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Optimizing current and emerging therapies in multiple myeloma: a guide for the hematologist

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Abstract: Multiple myeloma (MM) is the second most common hematologic malignancy. The diagnosis of MM requires ⩾10% clonal plasma cells in the bone marrow or biopsy-proven plasmacytoma, plus evidence of end-organ damage (hypercalcemia, renal failure, anemia, and lytic bone lesions). The definition of MM has recently been expanded to include a ⩾60% clonal plasma cell burden in the bone marrow, serum involved/uninvolved light chain ratio of ⩾100, or more than one focal lesion on magnetic resonance imaging ⩾5 mm in the absence of end-organ damage. MM is an incurable malignancy previously associated with poor survival rates. However, over the past two decades, the introduction of novel treatment options has resulted in a dramatic improvement in response rates and overall survival (OS). The combination of a proteasome inhibitor and an immunomodulator (IMiD) is the preferred induction treatment for newly diagnosed transplant-eligible MM patients. After induction, high-dose therapy with autologous stem cell transplant (ASCT) is still the standard of care for these patients. In patients who are transplant ineligible, dose adjusted IMiDs or proteasome inhibitor-based combinations are the preferred treatment option. With the recent approval of novel drugs like carfilzomib, ixazomib, pomalidomide, panobinostat, and monoclonal antibodies (elotuzumab and daratumumab), as well as improved understanding of risk stratification, management of comorbidities and treatment side effects, clinicians can optimize anti-MM therapy, particularly in relapse/refractory MM patients. In this review, we outline the current therapeutic approach to the management of MM.

Keywords: immunomodulator, multiple myeloma, novel treatment options, proteasome inhibitor

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Introduction

Approximately 86,000 new cases of multiple myeloma (MM) occur per year globally [Moreau *et al.* 2015a], constituting about 13% of hematological cancers and 1% of all cancers [Howlader *et al.* 2012].

In the past, MM was only defined as an accumulation of 10% clonal plasma cells in the bone marrow, resulting in end-organ damage as manifested by CRAB criteria (hypercalcemia, renal insufficiency, anemia, or bone lesions). The international myeloma working group (IMWG) has revised the definition of MM to include either ⩾60% clonal plasma cells in the bone marrow, serum involved/uninvolved light chain ratio of 100 or greater, or more than one focal lesion on magnetic resonance imaging of ⩾5 mm in the absence of CRAB criteria.

Melphalan-prednisone was introduced 50 years ago and remained the standard of care for more than 30 years. It induced a partial response (PR) in 40–60% of patients and led to a progression-free survival (PFS) of 18 months [San Miguel, 2015].

The combination of autologous stem cell transplant (ASCT) with novel agents such as immunomodulators (IMiDs), proteasome inhibitors, and monoclonal antibodies have resulted in improved PFS, overall survival (OS) and quality

of life (QoL). Therefore, the goal of MM treatment has now shifted toward achieving durable responses, long-term disease control and improved survival with the potential for cure [Munshi and Anderson, 2013]. In this review, we will provide a guide to the hematologist in order to optimize treatment regimens that are effective in the management of MM patients

Upfront treatment of transplant-eligible MM patients

The treatment algorithm for newly diagnosed MM (NDMM) has evolved over the last two decades with the incorporation of novel agents into myeloma induction regimens prior to ASCT. As reviewed below, numerous upfront regimens have evolved for the treatment of NDMM prior to ASCT. An induction regimen is administered for 2–4 months to achieve deeper response rates, although the optimal duration of induction treatment is not well established [Sonneveld *et al.* 2015] (Table 1).

The combination of bortezomib, lenalidomide, and dexamethasone (VRd) is one of the preferred frontline treatment options due to its tolerability and efficacy in prospective trials. In a single arm phase I/II study, VRd showed a PR rate of up to 100% [Jasielec and Jakubowiak, 2013]. A randomized phase III trial, SWOG S0777, compared six 28-day cycles of VRd *versus* eight 21-day cycles of lenalidomide and low-dose dexamethasone (Rd) in both transplant-eligible and transplant-ineligible NDMM patients [Durie, 2015]. Patients who received VRd had a significantly improved PFS (43 months *versus* 31 months) than Rd alone ($p = 0.0018$). OS was also improved in the VRd arm (75 months *versus* 64 months) compared with the Rd arm ($p = 0.025$).

Another triplet combination, bortezomib, cyclophosphamide, and dexamethasone (VCd or CyBorD), which is administered in a 28-day cycle, produces a rapid and deep response in patients with NDMM, and it has a tolerable side effect profile [Reeder *et al.* 2009]. For this reason, VCd is also a reasonable option, particularly for patients with poor renal clearance (CrCl $<$ 30). In the phase II EVOLUTION trial, NDMM patients were randomly assigned to receive induction treatment with VRd, VCd, CyBorD (mod-VCd) or VdCR (bortezomib, dexamethasone, cyclophosphamide and lenalidomide) [Kumar *et al.* 2012]. After an interim analysis, the protocol was amended to change the VCd regimen to include an additional dose of cyclophosphamide (CyBorD). Following four cycles of therapy, the overall response rates (ORRs) were 73%, 63%, 82%, and 80% in patients who received VRd, VCd, CyBorD and VdCR, respectively. The study found no substantial advantage of a four drug regimen (VdCR) over a three drug regimen (VRd, VCd, or CyBorD).

