Practical management of newly-diagnosed multiple myeloma: 2018 update for transplant eligible patients

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SUMMARY

With the introduction of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs), major improvements have been achieved in the treatment and outcome of multiple myeloma (MM). Different treatment combinations are now in use and newer therapies are being developed. Nevertheless, autologous stem cell transplantation (ASCT) remains the corner stone of therapy for fit, newly-diagnosed MM patients. Based on an extensive review of the recent literature, we propose recommendations on myeloma care, to be used by haematologists as a reference for daily practice.

INTRODUCTION

The treatment landscape for multiple myeloma (MM) is rapidly changing. Based on an extensive review of the recent literature, we propose an update of our recommendations on myeloma care for transplant-eligible patients in first-line therapy.[1] Levels of evidence and grades of recommendations are based on previously published methods.[2] We recommend participation in clinical trials to gain knowledge in the fast evolving field of MM treatment.

INITIAL THERAPY IN SYMPTOMATIC MULTIPLE MYELOMA

Treatment has to be initiated in all patients with a diagnosis of MM as defined by the IMWG 2014 criteria.[3] The recommended investigations to be performed at diagnosis are reported elsewhere in this issue (*Fostier et al*). All patients should undergo risk stratification using ISS and cytogenetic evaluation (FISH), even if risk-adapted therapy is not available in most cases at the moment. The goal of therapy in MM is to achieve the maximal response since MRD negativity is associated with better long-term outcome.[4]

Autologous stem cell transplantation (ASCT) remains the standard of care for fit, newly diagnosed MM (NDMM) patients, although remarkable results have been obtained in the non-transplant setting with novel agents.[5,6] Selection criteria for high-dose therapy (HDT) include age, performance status and comorbidities. As there is no definite age cut-off in the context of transplantation, specific risk-assessment models can be used to better evaluate the risk-benefit ratio of the procedure for each patient.[7,8]

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THERAPY FOR TRANSPLANT-ELIGIBLE PATIENTS

The current treatment paradigm for NDMM patient eligible for ASCT consists of 4 phases: induction, transplantation, post-transplant consolidation and maintenance.

INDUCTION

Induction therapy usually consists of 4-6 cycles of therapy with the aim to achieve rapid disease control, improve symptoms and allow for subsequent stem cell collection.

Bortezomib-dexamethasone (VD) is the standard backbone of induction therapy.[9,10] The addition of a **third agent**, thalidomide (VTD)[11], cyclophosphamide (VCD)[12], doxorubicine (PAD)[13] or lenalidomide (VRD)[14] provides higher response rates. In prospective trials, induction with **VTD** is superior to VCD in terms of response rate, at the cost of a higher incidence of peripheral polyneuropathy (PN) but lower incidence of haematological toxicities. Of note, progression-free (PFS) and overall survival (OS) were not assessed in this study.[15] To reduce the PN incidence, the IFM proposed the **vtD** regimen with reduced doses of bortezomib and thalidomide, which is associated with a lower incidence grade 3/4 PN (14% *vs.* 34%), but at the expense of lower response rates.[16] **VCD** was also shown to be as effective as PAD in terms of response, but less toxic.[17] Replacement of thalidomide by lenalidomide in the **VRD** regimen induces higher CR rates before and after ASCT (47% and 88% of patients with a very good partial response [VGPR] or better, respectively).[14] Current regimens used in front-line are listed in *Table 1*. Other highly effective combinations such as carfilzomib-lenalidomide-dexamethasone (KRd) or ixazomib-lenalidomide-dexamethasone (IRd) are currently under evaluation in phase 3 trials.

Four-drug regimens combining cyclophosphamide with VRD or KTD do not provide substantial advantage over 3-drug combinations, due to a higher incidence of adverse events.[18,19] However, the introduction of monoclonal antibodies will change the landscape of induction therapy in the near future. Ongoing prospective trials combining daratumumab with VTD (Cassiopeia) or VRD (Perseus), or elotuzumab with VRD are exploring the role of induction with antibody-based quadruplets.

Besides expected efficacy of the regimen chosen for induction, it is also important to take into account its expected toxicity. Patients should be evaluated for risks of infection, PN and thromboembolic disease. Vaccination and bisphosphonate therapy should be systematically recommended.

