Update on therapy of relapsed and refractory multiple myeloma

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SUMMARY

The prognosis for multiple myeloma patients has improved substantially over the past decade with the development of more effective chemotherapeutic agents and regimens that possess a high level of anti-tumour activity. However, nearly all multiple myeloma patients ultimately relapse, even those who experience a complete response to initial therapy. Management of relapsed disease remains a critical aspect of multiple myeloma care and an important area of ongoing research. This manuscript from the Belgian Haematology Society multiple myeloma subgroup provides some recommendations on the management of relapsed disease.
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INTRODUCTION

Despite the wide use of the novel agents bortezomib, thalidomide and lenalidomide, and the administration of high dose therapy (HDT) with autologous stem cell transplantation (ASCT), multiple myeloma (MM) remains incurable, with relapses occurring even in patients achieving prolonged and high quality duration of response with initial therapy, owing to development of drug resistance. To overcome this drug resistance, numerous therapeutic approaches have been developed, and include new-generation proteasome inhibitors such as carfilzomib and ixazomib, next-generation immunomodulatory drugs such as pomalidomide, and monoclonal antibodies. Management of relapsed MM remains challenging and requires a careful evaluation.

DEFINITION

Relapsed MM refers to a recurrence or a progression of the disease, defined as at least a 25% increase from baseline of the serum monoclonal protein (M-protein) (absolute increase ≥ 500 mg/dl), urine M-protein (absolute increase > 200mg/day), ≥ 25% difference between involved and uninvolved serum free light chain (FLC) level (absolute increase > 10mg/dl), or appearance of new bone lesions or plasmacytomas, or hypercalcemia, that cannot be attributed to other causes. In non-secretory

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TABLE 1. Definitions of relapsed and refractory multiple myeloma *(adapted from Rajkumar, Blood 2001).*

Primary refractory MM	Non responsive disease, in whom MR or better has never been achieved, with no significant change in M-protein level and no evidence of clinical progression
Refractory MM	Non responsive disease, while on primary or salvage therapy, or progressing withoin 60 days of last therapy
Relapsed MM	Previously responding disease, that progresses and requires initiation of salvage therapy, but does not meet criteria forveither primary refractory disease or relapsed and refractory disease
Relapsed and refractory MM	Non responsive disease, while on salvage therapy or progressing within 60 days of last therapy, in patients who have achieved at least MR at some point previously before, then progressing in their course
Double refractory MM	Disease refractory to both PI and IMiDs

Abbreviations: IMiDs, immunomodulatory drugs; MR, minimal response; PI, proteasome inhibitors.

MM, relapse is defined as an increase in the percentage plasma cells in bone marrow (absolute increase > 10%). Relapsed and refractory multiple myeloma (RRMM) refers to a progression occurring on salvage therapy or within 60 days after completion of the last treatment in patients who previously achieved at least a minimal response (MR) (*Table 1*).[1]

DIAGNOSTIC WORK-UP

Evaluation at relapse should include medical history and physical examination, complete blood count, serum creatinine, calcium and lactate dehydrogenase (LDH) determination, serum and urine (24-h collection) protein electrophoresis and immunofixation, serum FLC assay and a bone marrow (BM) aspirate with fluorescence in situ hybridisation (FISH) analysis performed on CD138 selected plasma cells (PC) to identify new chromosomal abnormalities. Imaging with skeletal survey (x-rays or low-dose CT), magnetic resonance imaging or in selected cases, FDG-positron emission tomography allows for assessment of new sites of disease, evaluation of pre-existing involved lesions or extramedullary (EM) disease. International staging system (ISS) stage determination is not mandatory since its role at relapse is unclear.[2]

INDICATION FOR TREATMENT: OPTIMAL TIMING TO INITIATE THERAPY AT RELAPSE

The goal of treatment at relapse is to relieve symptoms or prevent the appearance of CRAB features.