Bortezomib, thalidomide, and dexamethasone (VTd) is another triplet combination that has demonstrated high pre- and post-transplant complete response (CR) rates, as well as significantly longer PFS compared with thalidomide and dexamethasone (Td) [Cavo *et al.* 2012]. The Intergroupe Francophone du Myelome (IFM) conducted a randomized trial comparing bortezomib and dexamethasone (Vd) with VTd as induction therapy before ASCT [Moreau *et al.* 2011a]. The CR and very good partial response (VGPR) rate was significantly higher in the VTd arm (49% *versus* 36%, $p = 0.05$).

The prospective randomized trial IFM 2013-04, compared four cycles of VTd with VCd as induction treatment before ASCT. After four cycles, 66.3% in the VTd arm had a VGPR and 56.2% in the VCd arm had a VGPR ($p = 0.05$). The per-protocol analysis showed that VTd was superior to VCd. The ORR was 92.3% in the VTd arm *versus* 83.4% in the VCd arm ($p = 0.01$) [Moreau *et al.* 2015b]. Hematologic toxicities (anemia and thrombocytopenia) were more frequently seen with VCd and peripheral neuropathy with VTd. Based on these results, clinicians can consider using the VTd regimen as induction treatment prior to ASCT.

In another large, phase III trial transplant-eligible NDMM patients were randomized to receive upfront doxorubicin and Dexamethasone with either vincristine (VAD) or bortezomib (PAD) [Sonneveld *et al.* 2015]. Following high-dose melphalan and ASCT, VAD patients received thalidomide maintenance and PAD patients were continued on bortezomib. The median PFS was significantly better in the PAD arm (35 months *versus* 28 months) compared with VAD ($p = 0.002$). Initial results also showed that bortezomib improved PFS and OS in patients with del (17p) (PAD *versus* VAD: 22 *versus* 12 months, $p = 0.01$). Based on these data VAD is not recommended for the treatment of NDMM.

Carfilzomib, a second generation proteasome inhibitor that is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of relapsed and refractory myeloma, has emerged as an additional initial therapeutic option for NDMM patients [Jasielec and Jakubowiak, 2013]. A phase I/II study evaluating the combination of carfilzomib, lenalidomide, and low-dose dexamethasone (KRd) for upfront treatment of MM in both transplant-eligible and transplant-ineligible patients found that 62% of patients achieved at least a near-complete response (nCR) and 42% a stringent complete response (sCR) after 12 cycles [Jakubowiak *et al.* 2012].

In summary, triplet regimens such as VTd, VRd, VCd or CyBorD are recommended as upfront treatments of MM before ASCT owing to their good tolerability and consistently high response rates.

ASCT, consolidation and maintenance treatment

In the era of novel combination regimens, the role of ASCT has been questioned. Most studies to date support the finding that early ASCT improves the depth of response and PFS, but not OS [Mohty and Harousseau, 2014]. ASCT can be done immediately following induction therapy (e.g. four cycles) or can be delayed until first relapse. In either case, stem cells must be collected early in the disease course to avoid collection failure after prolonged lenalidomide exposure. Melphalan at a dose of 200 mg/m^2 is used as the standard conditioning regimen, but in the setting of renal insufficiency (CrCl $<$ 60) the melphalan dose should be reduced to 140 mg/m^2 [Abidi *et al.* 2012]. A large phase III IFM/DFCI (Dana-Farber Cancer Institute) 2009 study has recently demonstrated an increased PFS in patients who received early ASCT after VRd induction compared with delayed ASCT [Attal *et al.* 2015]. Another study demonstrated that tandem ASCT benefits patients whose disease fails to achieve CR or VGPR with the first transplant [Byrne *et al.* 2014]. A randomized phase III study, the HOVON trial, also found an improved PFS with upfront ASCT, as well as a 24% decreased risk of progression [Cavo *et al.* 2016]. In summary, clinicians should consider ASCT after four cycles of induction therapy in medically fit patients.

Consolidation and maintenance therapy after ASCT

Consolidation therapy is aimed at increasing the depth of response following ASCT. While the role of consolidation treatment has not been thoroughly explored, there is evidence that a higher CR rate can be obtained with additional therapy. It usually consists of a limited number of treatment cycles, either in combination therapy or with a second transplant. The Italian Myeloma Group conducted a pivotal trial comparing VTd with Td for induction, followed by double ASCT and VTd *versus* Td consolidation [Galli *et al.* 2013]. The median PFS was 50 months for patients receiving VTd consolidation *versus* 38 months for patients treated with Td (p = 0.015). Another study showed an increased sCR from 27% to 40%, after two consolidation cycles of VRd following three VRd induction cycles and ASCT, highlighting that consolidation improves the depth of response [Roussel *et al.* 2014].

Maintenance therapy refers to the administration of agents with low toxicity in an attempt to prevent progression of disease [Mohty *et al.* 2015]. It is given for a prolonged period of time, typically for at least 12 months, but often up to 2–3 years or until disease relapse. Thalidomide maintenance therapy has been investigated in a number of studies and has shown to prolong time to progression (TTP), PFS, and event-free survival as well as OS [Barlogie *et al.* 2010]. Unfortunately, thalidomide is poorly tolerated [Barlogie *et al.* 2006, 2008] and patients with poor risk cytogenetics do not appear to benefit [Attal *et al.* 2006; Morgan *et al.* 2012]. The post-transplant use of lenalidomide in three large randomized trials, compared with no maintenance therapy, illustrated a significant improvement in PFS, as well as a 3-year OS benefit (88 *versus* 80%) in one study [McCarthy *et al.* 2012, 2013; Palumbo, 2014]. Unfortunately, a higher risk of secondary malignancies was reported in the lenalidomide arms, with an incidence of approximately 7–8% at 3 years. As discussed above, in a phase III study, maintenance bortezomib in the PAD arm was also well tolerated. Patients randomized to PAD arm followed by ASCT who are then administered bortezomib maintenance for 2 years have shown improved OS compared with those who received VAD followed by thalidomide maintenance (49% *versus* 34%) [Scheid *et al.* 2013; Sonneveld *et al.* 2015].