STEM CELL COLLECTION

Peripheral blood progenitor cells are usually collected for more than one ASCT (at least 2.5 x10^6 CD34+ cells/kg per transplantation). Since the use of lenalidomide can impair stem cell collection, apheresis in this situation should be performed after 3-4 cycles, and may require the use of cyclophosphamide or plerixafor.

HDM-ASCT

High-dose melphalan (melphalan 200 mg/m^2, MEL200) remains the standard conditioning regimen prior to ASCT. A dose reduction (100 to 140 mg/m^2) is recommended in case of renal impairment (estimated GFR <60ml/min). In this group of patients, including those requiring dialysis, ASCT is feasible but exposes the patient to severe mucositis, prolonged hospitalisation and an increased risk of transplant-related mortality (4% *vs.* <1%).[20]

Despite encouraging results from phase 2 studies, the addition of bortezomib (1 mg/m^2 on days -6, -3, +1, +4) to HDM fails to show any additional benefit in a prospective randomised trial.[21,22]

UPFRONT OR DELAYED ASCT

Based on the efficacy and safety profile of novel agents in the non-transplant setting, the question to delay ASCT at the time of first relapse has been raised in 2 phase 3 trials. In the IFM 2009 trial, VRD induction plus ASCT was associated with a significantly longer PFS than VRD alone (50 *vs.* 36 months), without an effect on OS.[14] ASCT could not be performed in 21% of the patients in the VRD arm, mainly because of disease refractoriness at relapse. In the EMN02-HOVON95 trial, upfront ASCT resulted in a significantly longer PFS compared with non-transplant (not reached *vs.* 46 months) but in the setting of PI-based induction (VCD) and consolidation (VMP). There was no impact on OS (immature follow-up), except in high-risk patients defined by the presence of del(17p) and/or t(4;14) and/or t(14;16) or a stage III R-ISS).[23]

A second, Italian phase 3 trial confirmed a significant PFS advantage with upfront ASCT compared to conventional treatment with cyclophosphamide-lenalidomide-dexamethasone (43.3 *vs.* 28.6 months).[24] In the absence of an OS benefit, the decision to proceed to ASCT upfront can be evaluated in perspective of patient preferences or risk of toxic effects, particularly in case of co-morbidities. In the near future, these decisions will probably be guided by the MRD status achieved after induction therapy, although this needs to be explored prospectively.

POST-TRANSPLANT STRATEGIES

The concept of consolidation and/or maintenance is a commonly adopted approach after transplantation. The objective

TABLE 1. Currently used first-line regimens in transplant-eligible newly-diagnosed MM.

Front-line regimens	Schedule	≥PR	≥VGPR	Median PFS	3-year OS rate
VTD [11]	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%
vTD [16]	Bortezomib: 1 mg/m² 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%	26 months	NA
VCD [12]	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
PAD [13]	Bortezomib: 1.3 mg/m² sq days 1, 8, 15, 22 Adriamycine: 9 mg/m² days 1-4 Dexamethasone: 40 mg orally days 1-4,9-12,17-20 28-day cycles	90%	42%	35 months	61%
VRD [14]	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, 49%	50 months	81% at 4 years

A: doxorubicin; C: cyclophosphamide; D: dexamethasone; 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

of such an approach is to improve the depth of response (consolidation) and extend the duration of response (maintenance) to ultimately prolong the PFS and eventually also the OS. Consolidation relates to the administration of a short-term intensive therapy aimed at improving the quality of response after transplant. Maintenance, on the other hand, consists of the administration of a therapy for a prolonged period in order to maintain the response achieved after ASCT and prevent progression.

Consolidation with second ASCT

Before the era of novel agents, the main approach was to propose a second ASCT. However, tandem ASCT did not provide any OS or PFS advantage, except in patients not achieving VGPR after the first transplant.[25,26] With the introduction of novel agents, this concept has been revisited. With tandem ASCT, the HOVON-65/GMMG-HD4 trial showed a benefit in OS, particularly in patients with a del(17p),[27] when using bortezomib in induction and maintenance, but the study was not powered for a comparison between single and double ASCT.[13] The EMN02/H095 trial compared single *vs.* tandem ASCT, the second transplant being conducted according to the transplant policy of each centre. Tandem ASCT was associated with a significant improvement in PFS and OS (3 year PFS rate: 73% *vs.* 64%; 3 year OS rate: 89% *vs.* 81%), with a more pronounced benefit in patients with high-risk cytogenetics (3 year PFS: 69% *vs.* 44%). Double transplant emerged as an independent prognostic factor predicting PFS.[28] Contradictory results were reported by the StaMINA trial in which a second ASCT offered no PFS or OS advantage over single ASCT in the context of lenalidomide maintenance.[29] Nevertheless, tandem ASCT with HDM as conditioning can currently be recommended for transplant-eligible patients with high-risk cytogenetic features at diagnosis.