Treatment is mandatory in patients with a symptomatic relapse, but should also be considered in case of rapidly increasing M-protein concentration (doubling time of ≤ 3 months) or light chain (LC) escape even without associated symptoms, as well as in high-risk MM, characterised by adverse cytogenetics or previous renal failure related to LC at diagnosis.[3,4]

In asymptomatic biochemical relapse or in case of slow rise in the M-protein level, strict follow-up at least every three months is recommended until significant progression.[5]

DETERMINANTS OF THERAPY

Several factors should be taken into account while determining the treatment strategy in the setting of relapse. They are based on both patient- and disease-related factors, including pre-existing toxicities, co-morbidities, prior response to therapy, aggressiveness of relapse and cytogenetics (*Table 2*).[6,7]

Performance status, frailty, patient's preferences and expectations should also be taken into account, particularly in the elderly, since toxicity is a major problem that can result in early treatment discontinuation and poorer outcome.[8] Salvage regimen should therefore offer an adequate balance between efficacy and toxicity, with quality of life as a major goal.

Risk should be determined based on prior cytogenetic abnormalities, but also on aggressive clinical features such as extensive bone disease, EM disease or organ dysfunction such as renal failure.[9,10] Time to relapse should also be considered in determination of risk, since short duration of response (DOR) to prior treatment or progression under current therapy are associated with poorer outcome (*Table 3*).[9,11]

TABLE 2. Factors influencing choice of therapy.

Disease-related factors	Treatment-related factors	Patient-related factors
risk stratification	prior drug therapy	renal and hepatic impairment
acquired chromosomal aberrations	regimen-related toxicities	co-morbidities
presence of end-organ damage	polyneuropathy, myelosuppression	susceptibility to infections
presence of extramedullary disease	depth and duration of response to prior drug	performance status
		frailty
		preferences regarding the mode of treatment administration

KEY PRINCIPLES: GENERAL CONSIDERATIONS

MM is characterised by relapses and remissions, the remission duration in RRMM decreasing with each regimen.[12] This is in relation to a more aggressive tumour behaviour at each relapse due to the selection of resistant clones responsible for progressive disease refractoriness.[13] In patients refractory to lenalidomide and bortezomib, median progression-free survival (PFS) and overall survival (OS) do not exceed five and nine months, respectively.[14]

Front line regimens can be considered in the relapsed setting. Patients should, however, always be considered for enrolment on to clinical trials.

Eligibility for HDT should also be considered, as ASCT remains a reasonable option in eligible patients who have not previously undergone ASCT and in those who experienced a remission duration of at least 18-24 months without maintenance therapy after the first procedure.[15,16]

Patients naïve to an agent or a class of drugs are preferably treated with a regimen incorporating this agent. Re-administration of an agent initially proven to be effective can be proposed, provided it induced at least a partial response (PR) with a DOR of at least six to nine months, or a response duration that averaged or exceeded the median duration based on clinical trial results with that agent or regimen used in a similar setting. If an effective alternative therapy is available, switching drug class is preferred.[17]

Usually, doublet or triplet regimens are preferred above single agents in order to achieve a maximal response, but selected frail patients or indolent relapses can often be treated with less intense regimens.[18]

Duration of therapy should be determined by the drug label and by the clinical context of the patient. In the absence of toxicity, most regimens are continued until progression, but stopping therapy may be reasonable once a stable plateau has been reached, especially when using thalidomide, bortezomib, carfilzomib or alkylators, in order to minimise risk of serious toxicity.

CURRENT TREATMENT OPTIONS

Major regimens used in relapse are listed in *Tables 4 & 5*.

IMMUNOMODULATORY DRUGS (IMiDs)

Immunomodulatory drugs are effective in MM through several mechanisms including the recently discovered binding to cereblon, a critical component of the E3 ubiquitin ligase complex, responsible for the degradation of two important factors for myeloma cell survival, Aiolos (IKZF3) and Ikaros (IKZF1), leading to myeloma cell death.[19]

Thalidomide has long been considered a valuable treatment option in RRMM. Its current role is restricted by the lack of randomised phase III data supporting its use as single agent, the use of next-generation IMiDs, the absence of data on its efficacy in lenalidomide- and pomalidomide-refractory patients and the important side-effects observed with prolonged use.