In summary, both consolidation and maintenance therapies improve the depth of response after induction treatment and ASCT. The role of thalidomide as maintenance treatment is limited due to its poor tolerability and side effects, especially neuropathy. Lenalidomide maintenance is best supported by phase III trial evidence, although the duration of therapy needs to be clarified and there are concerns of an increased risk of second primary malignancies. Bortezomib maintenance, administered twice monthly after ASCT, has shown benefit and may be considered for patients with high- or intermediate-risk cytogenetics. However, several questions remain unanswered including the toxicity, QoL considerations, duration of treatment, minimal residual disease (MRD) assessment and its impact on OS. Table 1 describes list of induction regimens in transplant eligible MM.

Upfront treatment of transplant-ineligible MM patients

Over two-thirds of NDMM patients are over the age of 65 years [Siegel *et al.* 2014]. For older patients or those with medical comorbidities not amenable to ASCT, the goals of treatment are to prolong survival and improve QoL. Similar to transplant-eligible patients, the use of novel agents in different combination regimens have been associated with a higher ORR compared with previous standard treatments. Table 2 describes the firstline treatment in NDMM transplant-ineligible patients.

In Europe, melphalan, prednisone, and thalidomide (MPT) and bortezomib, melphalan, and prednisone (VMP) are considered standard of care for MM patients >65 years of age or those not eligible for ASCT. A randomized trial comparing MPT with melphalan and prednisone (MP) showed a significantly better OS (51.6 months) for MPT compared with MP (33.2 months) after a median follow up of 51.5 months [Facon *et al.* 2007]. However, MPT is associated with higher rates of grade 3 and grade 4 toxicities, including neutropenia and peripheral neuropathy. A meta-analysis comparing MPT with MP found a significant benefit to OS from adding thalidomide to MP ($p = 0.004$) [Fayers *et al.* 2011]. Similarly, the phase III VISTA trial has shown a significant OS survival benefit (13.3 months) with the addition of bortezomib to the MP regimen (MPR). However, VMP was associated with higher rates of peripheral neuropathy (14%) and gastrointestinal disturbances (19%) [Mateos *et al.* 2010].

Two large phase III trials demonstrated superior outcomes with lenalidomide-containing regimens in elderly patients with NDMM compared with standard melphalan-based therapies. The MM-015 trial incorporated lenalidomide into MPR followed by lenalidomide maintenance (MPR-R). This approach has significantly prolonged PFS (31 months) compared with MP (13 months, $p < 0.001$) or MPR without maintenance (14 months, $p < 0.001$) [Palumbo *et al.* 2012a]. In a randomized phase III trial, MPT followed by thalidomide maintenance and MPR followed by maintenance lenalidomide have shown similar efficacy in both arms. However, neuropathy is more common with MPT and myelosuppression with MPR [Zweegman *et al.* 2016].

The FIRST trial, a large phase III randomized trial, established that lenalidomide plus low-dose dexamethasone (Rd) administered until disease progression was also associated with a significant improvement in PFS (25.5 months) when compared with MPT (21.2 months) or Rd (20.7 months) for a fixed period of 18 months [Benboubker *et al.* 2014]. The safety profile of continuous Rd was manageable, and the incidence of second primary cancers was low across treatment groups. In contrast with young patients, the triplet lenalidomide-based regimens did not induce any advantage over doublet lenalidomide-based regimens in elderly myeloma patients [Magarotto *et al.* 2016].

Recently, the KRd regimen has shown an impressive response rate in NDMM patients, including elderly patients [Jakubowiak, 2014]. With a median follow up of 25 months, the ORR was 98% with a CR rate of 64%. At 2 years, the estimated PFS was 94% and OS was 98% [Mateos *et al.* 2010]. Other carfilzomib-based combinations, including carfilzomib plus MP (KMP) [Kolb *et al.* 2012], carfilzomib plus cyclophosphamide and dexamethasone (KCd) [Palumbo *et al.* 2012b], and carfilzomib plus bendamustine and dexamethasone [ClinicalTrials.gov identifier: NCT02002598] are active in transplant-ineligible patients based on early results from single arm phase I/II studies.

Ixazomib, an oral proteasome inhibitor, has shown promising results in combination with Rd. In a randomized trial of transplant-ineligible NDMM patients, weekly ixazomib in combination with Rd induced PR in 96% of patients with

Table 1. Induction treatment in newly diagnosed transplant-eligible multiple myeloma.