Consolidation with new drugs

Initially, bortezomib or VT(D) consolidation were shown to increase the quality of response by 30% and were considered at least in patients who failed to achieve a VGPR or a complete

TABLE 2. Selected maintenance regimens used after ASCT.

Maintenance	Schedule	PFS/EFS	OS	Discontinuation and SE
IFM 2005-02 R consolidation 2 cycles, then R maintenance *vs.* placebo[38]	R, 10-15mg, 21/28 d until progression (stopped after 2y)	PFS, 41m *vs.* 23m 5y-PFS2, 60%	5y-OS, 68% *vs.* 67%	21% 2.4x higher risk of SPM
CALGB R maintenance *vs.* placebo[39]	R, 10-15mg, 21/28 d until progression	mTTP, 53m *vs.* 23m 3y-PFS, 66%	NR *vs.* 76m	12% 3x higher risk of SPM
MM XI R maintenance *vs.* placebo[41]	R, 10 mg 21/28 d until progression	mPFS, 60 m	3y-OS, 88% *vs.* 80%	-
HOVON VAD-ASCT-T *vs.* PAD-ASCT-V[13]	T, 50mg/d or V, 1.3mg/m2 qw, for 2 years	28m vs. 35m CR/nCR, 34% *vs.* 49%	5y-OS, 55% *vs.* 61%	5% *vs.* 3% at 5y

ASCT: autologous stem cell transplantation; CR: complete response; d: day; EFS: event-free survival; m: months; NA: not available; nCR: near complete response; NR: not reached; OS: overall survival; PAD: bortezomib, adriamycin, dexamethasone; PFS: progression-free survival; R: lenalidomide; SE: side effects; SPM: secondary primary malignancies; T: thalidomide; V: bortezomib; VAD: vincristine, adriamycin, dexamethasone

response (CR)/near CR (nCR) after ASCT.[9,30] Nowadays, the role of consolidation remains unclear. In the EMN02-HO95 trial, consolidation with VRD was associated with a significant prolongation of PFS compared to no consolidation,[28] while in the StaMINA-BMT CTN 0702 trial, no significant benefit in terms of PFS was demonstrated using either a second transplant or 3 cycles of VRD as consolidation.[29] Of note, both studies were different in terms of design, and the lack of OS benefit may be influenced by the follow-up as well as the maintenance given to all patients. Trials using either carfilzomib or ixazomib in this setting are currently ongoing. Overall, consolidation remains a reasonable practice in patients who failed to achieve a VGPR or nCR/CR after transplantation.

Maintenance

The positive role of **IMiDs** given in maintenance has been demonstrated in several phase 3 trials. Variable doses and duration of **thalidomide** significantly improved the quality of response and PFS (6 to 12 months) with a variable effect on OS,[31-37] except in patients with adverse cytogenetics where it has a negative impact on OS.[33] However, prolonged use of thalidomide is associated with adverse side effects like irreversible PN, which significantly impact the quality of life of patients. **Lenalidomide** is more suitable in this setting. Given daily in monotherapy at the dosage of 10-15 mg until progression, lenalidomide maintenance was associated with a doubling of the median PFS, compared to placebo or observation.[38,39] In a meta-analysis, it was also associated with an overall OS benefit of more than 2 years (median OS not reached with lenalidomide *vs.* 86 months with observation/placebo), leading to its approval in maintenance therapy of NDMM after ASCT. This OS benefit was less convincing in patients with high-risk cytogenetics or with ISS stage 3.[40] Conversely, continuous maintenance with lenalidomide given in the Myeloma XI trial was associated with an improved PFS, irrespective of cytogenetic risk.[41] The optimal duration of maintenance is still a matter of debate but an average duration of 2 years with a 3-week on/1-week off treatment schedule has become widely adopted. Concerns were raised about a potential rise in secondary primary malignancies (SPM), but this incidence was not subsequently increased after long-term follow-up.[42] As such, the OS benefit with lenalidomide maintenance largely outweigh the risk of developing a SPM. There is no evidence of increased mutational instability or significant toxicity with lenalidomide maintenance.[41]

Bortezomib maintenance has also been studied. Given at the dose of 1.3 mg/m^2 every other week for 2 years after a tandem ASCT, it was the first to demonstrate a survival advantage compared to thalidomide. However, in this trial the induction regimen was different in the 2 arms, the survival effect might be related to the use of bortezomib in the induction phase. Bortezomib was also able to overcome

TABLE 3. 2011 response assessment.[54]

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 analyzed by multiparametric flow cytometry (with > four colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5})
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
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.
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 pâtients 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.

