapse failed to show any difference in OS.[64,65] The role of ASCT as upfront therapy is actually being challenged in the era of novel agents.

v. Single versus tandem ASCT

A systematic review including more than 1.800 patients from six RCTs failed to demonstrate any improvement in OS or PFS with the use of tandem ASCT in de novo

MM except in patients not achieving at least VGPR after the first ASCT.[66-68] A recent analysis suggests a possible benefit for double ASCT in patients who failed to achieve CR after exposure to bortezomib as part of induction therapy, and those with a high-risk cytogenetic profile.[69] These data need to be confirmed by further prospective studies.

It is, however, suggested to collect sufficient stem cells to support two autografts, and to propose a second ASCT as salvage therapy at relapse, provided that the response duration after the first ASCT was more than 12m.

Recommendations

- *Induction therapy should preferentially incorporate bortezomib.*
- *Bortezomib-based regimens are preferred in high-risk MM with adverse cytogenetic features or renal impairment.*
- *Three-drug regiments (VTD, vtD, VCD) are favoured over two-drug schemes (I,A).*
- *Incidence and severity of bortezomib associated PN can be reduced by weekly dosing and subcutaneous administration.*
- *Bortezomib is reimbursed for induction treatment since September 2014.*
- *CTD can be an alternative when bortezomib is contra-indicated.*
- *Thalidomide-based regimens require prophylactic anticoagulation, while bortezomib-based regimens require antiviral prophylaxis to prevent herpes zoster infection.*
- *Lenalidomide for induction therapy before ASCT is not reimbursed in Belgium.*
- *Outside the context of a clinical trial, HDM followed by ASCT remains the first-line standard of care in patients up to 65y with an adequate performance status and organ function (I,A) and should be considered in patients aged 65-70y with good performance status (II,B).*
- *Conditioning with melphalan 200mg/m^2 is recommended (II,B).*
- *Dose reduction is proposed when GFR is <30ml/min.*
- *Tandem ASCT are not routinely recommended. However, enough stem cells should be collected to support a second ASCT at relapse in patients with good performance status, provided that the response duration after the first ASCT was more than 12m (IV,C).*

Consolidation and maintenance therapy

Deep responses (CR or VGPR) are associated with a prolonged survival. Consolidation consists of the administration of a short-term treatment aimed to improve the quality of response following the induction therapy. Maintenance is referred to as a therapy given for a prolonged period in order to maintain the response achieved and prevent progression.

i. Consolidation post-ASCT

Two phase III trials reported the interest of consolidation after ASCT. The Italian group compared consolidation with TD or VTD after a VTD induction followed by a double ASCT, while the Nordic group compared weekly bortezomib consolidation with no consolidation after a single ASCT.[70,71] Both studies demonstrated a significant increase in CR and PFS, with a very low incidence of grade 3-4 PN, but without an OS benefit. A benefit in PFS was also observed in high-risk cytogenetic MM.[70] Other groups reported similar encouraging results using bortezomib or lenalidomide in monotherapy or in combination, supporting the fact that consolidation improves the depth of response and might be considered as a reasonable option following ASCT.[72,73] Further data are needed to define the optimal strategy in this setting.

ii. Maintenance post-ASCT

RCT with variable doses and durations of thalidomide maintenance after ASCT consistently demonstrated a significant improvement in quality of response and PFS (6 to 12m) with variable effect on OS.[74-80] OS was adversely impacted by thalidomide maintenance in patients with adverse cytogenetic features.[76] In addition, adverse effects such as PN and thrombotic events negatively affect quality of life.[80]

Lenalidomide is more suitable for maintenance because of its low toxicity profile and higher potency. Two phase III studies compared lenalidomide (10-15mg) with placebo until disease progression after first-line ASCT.[72,81] In the IFM 2005-02 trial, lenalidomide maintenance significantly improved PFS (from 23 to 41m), regardless of risk factors.[72] In the CALBG trial, TTP was prolonged from 27 to 46m.[81] Only the CALGB study reported an OS benefit.[81] Concerns have been raised about a potential increase in SPM with lenalidomide maintenance. Even if the benefits of lenalidomide maintenance outweigh the risk for SPM, longer follow-up is required to better define its impact

Appendix 2. Regimens for young patients with multiple myeloma.