Study by induction regimen	Treatment schema	Number of patients	Post-induction (%)		Post-transplant (%)		Long-term outcomes (%)
			ORR	CR /VGPR	ORR	CR /VGPR	
GIMEMA Cavo *et al.* [2012]							
VTd	VTd × 3-ASCT Mel200 × 2-VTd × 2-D_m	236	93	19 CR 62 ⩾ VGPR	93	42 CR 82 ⩾ VGPR	3-year PFS: 68 3-year OS: 86
versus							
Td	Td × 3-ASCT Mel200 × 2-Td × 2-D_m	238	79	5 CR 28 ⩾ VGPR	84	30 CR 64 ⩾ VGPR	3-year PFS: 56 3-year OS: 84
IFM Moreau *et al.* [2011a]							
Vd	Vd × 3-ASCT Mel200	99	81	36 ⩾ VGPR	86	58 ⩾ VGPR	Median PFS: 30 months
versus							
VTd	VTd × 3-ASCT Mel200	100	88	49 ⩾ VGPR	89	74 ⩾ VGPR	Median PFS: 26 months
SWOG S0777 Durie *et al.* [2015]							
VRd	VRd × 8-Rd_m	242	82	CR 16	NA	NA	Median PFS: 43 months Median OS: 75 months
versus							
Rd	Rd × 6-Rd_m	232	72	CR 8	NA	NA	Median PFS: 30 months Median OS: 64 months
Reeder *et al.* [2009]							
VCd (CyBorD)	VCd × 4-ASCT Mel200	33	88	39 CR/nCR 61 ⩾ VGPR	NR	70 CR/nCR 74 ⩾ VGPR	NR
HOVON-65/GMMG-HD4 Sonneveld [2015]							
VAD	VAd × 3-VAD × 3-ASCT Mel200-T_m × 2 year	414	54	2 CR 14 ⩾ VGPR	75	9 CR 36 ⩾ VGPR	Median PFS: 28 months 5-year OS: 55
versus							
PAD	PAd × 3-PAD × 3-ASCT Mel200-V_m × 2 year	413	78	7 CR 42 ⩾ VGPR	88	21 CR 62 ⩾ VGPR	Median PFS: 35 months 5-year OS: 61
EVOLUTION Kumar *et al.* [2012]							
VRd	VRd × 4-ASCT Mel200 *versus* VRd × 4-V_mx4	42	73	7 CR 32 ⩾ VGPR	NR	NR	1-year PFS: 83 1-year OS: 100
versus							
VCd	VCd × 4-ASCT Mel200 *versus* VCd × 4-V_mx4	33	63	3 CR 13 ⩾ VGPR	NR	NR	1-year PFS: 93 1-year OS: 100

(Continued)

Table 1. (Continued)

Study by induction regimen	Treatment schema	Number of patients	Post-induction (%)		Post-transplant (%)		Long-term outcomes (%)
			ORR	CR /VGPR	ORR	CR /VGPR	
versus							
VdCR	VdCR × 4-ASCT Mel200 *versus* VdCR × 4-V_m × 4-R_m (off protocol)	48	80	5 CR 33 ⩾ VGPR	NR	NR	1-year PFS: 86 1-year OS: 92
versus							
VCd-mod	VCd-mod × 4-ASCT Mel200 *versus* VCd-mod × 4-V_m × 4	17	82	12 CR 41 ⩾ VGPR	NR	NR	1-year PFS: 100 1-year OS: 100
IFM 2013-14 Moreau *et al.* [2015b]							
VTd	VTd × 4-ASCT	170	92	11 CR 67 ⩾ VGPR	NR	NR	NR
versus							
VCd	VCd × 4-ASCT	170	84	9.5 CR 56 ⩾ VGPR	NR	NR	NR

ASCT, autologous stem cell transplant; CR, complete response; D_m, dexamethasone maintenance; NA, not applicable; NR, not reported; ORR, overall response rate; OS, overall survival; PAd, bortezomib-doxorubicin-dexamethasone; PFS, progression-free survival; Rd_m, lenalidomide-dexamethasone maintenance; Td, thalidomide-dexamethasone; T_m, thalidomide maintenance; VAd, vincristine-doxorubicin-dexamethasone; VCd, bortezomib-cyclophosphamide-dexamethasone; Vd, bortezomib-dexamethasone; VdCR, bortezomib-cyclophosphamide-dexamethasone-lenalidomide; VGPR, very good partial response; V_m, bortezomib maintenance; VRd, bortezomib-lenalidomide-dexamethasone; VTd, bortezomib-thalidomide-dexamethasone.

good tolerability [Mateos *et al.* 2010]. Dimopoulos and colleagues studied ixazomib in combination with cyclophosphamide and dexamethasone (ICd) in an open-label, multicenter phase II trial of NDMM transplant-ineligible MM patients [Dimopoulos *et al.* 2015a]. The regimen is very effective and the median PFS and TTP were not yet reached. Table 2 describes list of regimens in newly diagnosed transplant ineligible MM.

In summary, NDMM transplant-ineligible patients were previously treated with only alkylating agents and fixed-duration of therapy. But Rd as continuous therapy has demonstrated superiority over MPT and has likely become a new standard of care in elderly patients. However, a melphalan-based combination is still a viable option in these patients. Dose adjusted triplets (VRd) can be considered in high risk cytogenetics. The roles of ixazomib or carfilzomib-based combinations are under further investigation in clinical trials. Figure 1 describes the guideline for the management of MM.

Treatment of relapse and refractory multiple myeloma patients

Treatment of relapsed/refractory multiple myeloma (RRMM) presents a special therapeutic challenge. The IMWG has divided RRMM into four categories: primary refractory, refractory or relapsed, relapsed and refractory or double refractory MM.

Relapsed and refractory myeloma is defined as progression of therapy in patients who achieve minor response or better, or progression within 60 days of last therapy. Patients who progress while on therapy are considered as primary refractory [Nooka *et al.* 2015]. Unfortunately, there is no clear biological-based recommendation regarding the choice of salvage therapy at various points of disease progression [Rajkumar *et al.* 2011; Cornell and Kassim, 2016]. Treatment options include (1) salvage chemotherapy, (2) salvage ASCT, (3) allogeneic hematopoietic stem cell transplantation or (4) post-transplant consolidation/maintenance therapy.