ASCT: autologous stem cell transplantation; CR: complete response; d: day; EFS: event-free survival; m: months; NA: not available; nCR: near complete response; NR: not reached; OS: overall survival; PAD: bortezomib, adriamycin, dexamethasone; PFS: progression-free survival; R: lenalidomide; SE: side effects; SPM: secondary primary malignancies; T: thalidomide; V: bortezomib; VAD: vincristine, adriamycin, dexamethasone

TABLE 4. 2016 response assessment: MRD negativity criteria.[55]

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 disappearence 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

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

the adverse prognosis linked to the presence of a del(17p),[13] making it an interesting apprdoach for this subcategory. Trials incorporating ixazomib, pomalidomide, carfilzomib and monoclonal antibodies as maintenance are currently ongoing. Bortezomib and thalidomide are not approved as maintenance treatment post-ASCT. Selected maintenance regimens used in this setting are listed in *Table 2*.

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation (allo-SCT) remains a curative option for MM, but its role is still controversial due to a 10-20% treatment-related mortality (TRM), the risk of graft-versus-host disease (GvHD), even with reduced intensity conditioning (RIC), and the occurrence of long-term post-transplant relapses.[43,44] Consequently, there is no routine indication for allo-SCT in frontline therapy.

SPECIAL CONDITIONS

PLASMA CELL LEUKAEMIA

Plasma cell leukaemia (PCL) is the most aggressive form of PC dyscrasia, with a median OS of around 1 year. It is defined by the presence of PC 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 2.0×10^9 cells/l. Primary PCL (pPCL) refers to PCL detected *de novo* at diagnosis in patients with no prior history of MM, while secondary PCL (sPCL) arises in patients with a known history of MM. Primary PCL is associated with more immature or 'plasmablastic' PC clones, and more high-risk cytogenetic features.[45,46]

Upfront therapy should include a triplet regimen with novel agents (VRd or KRd). The IFM proposed as induction, 4 alternating cycles of PAD and VCD.[44] In patients with extensive disease burden or who are non-responsive to initial therapy, VTD-PACE or VRD-PACE should be considered since drugs such as doxorubicin and cyclophosphamide are particularly active in lymphoproliferative diseases. ASCT upfront, if possible in tandem, is recommended to achieve a deeper response and likely a longer disease control. Allo-SCT should not be considered except in the setting of a clinical trial, since this procedure has been associated with a higher relapse mortality compared with tandem ASCT.[48] Consolidation should be proposed in patients not achieving a CR, followed by maintenance with either bortezomib or lenalidomide.[49] In frail patients, induction with VCD or PAD can be used as a milder alternative, given for up to 8-10 cycles, followed by indefinite maintenance therapy to keep the disease under control.[49]

RENAL IMPAIRMENT

Renal failure (creatinine >2mg/dl) is seen in around 20% of NDMM patients at diagnosis. It requires prompt rehydration and treatment of precipitating events such as hypercalcaemia, acidosis, infection and discontinuation of nephrotoxic drugs. **Bortezomib** can safely be used without dose modification, even in patients under dialysis, and acts rapidly (responses in 0.7-1.6 months). It can be used in association with **dexamethasone** (40 mg, days 1-4) ± **thalidomide, doxorubicine or cyclophosphamide**.[50,51] Thalidomide does not require dose reduction, but may induce severe hyperkalemia, particularly in patients under dialysis. **Lenalidomide** requires appropriate dose reductions. **Bendamustine** can

RECOMMENDATIONS FOR UPFRONT THERAPY IN TRANSPLANT-ELIGIBLE NDMM

1 **Diagnosis and risk assessment:** Diagnosis of MM requires the fulfilment of the 2014 IMWG criteria (IV, C). All patients should undergo risk stratification using ISS (I, A) and cytogenetics (FISH)(II, B), even if risk-adapted therapy is not available in most cases at the moment.