Combination	Schedule	≥PR, %	≥VGPR, %	Median PFS months	3y-OS %	Ref
TAD	T : 100-200mg/day on days 1-28 A : 9mg/m^2 on days 1-4 D : 40mg on days 1-4, 9-12, 17-20 of each 28-day cycle	72	66	34	73	79
CTD	C : 500mg/week T : 100mg/day, up to 200 mg D : 40mg/day on days 1-4, 12-15	NA	50	27	NR	48
VRD	V : 1.3mg/m^2 on days 1,4,8,11 R : 25mg on days 1-14 D : 20mg on days 1,2,4,5,8,9,11,12	100	67	75% at 18m	97% at 18m	45
VD	V : 1.3mg/m^2 on days 1,4,8,11 D : 40mg on days 1,4,8,11, every 3 weeks for up to 6 cycles	79	38	36	81	39
PAD	V : 1.3mg/m^2 on days 1,4,8,11 Doxo : 9mg/m^2 on days 1-4 D : 40mg on days 1-4, 9-12, 17-20, every 28 days	90	42	35	61	40
VTD	V : 1.3mg/m^2 on days 1,4,8,11 T : 100mg/day for the first 14 days, then 200mg D : 40mg on days 1,2,4,5,8,9,11,12, every 21-day cycles	93	63	NR	90	42
vtD	V : 1mg/m^2 on days 1,4,8,11 T : 100mg/day D : 40mg on days 1-4, 9-12 on cycles 1-2, on days 1-4 on cycles 3-4, every 21-day cycles	89	51	26		44
VCD	V : 1.3mg/m^2 days 1,4,8,11 or 1.5mg/m^2 on days 1,8,15,22 C : 300mg/m^2 on days 1,8,15,22 D : 40mg/day on days 1-4, 9-12, 17-20 every 28-day cycle for 4-12	88	71	NA		46

Abbreviations: A, doxorubicin; C, cyclophosphamide; D, dexamethasone; m, months; M, melphalan; P, prednisone; NA, not available; NR, not reached; PAD, bortezomib, doxorubicin, dexamethasone; R, lenalidomide; Ref, references; T, thalidomide; V, bortezomib.

on OS and to establish the optimal duration of maintenance therapy.

Few studies have investigated the role of bortezomib in maintenance. PAD induction followed by ASCT and bortezomib maintenance (1.3mg/m^2 every two weeks) (PAD-V) compared to VAD followed by ASCT and low-dose thalidomide maintenance (50mg once a day) (VAD-T), was associated with a significantly higher level of CR/nCR, better PFS (median 35 versus 28m) and was the first to demonstrate a survival benefit (5y OS 61% versus 55%). However, as the induction therapy was different in the two arms, this effect can be related to the use of bortezomib in induction.[40] In another study, VT maintenance led to a significantly higher PFS compared to thalidomide or -interferon alone, without increased toxicity.[48]

iii. Maintenance/continued treatment in the non-transplant setting

Maintenance with low dose (50-100mg) thalidomide showed a statistically significant improvement in PFS (23 versus 15m) but no difference in median OS, although a meta-analysis showed a late survival benefit.[76] Patients with adverse interphase-FISH had a worse OS. Maintenance with bortezomib plus either thalidomide (VT) or prednisone (VP) extended PFS in patients initially treated with MPV, VTP or MPVT.[33,82] Both VT and

VP increased the CR rate without increasing toxicity, but with no effect on OS.

Lenalidomide maintenance in MPR-R compared to MPR and MP significantly prolonged PFS compared to placebo (31m versus 14m with MPR and 13m with MP), reducing the risk of progression by 66%, but without significant OS benefit. Lenalidomide was also related to the occurrence of SPM (7% at 3y for both MPR-R and MPR, but only 3% for MP).[37]

Recommendations

- *Consolidation with bortezomib or VT(D) increases the quality and duration of response, with a low level of grade 3-4 PN, and should be recommended in patients after ASCT, especially for those who failed to achieve VGPR or CR/nCR after ASCT (II,A), but is not reimbursed at present.*
- *Post-ASCT maintenance with thalidomide could benefit patients who do not achieve CR/VGPR after ASCT (I,B), but should be avoided in patients with adverse cytogenetics (I,A). Because of its toxicity profile, it should be administered at low doses (50-100mg a day) and no longer than 1y (IV,C).*
- *Maintenance with lenalidomide decreases the risk of progression (I,A) but raised suspicion with regard to SPM. Therefore, there is no indication outside a clinical trial. Lenalidomide is not reimbursed in this setting.*
- *In elderly, long-term data are too immature to recommend maintenance therapy after conventional upfront treatment.*
- *In Belgium, only thalidomide is reimbursed for maintenance therapy.*