Table 2. Upfront treatment in newly diagnosed transplant-ineligible MM.

Study by induction regimen	Treatment schema	Number of patients	Post induction (%)		Long-term outcomes (%)
			ORR	CR VGPR	
IFM 99-06 Facon *et al.* [2007]					
MPT	MPT ± T_m	774	42 to –76	NR	Median PFS: 14 to –28 month
versus					
MP	MP	848	28 to –48	NR	Median PFS: 10 to –19 month
VISTA Mateos *et al.* [2010]					
VMP	VMPxx9	344	71	30 CR	Median OS: NR 3-year OS: 68.5
versus					
MP	MPxx9	338	35	4 CR	Median OS: 43 months 3-year OS: 54
MM-015 Palumbo *et al.* [2012]					
MPR-R	MPRxx9-R_m	152	77	18 CR 33 ⩾ VGPR	Median PFS: 31 months 3-year median OS: 70
versus					
MPR	MPRxx9	153	67	13 CR 33 ⩾ VGPR	Median PFS: 14 months 3-year median OS: 62
versus					
MP	MPxx9	154	49	5 CR 12 ⩾ VGPR	Median PFS: 13 months 3-year median OS: 66
FIRST Benboubker *et al.* [2014]					
Continuous Rd	Rd until PD	535	75	15 CR 44 ⩾ VGPR	Median PFS: 2.5 months 3-year OS: 70 4-year OS: 59
versus					
Rd	Rdxx18	541	73	14 CR 43 ⩾ VGPR	Median PFS: 20.7 months 3-year OS: 66 4-year OS: 56
versus					
MPT	MPTxx12	547	62	9 CR 28 ⩾ VGPR	Median PFS: 21.2 months 3-year OS: 62 4-year OS: 51
Magarotto *et al.* [2016]					
MPR	MPRx9-R_m or Rd_m	217	71	23 ⩾ VGPR	Median PFS: 24 months 4-year OS: 65
versus					
CPR	CPRx9-R_m or Rd_m	220	68	20 ⩾ VGPR	Median PFS: 20 months 4-year OS: 68
versus					
Rd	Rdx9-R_m or Rd_m	217	74	31 ⩾ VGPR	Median PFS: 58 months

MPT, melphalan-prednisone-thalidomide; MP, melphalan-prednisone; VMP, bortezomib-melphalan-prednisone; MPR, melphalan-prednisone-lenalidomide; R_m, lenalidomide maintenance; Rd, lenalidomide-dexamethasone; CPR, cyclophosphamide-prednisone-lenalidomide; ORR, overall response rate; CR, complete response; VGPR, very good partial response; MM, multiple myeloma; NR, no reported; OS, overall survival; PFS, progression-free survival.

The MM-009/MM-010 phase III trials demonstrate superior PFS and OS in patients with RRMM receiving Rd compared with dexamethasone plus placebo [Dimopoulos *et al.* 2007]. The ORR was 61.0% in the Rd arm *versus* 19.9% in the placebo arm ($p < 0.001$). Pomalidomide is a third generation IMiD, which has shown significant responses in RRMM. In a randomized phase

III MM-003 study, pomalidomide has induced significantly longer PFS and OS in combination with low-dose dexamethasone (Pd) compared with high-dose dexamethasone (4.0 months *versus* 1.9 months, $p < 0.0001$) [San Miguel *et al.* 2013].

Bortezomib, and carfilzomib, are also active in patients with RRMM. In the APEX trial, patients treated with intravenous bortezomib had significantly higher rates of ORR, PFS and 1-year OS compared with high-dose dexamethasone [Richardson *et al.* 2005]. The MMY-3021 trial demonstrated that subcutaneous bortezomib was comparable in efficacy with intravenous bortezomib and resulted in significantly reduced peripheral neuropathy (38% *versus* 53%; $p = 0.04$) [Moreau *et al.* 2011b]. Carfilzomib as a single agent also achieved an ORR of 23.7% with a median duration of response of 7.8 months and median OS of 15.6 months [Siegel *et al.* 2012].

In the phase III ENDEAVOR trial, carfilzomib plus dexamethasone (Kd) was compared with bortezomib plus dexamethasone (Vd) in RRMM patients ($n = 929$) [Dimopoulos *et al.* 2015b]. Results from an interim analysis showed significantly longer PFS with the carfilzomib combination (Kd *versus* Vd: 18.7 *versus* 9.4 months, respectively; $p < 0.0001$). In the subgroup analysis, patients receiving Kd demonstrated improved PFS and ORR compared with those receiving Vd regardless of prior exposure to either lenalidomide or bortezomib [Moreau, 2015c].

The triplet combinations with proteasome inhibitor and IMiD are also very potent options in RRMM. In a single arm phase II study in patients with RRMM, VRd led to an ORR of 64%, a median PFS of 9.5 months, and an OS of 30 months [Richardson *et al.* 2014]. In this study, 6% of the patients had received prior bortezomib, thalidomide and lenalidomide therapy. KRd has also led to significantly improved outcome in patients with RRMM, with 31% decrease of risk of disease progression and improved median PFS by 8.7 months (26.3 months in KRd arm *versus* 17.6 months in the Rd arm) [Stewart *et al.* 2015]. Other regimens, such as KPd (carfilzomib, pomalidomide and dexamethasone) or CyPomD (cyclophosphamide, pomalidomide and dexamethasone) are also very effective in RRMM. [Martin *et al.* 2013]. Table 3 summarizes treatment regimens for RRMM.