As a single agent, it provides an overall response rate (ORR)(PR or better) of 30% with a median OS of fourteen months.[20] Efficacy is further improved in combination with dexamethasone (ORR of 41-56%, PFS of

TABLE 3. High-risk disease characteristics in RRMM *(adapted from Laubach, Leukemia 2016).*

Adverse cytogenetic abnormalities (hypodiploidy, t(4;14), del (17p), amp(1q21))
ISS stage II or III
Extramedullary disease
Short duration of response to prior therapy or progression while on current therapy
Aggressive clinical features including • Rapid onset of clinical symptoms • Extensive disease at relapse based on laboratory, pathology, or radiographic findings • Disease-associated organ dysfunction at relapse including renal failure, hypercalcemia or bone event such as fracture
High LDH level
Circulating plasma cells

seventeen months, 3-year survival probability of 60%) or with other drugs such as bortezomib, cyclophosphamide, or pegylated liposomal doxorubicin, in triplet or quadruplet combinations (ORR of 63-90%, complete response (CR) in 2-35%)(*Table 4*).[21-28]

Lenalidomide is more potent and less toxic than thalidomide, and is active as a single agent with PR rates of 24-29%.[29] Addition of dexamethasone improves response rates by up to 30%.[30] Analysis of the pooled data from the MM-009 and MM-010 trials after a follow-up of 48 months reported a significantly improved ORR (60.6% versus 21.9%), DOR (15.8 months versus 7 months), median time-to-progression (TTP)(13.4 months versus 4.6 months) and OS (38 months versus 31.6 months).[31] To achieve a maximum PFS, treatment requires at least twelve months full-dose lenalidomide plus dexamethasone, followed by lower-dose continued therapy.[32] In patients with suboptimal response, addition of cyclophosphamide can provide a clinical benefit.[33] In patients achieving at least PR, continued lenalidomide therapy until disease progression is associated with a survival advantage.[34] The combination of lenalidomide, bortezomib and dexamethasone (RVD) is a very active and well-tolerated regimen that can overcome drug resistance in patients previously treated with lenalidomide, bortezomib, thalidomide or ASCT. With a follow-up >2 years, CR/nCR are reported in 25% of patients, ≥PR in 64% of them, with a median PFS of 9.5 months and a median OS of 26 months (*Table 4*).[35]

Pomalidomide is a third generation IMiD, with significant activity in RRMM, even in patients failing lenalidomide and lenalidomide plus bortezomib.[36-39] It has been approved for the treatment of patients who received at least three prior lines of therapies including lenalidomide and bortezomib. In patients refractory to both bortezomib and lenalidomide, response rate is approximately 30% with a DOR of 7-8 months.[39,40] Compared to high-dose dexamethasone alone, pomalidomide with weekly dexamethasone provides a significantly longer PFS (4 months versus 1.9 months) and OS (12.7 months versus 8.1 months).[41] Pomalidomide is also the first drug to have shown increased activity in patients with del(17p).[42] It can be safely combined with other drugs such as bortezomib, carfilzomib, cyclophosphamide or clarithromycin, resulting in deeper responses in RRMM patients (*Tables 4 & 5*).[43-46]

PROTEASOME INHIBITORS (PIs)

PIs alter the ability of the proteasome to degrade intracellular proteins that have been targeted for destruction, leading to protein accumulation and eventually plasma cell apoptosis.[47]

Bortezomib is the first-in-class PI developed for the treatment of MM. As single agent, compared with high-dose dexamethasone in the APEX trial, bortezomib is associated with higher ORR (38% versus 18%), TTP (6.2 months versus 3.5 months), and 1-year OS (80% versus 66%).[48] All-grade polyneuropathies (PN) occur in one-third of patients, a side effect that can be reduced

TABLE 4. Selected regimens used in RRMM.