Allogeneic stem cell transplantation

Most patients are not eligible for allogeneic stem cell transplantation (allo-SCT) because of age and co-morbidities. But even in eligible patients, the role of allo-SCT remains controversial due to TRM (10-20%) and graft-versus-host disease (GvHD), even when using reduced intensity conditioning (RIC) approaches. In addition, long-term follow-up has shown continuing relapses post-transplant.[83,84]

It is also unclear whether allo-SCT with RIC is more effective than ASCT. Two recent reports show conflicting data. While the BMT Clinical Trials Network 0102 study fails to demonstrate any PFS or OS benefit at 3y, a European study demonstrated a superior 5y outcome after ASCT/allo-SCT compared with tandem ASCT in previously untreated MM patients.[85,86]

Recent findings raise the question of whether allo-SCT, performed early in the course of the disease, may benefit very high-risk young patients, in particular those with ISS II and III and del(1p)/(1q)gain, t(4;14), del(17p) or t(14;16), in whom the projected 4y PFS and OS do not exceed 11% and 33%, respectively.[15]

Recommendations

- *Allo-SCT is still considered investigational for MM.*
- *Because of the risk of severe transplant-related morbidities and mortality, it should only be considered for patients with high-risk disease either in first response or as consolidation in second remission, and in the context of a clinical trial (IV,C).*

Recommendations for high-risk disease

We will focus on specific situations such as renal failure at diagnosis, primary refractory disease and PC leukaemia.

i. Renal impairment

In case of renal failure, reducing light chains production is the most successful way to avoid further kidney damage. High-dose dexamethasone is highly effective as a single agent and should be started without delay. Bortezomib induces rapid responses (0.7 to 1.6m) and can be safely used without dose reductions in patients with renal failure.[87] VD is the treatment of choice in this setting.[88] Triplets such as VTD and VCD can also be used safely. Melphalan must be reduced by 25% in case GFR <30ml/min, and further adapted according to marrow toxicity (*Table 7*).[88] Cyclophosphamide needs a dose reduction of 25% if GFR is 10-50ml/min, 50% if GFR is <10ml/min, and further adaptation according to marrow toxicity. Thalidomide does not require dose reduction, but may induce severe hyperkalemia, particularly in patients undergoing dialysis.[89] Usual adverse events such as PN, constipation, lethargy and bradycardia are more frequent when serum creatinine is >3mg/dl. Lenalidomide, mainly excreted by the kidneys, is effective, but requires dose reductions to avoid increased myelosuppression (*Table 8*).[88] Bendamustine can be an option, particularly in combination with bortezomib and prednisone.[89]

ASCT is feasible in patients with renal failure including those requiring dialysis, inducing similar ORR. A re-

duced dose of melphalan (140mg/m^2) should be used if GFR <30ml/min.[91] Toxicity can be significant with prolonged mucositis and hospitalisation.

Recommendations

- *Renal failure in MM patients requires prompt rehydration and treatment of precipitating events (e.g. hypercalcemia, infection and discontinuation of nephrotoxic drugs e.g. NSAIDs) (IV,C).*
- *Physical methods to remove FLC from the blood should be performed in the context of a clinical trial (IV,C).*
- *Administration of high-dose dexamethasone in association with bortezomib (VD, VTD, and VCD) is recommended (IV,C).*
- *Thalidomide does not require dose reduction, but may induce severe hyperkalemia, particularly in patients under dialysis.*
- *Lenalidomide, mainly excreted by the kidneys, requires dose reduction.*
- *ASCT can be proposed for patients with GFR <30ml/min, using melphalan 100-140mg/m^2 (II,B).*

ii. Primary refractory disease

Primary refractory patients refers to patients with either PD on induction therapy, or with a stationary M-protein without clinical progression.