2 **Goal of therapy:** The goal of therapy is to achieve CR, the most important surrogate marker of OS. However, in the elderly population, increased PFS is a worthwhile goal if QoL is maintained and can delay the onset of disease side effects.

3 **Indication for therapy:** Treatment should be considered in all patients with a diagnosis of symptomatic MM as defined by the IMWG 2014 criteria (IV, C). Treatment choice depends on patient's eligibility for ASCT based on biological age, performance status and co-morbidities (I, B). Objective risk-assessment scores can be used (I, B).

4 **Transplant-eligible NDMM patients:** Induction followed by HDM with ASCT remains the standard of care in patients in good clinical condition (I, A). Based on response rates, depth of response and PFS, 3-drug combination including at least bortezomib and dexamethasone are considered the standard of care before ASCT (I, A). VTD is superior to VCD but at the cost of more peripheral polyneuropathy (II, B). Three to four cycles are recommended before stem cell collection. Switching therapy is recommended in case of progressive disease (PD) after 2 cycles or less than partial response (PR) after 4 cycles. The role of consolidation remains not clear while maintenance has been proven to improve OS.

5 **Allo-SCT** is still considered investigational for MM. Because of the risk of severe TRM and GvHD, it should only be performed in patients with high-risk disease in good response, within clinical trials (IV, C).

6 **Plasma-cell leukaemia:** Upfront therapy should include a 3-drug bortezomib-based regimen (VCD, VTD, PAD, VRD or VDT-PACE) 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 (<50), in the setting of a clinical trial.

7 **Renal failure:** Renal failure requires prompt rehydration and treatment of precipitating events (IV, C). High-dose dexamethasone should be started immediately (IV, C). Bortezomib is safely used without dose modification, even in patients under dialysis (IV, C). Lenalidomide requires appropriate dose reductions (IV, C).

8 Physical methods to remove FLC from the blood should be performed within clinical trials (IV, C). ASCT can be proposed for patients with GFR <30ml/min, using melphalan 100-140mg/m2 (II, B).

Supportive care – Recommendations should follow the Belgian guidelines published in 2014.

be an option, particularly in combination with bortezomib and prednisone.[52]

Mechanical methods of removing FLC from the blood should only be considered within the context of a clinical trial. Plasma exchange is theoretically useful in cast nephropathy, but removes FLC only from the intravascular compartment (17% of total body FLC). Compared to conventional hemodialysis, use of extended high-cut off haemodialysis in combination with bortezomib-based chemotherapy does not offer any significant advantage in terms of haemodialysis independence at 3 months.[53]

RESPONSE ASSESSMENT AND FOLLOW-UP

Responses to therapy should be assessed using the 2011 IMWG response criteria (*Table 3*), updated in 2016 (*Table 4*).[54,55] The M-protein level should be evaluated by serum and urine protein electrophoresis every month while on therapy, and every 3-4 months when off-therapy. The FLC assay is used to monitor patients who lack a measurable M-protein, particularly in oligo- or non-secretory and light-chain MM, provided the FLC ratio is abnormal and the involved FLC level is ≥100mg/l.

TABLE 5.	
Drugs	Terms of reimbursement in first-line for transplant-eligible NDMM patients
Velcade	Reimbursed for induction (6 cycles)
Carfilzomib	No access
Ixazomib	No access
Thalidomide	Reimbursed
Lenalidomide	Reimbursed as maintenance therapy
Bendamustine	No access
Daratumumab	No access
Elotuzumab	No access

SUPPORTIVE CARE

Recommendations on supportive care, already described in the previous update, have been updated in this special issue of the BJH (*Meuleman et al*).

BELGIAN ACCESS TO DRUGS – REIMBURSEMENT

In *Table 5*, the reimbursement criteria for the different drugs discussed above are listed.

CONCLUSIONS

The changes in the treatment paradigm of MM patients in the last 2 decades dramatically improved survival, with most patients expecting a long-term disease control. In the era of novel agents, ASCT remains the standard of care for NDMM eligible for transplant. In the near future, new classes of drugs (such as monoclonal antibodies) and second-generation PIs and IMiDs will probably move to the upfront setting, and clinical research will also focus on quality of life, optimal sequencing of therapy, appropriate tools for patients selection, optimal strategies for high-risk diseases and costs of prolonged novel-agents strategies.

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