Emerging therapies in RRMM

Ixazomib

Ixazomib, formerly known as MLN9708, is an oral proteasome inhibitor. As a single agent, ixazomib induces 34% ORR in patients with RRMM [Roy *et al.* 2013]. The US FDA recently approved ixazomib in combination with Rd (IRd) for the treatment of patients with MM who have received at least 1–3 prior therapies. The approval was based on the phase III TOURMALINE-MM1 study, a double-blind, placebo-controlled trial that examined Rd with or without ixazomib in RRMM. Median PFS improved from 14.7 months in Rd treated patients to 20.6 months in patients treated with IRd. The improvement in PFS was observed in subgroups including PI-exposed or IMiD-exposed patients and those with high risk cytogenetics. The addition of ixazomib to Rd slightly increased the incidence of gastrointestinal adverse events such as diarrhea, constipation, nausea and vomiting compared with Rd. However, any-grade peripheral neuropathy, peripheral edema, thromboembolism, and neutropenia were all similar between arms [Moreau *et al.* 2015d]. Clinicians should consider using IRd regimen in patients who had previously received 1–3 prior therapies.

Monoclonal antibodies

In late 2015, the US FDA approved two monoclonal antibodies in the US for use in patients with RRMM: elotuzumab, in combination with Rd, and daratumumab as a single agent. Use of monoclonal antibodies directly targeting MM cells is a profound change compared with earlier treatment approaches.

Elotuzumab. Elotuzumab, is a humanized monoclonal antibody specifically targeting cell surface 1 (CS1, also called SLAM7), a glycoprotein highly expressed on the surface of MM cells. Binding of elotuzumab leads to recruitment of natural killer cells and tumor cell death *via* antibody-dependent cellular cytotoxicity (ADCC) [Cornell and Kassim, 2016]. Although elotuzumab has no significant single agent activity, it has shown impressive results in an open-labeled, multicenter phase III ELOQUENT-2 trial comparing Rd with or without elotuzumab in patients with RRMM with 1–3 prior treatments [Lonial *et al.* 2015]. The study demonstrated that elotuzumab in combination with Rd improved PFS by approximately 4.5 months and sustained improvement in PFS benefit at 1, 2, and 3 years. With

Table 3. Treatment regiments for relapsed and refractory multiple myeloma.

Study by induction regimen	Treatment schema	Number of prior antimyeloma therapies	Number of patients	Overall response rate (%)	Long-term outcomes (%)
MM-09/MM-010 Dimopoulos *et al.* [2007]					
Rd	Rd until PD	⩾1	176	60	Median OS: 29.6 months
versus					
D	D until PD	⩾1	175	24	Median OS: 20.2 months
MM-003 San Miguel *et al.* [2013]					
Pd	Pd until PD	⩾2, with R and V	302	31	Median PFS: 4 months Median OS: 12.7 months
versus					
D	D until PD	⩾2, including with R and V	153	10	Media PFS: 1.9 months Median OS: 8.1 months
PX-171-003-A1 Siegel *et al.* [2012]					
Carfilzomib	Carfilzomib × 12	⩾1	257	23.7	Median PFS: 3.7 months Median OS: 15.6 months
ENDEAVOR Dimopoulos *et al.* [2015b]					
Kd	Kd until PD	1–3	464	77	Median PFS: 18.7 months
versus					
Vd	Vd until PD	1–3	465	63	Median PFS: 9.4 months
Richardson *et al.* 2014					
VRd	VRd × 8-VRd$_m$	1–3	64	64	Median PFS: 9.5 months Median OS: 30 months
ASPIRE Stewart *et al.* [2015]					
KRd	KRd until PD	1–3	396	87.1	Median PFS: 26.3 months 2-year OS: 73.3
versus					
Rd	Rd until PD	1–3	396	66.7	Median PFS: 17.6 months 2-year OS: 65
Martin *et al.* [2013]					
CyPD	CyPD until PD	R refractory	70	48.5	Median PFS: 6.4 months
TOURMALINE-MM1 Moreau *et al.* [2015d]					
IRd	IRd until PD	1–3	360	78.3	Median PFS: 20.6 months
versus					
Rd	Rd until PD	1–3	362	71.5	Median PFS: 14.7 months
ELOQUENT-2 Lonial *et al.* [2015]					
Elotuzumab + Rd	Elo + Rd until PD	1–3	321	79	Median PFS: 19.4 months 1-year PFS: 68 2-year PFS: 41 Median OS: 43.7
versus					
Rd	Rd until PD	1–3	325	66	Median PFS: 14.9 months 1-year PFS: 57 2-year PFS: 27 Median OS: 39.6 months

(Continued)

Table 3. (Continued)

Study by induction regimen	Treatment schema	Number of prior antimyeloma therapies	Number of patients	Overall response rate (%)	Long-term outcomes (%)
SIRIUS Lonial *et al.* [2016]					
Daratumumab	DARA until PD	⩾3, including PI and IMiD, or PI/IMiD double refractory	124	29.2	Median PFS: 3.7 months 1-year OS: 64.8 Median OS: 17.5 months
MMY1001 Chari *et al.* [2015]					
Daratumumab + Pd	DARA + Pd until PD	⩾2, including lenalidomide and bortezomib	77	58.5	NR
PANORAMA-1 San Miguel *et al.* [2013]					
Panobinostat + Vd	Panobinostat + Vd ×12	1–3	387	60.7	Median PFS: 12 months 2-year PFS: 20.6
versus					
Vd	Vd × 12	1–3	381	54.6	Median PFS: 8 months 2-year PFS: 8.4