In patients with progressive disease, salvage/experimental regimens should be used to decrease tumour burden before ASCT. In contrast, patients with non-responding, stable disease have an OS comparable to patients with chemosensitive disease.[92]

iii. Plasma cell leukaemia

Primary PC leukaemia (pPCL) defined by the presence of >2x10^9 PCs per litre in the blood or a plasmacytosis >20%, is the most aggressive form of PC dyscrasia. In contrast, secondary PCL (sPCL) is a leukemic transformation of end-stage MM. Extramedullary involvement is more common in pPCL, reflecting a high tumour load. Hypodiploidy, del(13q), del(17p), del(1p) or amp(1q), and complex karyotype have been associated with reduced OS.[93]

Recommendations

- *In transplant eligible patients, upfront therapy should include a 3-drug bortezomib-based induction regimen (VCD, VTD, PAD or VRD) followed by HDM and ASCT, consolidation with 2-4 cycles (VTD or RVD), and maintenance with bortezomib until progression.*
- *Consolidation with allo-SCT can be considered in young patients, in the setting of a clinical trial.*
- *In transplant non-eligible patients, treatment should include a bortezomib-based regimen (MPV or RVD) followed by maintenance.*

Follow-up and response evaluation

Responses to therapy are assessed using the IMWG response criteria.[94] The M-protein level is evaluated by serum and urine protein electrophoresis every month while on therapy, and every 3-4m when off therapy. The FLC assay is used to monitor patients who lack a measurable M-protein, particularly in oligosecretory, non-secretory and light chains MM, provided the FLC ratio is abnormal and the involved FLC level is ≥100mg/l.[95] The serum FLC assay is reimbursed in Belgium for the follow-up of patients with these specific entities.

Conclusion

Major advances have occurred over the past few years, especially with the use of IMiDs and proteasome inhibitors. The ISS and cytogenetics are used to risk stratify patients. Younger patients can now enjoy a median survival of 7y with induction therapy followed by ASCT. Older patients also have longer survivals with MPT/MPV/MPR. Consolidation therapy is actively pursued, as achieving CR is an important surrogate for improved OS. Maintenance seems to prolong survival further but more data on long-term safety, especially with regards to SPM, is needed. Supportive care is essential, in order to prevent complications related to the disease and its therapy.

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For the complete list of references we refer to the electronic version of this article which can be downloaded from www.ariez.com.

Abbreviations

Allo-SCT	Allogeneic stem cell transplantation
ASCT	Autologous stem cell transplantation
BM	Bone marrow
BMT	Blood and marrow transplant
BP	Bendamustine-prednisone
CR	Complete response
CRAB	C, hypercalcemia, R, renal dysfunction, A, anaemia, B, bone lesions
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
FISH	Fluorescence in situ hybridization
FLC	Free light chains
GFR	Glomerular filtration rate
GvHD	Graft versus host disease
HCO-HD	High cut-off haemodialysis
HDM	High-dose melphalan
HOVON	Stichting Hemato-Oncologie voor volwassenen Nederland
IMiDs	Immunomodulatory drugs
IMWG	International Myeloma Working Group
IFM	Intergroupe Francophone du Myélome
ISS	International Staging System
LMWH	Low molecular weight heparin
m	months
MGUS	monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MP	Melphalan-prednisone
MPT	Melphalan-prednisone-thalidomide
MPR	Melphalan-prednisone-lenalidomide
MPR-R	Melphalan-prednisone-lenalidomide with lenalidomide maintenance
MPV	Melphalan-prednisone-bortezomib
MRC	Medical Research Council
MRI	Magnetic resonance imaging
mSMART	stratification for myeloma and risk-adapted therapy
NA	Not available
nCR	Near complete response
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PAD	Bortezomib-adriamycin-dexamethasone
PBSC	Peripheral blood stem cell
PC	Plasma cell
PD	Progressive disease
PE	Plasma exchange
PET-CT	Positron emission tomography with computed tomography
PFS	Progression-free survival
pPCL	Primary plasma cell leukaemia
PN	Peripheral neuropathy
PR	Partial response
RCT	Randomised clinical trial
Rd	Lenalidomide-low dose dexamethasone
RD	Lenalidomide-high dose dexamethasone
RIC	Reduced intensity conditioning
sPCL	Secondary plasma cell leukaemia
SWOG	Southwest Oncology Group
RCT	Randomised controlled trial
SMM	Smoldering multiple myeloma
SPM	Secondary primary malignancy
TD	Thalidomide-dexamethasone
TRM	Treatment-related mortality
TTP	Time-to-progression
VCD	Bortezomib-cyclophosphamide-dexamethasone
VCRD	Bortezomib-cyclophosphamide-lenalidomide-dexamethasone
VD	Bortezomib-dexamethasone
VGPR	Very good partial response
VP	Bortezomib-prednisone
VRD	Bortezomib-lenalidomide-dexamethasone
VT	Bortezomib-thalidomide
VTD	Bortezomib-thalidomide-dexamethasone
VTE	Venous thromboembolic disease
y	years

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