Kd, carfilzomib-dexamethasone; CyPD, cyclophosphamide-pomalidomide-dexamethasone; D, dexamethasone; DARA, daratumumab; Elo, elotuzumab; IMiD, immunomodulator; IRd, ixazomib-lenalidomide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; OS, overall survival; PD, progression of disease; Pd, pomalidomide-dexamethasone; PI, proteasome inhibitor; PFS, progression-free survival; R, lenalidomide; Rd, lenalidomide-dexamethasone; V, bortezomib; Vd, bortezomib-dexamethasone; VRd, bortezomib-lenalidomide-dexamethasone; VRd_m, bortezomib-lenalidomide-dexamethasone maintenance.

extended follow up, median PFS was 19.4 months in the elotuzumab arm and 14.9 months in the Rd arm. The 3-year PFS was 26% *versus* 18%, translating into relative improvement of 44% [Dimopoulos, 2015c].

Daratumumab. Daratumumab is a humanized monoclonal antibody specific for CD38 [immunoglobulin (Ig)G_1, κ subclass] that targets tumor cells *via* ADCC, complement-dependent cytotoxicity, and phagocytosis. Daratumumab may also initiate CD38-mediated signal transduction leading to cell death. In preliminary studies, daratumumab has demonstrated promising activity in combination with Rd [Cornell and Kassim, 2016]. Daratumumab was recently approved by the US FDA as a single agent treatment for patients with RRMM who have failed >3 lines of treatment regimens, including patients refractory to IMiDs and proteasome inhibitors. The median duration of response was 7.4 months. Responses were also observed across all subgroups of age, number and types of lines of prior therapy, and presence or absence of extramedullary disease. Daratumumab at 16 mg/kg was associated with a 1-year OS of 64.8% (95% confidence interval: 51.2–75.5) and, at a subsequent cutoff, median OS of 17.5 months [Lonial *et al.* 2016].

Chari and colleagues, evaluated daratumumab in combination with Pd in heavily pretreated (⩾2 previous lines of therapy) patients with RRMM (n = 98) in an expansion cohort [Chari *et al.* 2015]. The ORR was 71% with a median time to first response of 1.2 months. After 6 months, 66% of patients still had an ongoing remission. No new or unexpected safety signals were detected with the addition of daratumumab to Pd. Based on these studies it is clear that daratumumab is an active treatment option for MM and is associated with relatively few adverse events except for infusion-related reactions, which typically occur during the first infusion and are quite manageable.

Panobinostat

Panobinostat is the first histone deacetylase (HDAC) inhibitor targeting epigenetic silencing of tumor suppressor genes in MM cells. It is approved

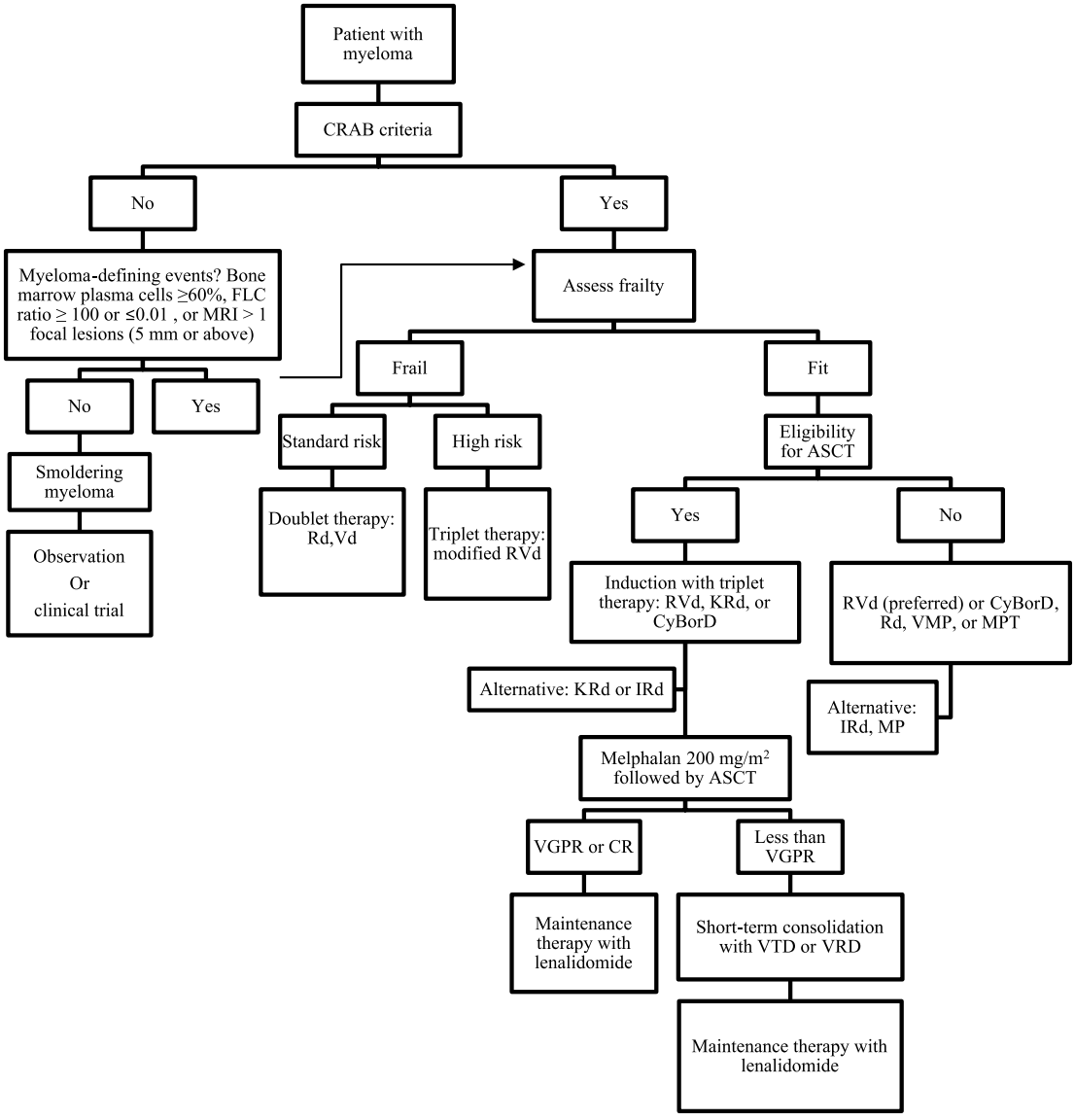

Figure 1. Guideline of treatment for newly diagnosed multiple myeloma.
Modified with permission from Lonial and Nooka [Lonial and Nooka, 2016].
ASCT, autologous stem cell transplant; CR, complete response; CyBorD, bortezomib, cyclophosphamide, and dexamethasone; FLC, free light chains; IRd, ixazomib-lenalidomide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; MP, melphalan and prednisone; MPT, melphalan, prednisone, and thalidomide; MRI, magnetic resonance imaging; Rd, lenalidomide-dexamethasone; RVd, lenalidomide, bortezomib, dexamethasone; Vd, bortezomib-dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib-lenalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

in combination with bortezomib for patients who received at least two prior treatment regimens, including bortezomib and an IMiD. Based on a phase III randomized study (PANORAMA-1), panobinostat has been approved in combination with bortezomib and dexamethasone (Vd) [Einsele *et al.* 2015]. However, the combination of panobinostat, bortezomib and dexamethasone increased the rates of grade 3 or 4 diarrhea to 25% from 8%. PANORAMA 2 demonstrated that the addition of panobinostat to bortezomib in bortezomib-refractory patients resulted in a ORR of 34.5% and PFS of 5.4 months with a median OS of 17.5 months [Chari, 2015]. Table 3 describes the treatment regimens of relapse and refractory MM.

Choice of treatments based on functional status assessment

Age is the main factor currently used to decide on the treatment in patients with MM. There is growing recognition that frailty, determined on the basis of comorbidities at diagnosis, is a better marker to determine treatment. Palumbo and colleagues utilized a geriatric assessment scale in NDMM at diagnosis to assess comorbidities, cognitive and physical conditions and identified three groups; fit (score = 0, 39%), intermediate-fitness (score = 1, 31%), and frail (score ⩾2, 30%) [Palumbo *et al.* 2015]. The 3-year OS was 84% in fit, 76% in intermediate-fit and 57% in frail patients, suggesting that the frailty score helps to predicts mortality and the risk of toxicity in elderly myeloma patients. Therefore, we recommend utilizing a frailty score before starting treatment. Regimens that are less toxic and improve responses, like Rd, may be more suitable in these patients [Benboubker *et al.* 2014; Lonial *et al.* 2016]. However, the approach should be individualized and clinicians should discuss the clinical data with their patients.

Role of MRD in MM

MRD assessment has gained importance in the evaluation of treatment responses in MM. Several cooperative groups using different MRD techniques indicate that persistence of MRD is an adverse prognostic feature, even among CR patients. Recently, Barlogie and colleagues showed that the vast majority of CR patients (94%) who are MRD negative achieved long-term survival (10 years relapse free) [Barlogie *et al.* 2014]. Thus, MRD could potentially be used as a biomarker to evaluate the efficacy of treatment at different stages (induction, transplantation, consolidation, or maintenance) and a decision tool as to when to stop maintenance [Paiva *et al.* 2015].

The most sensitive techniques, such as next generation flow cytometry and next generation sequencing, have the potential to achieve a detection sensitivity up to 1 in 10^6 cells with an improved quantifiable range [Biran *et al.* 2014]. However, there is a need for a standardized technique regarding MRD assessment. As such, the optimal MRD sample type (bone marrow aspirate *versus* peripheral blood) and method (flow cytometry *versus* molecular testing) are unresolved questions in MRD testing.

Recommendations

- Clinicians should consider the combination of a proteasome inhibitor and an IMiD such as VTd or VRd (in the USA) to treat NDMM transplant-eligible patients.
- ASCT is the standard of care for NDMM transplant-eligible patients.
- Clinicians should have an informed discussion with their patients regarding the role of maintenance therapy after ASCT.
- The optimal duration of maintenance treatment is unknown, but maintenance therapy should be given for at least 2 years or continued until disease progression.
- Patients who achieve less than a VGPR after ASCT should be considered for a second transplant or consolidation treatment with VRd or VTd.
- The choice of regimen in a transplant-ineligible NDMM patient should be based on patient risk factors, including frailty and clinical staging. Rd as continuous therapy has demonstrated superiority over MPT and can be offered to these patients as first-line treatment.
- The best sequence of treatment for RRMM is not known, but triplets are recommended in fit patients.
- Recently, MRD testing has been more frequently used to evaluate the efficacy of treatment regimens and outcome. However, MRD testing is not the standard of care and is recommended for clinical trials.
- Although the role of MRD negativity has not been completely established, patients with MRD negativity have a better outcome and MRD negativity might be used to define the lengths and intensity of treatment in the future.

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