Drug	Regimens	N	dose	phase
Thalidomide	TD	44	T 200mg orally	2
			D 20mg/m2 d1-4,d9-12,d17-20 (cycle 1), d1-4 (cycles 2+)	
	CTD	53	C 150mg/m2 q12h orally d1-5	2
			T 400mg orally d1-5,d14-18	
			D 20mg/m2 d1-5,d14-18	
	PLD-TD	47	T 100mg	matched cases
			PLD 40mg/m2 d1	
			D 40mg orally d1-4,d9-12, 28d-cycles	
Lenalidomide	RD	176	R 25mg orally d1-21	3
			D 40mg orally d1-4,d9-12,d17-20, 28d-cycles	
	REP	14	R 10mg orally d1-21	-
			E (C) orally 100mg d1-28	
			P orally 20/10mg d1-28, 28d-cycles	
	RVD	64	R 15mg orally d1-14	2
			V 1mg/m2 IV d1,d4,d8,d11	
			D 40/20mg	
Pomalidomide	PD	302	P 4mg orally d1-21	3
			D 40mg orally d1,d8,d15,d22	
	PCD	80	P 4mg orally d1-21	2
			C 300-500mg d1,d8,d15	
			D 40mg orally d1,d8,d15,d22, 28d-cycles	
	PKD	32	P 4mg orally d1-21	1
			K 20/27mg/m2 IV d1,d2,d8,d9,d15,d16	
			D 40mg orally d1,d8,d15,d22, 28d-cycles	
Bortezomib	VD	315	V 1mg/m2 IV d1,d4,d8,d11	3
			D 40mg d1,d8,d15,d22, 28d-cycles	
	V-PLD	324	V 1mg/m2 IV d1,d4,d8,d11	3
			PLD 30mg/m2 IV d4	
	VTD	135	V 1-1.3mg/m2 d1,d4,d8,d11	3
			T 200mg orally	
			D 40mg orally d1,d8,d15,d22	
	VCD	96	V 1-1.3mg/m2 d1,d8,d15	-
			C 300mg/m2 orally d1,d8,d15,d22,	
			D 40mg orally d1,d8,d15,d22, 28d-cycles	
	Pan-VD	387	Pan 20mg d1, d3, d5, d8, d10, d12, 21d-cycles	3
			V 1.3mg/m2 d1,d4,d8,d11	
			D 20mg orallyd1, d2, d4, d5, d8, d9, d11, d12	
	VDB	75	V 1.3mg/m2 IV d1,d4,d8,d11	2
			D 20mg orally d1, d2, d4, d5, d8, d9, d11, d12	
			B 70mg/m2 IV d1,d8, 28d-cycles	
Carfilzomib	Kd	464	K 20/56mg/m2 IV d1,d2,d8,d9,d15,d16	3
			D 20mg d1,d2,d8,d9,d15,d16,d22,d23	
	KRD	396	K 20/27mg/m2 IV d1,d2,d8,d9,d15,d16	3
			R 25mg orally d1-21	
			D 40mg orally d1,d8,d15,d22, 28d-cycles	
Elotuzumab	Elo-RD	321	Elo 10mg/kg weekly cycles 1-2, every other week cycles 3+	3
			R 25mg d1-d21	
			d 40mg d1,d8,d15,d22, 28d-cycles	
	Elo-VD	77	Elo 10mg/kg weekly cycles 1-2, every other week cycles 3+	2
			V 1.3mg/m2 d1,d4,d8,d11	
			d 20mg d1,d8,d15,d22, 28d-cycles	
Daratumumab	Dara	72	Dara 8-16mg/kg 1x/w (2m), 1x/2w (4m), 1x/m (18m)	1/2
	Dara-VD	240	Dara 16mg/kg IV d1, d8, d15 (cycles 1-3), d1 (cycles 4+)	3
			V 1mg/m2 IV d1,d4,d8,d11	
			D 20mg d1, d2, d4, d5, d8, d9, d11, d12	
	Dara-RD	286	Dara 16mg/kg IV d1, d8, d15 (cycles 1-2), d1 (cycles 3+)	3
			R 25mg d1-d21	
			D 40mg/week, 28d-cycles, until progression	

Abbreviations: B, bendamustine; C, cyclophosphamide; Cla, clarithromycin; D, dexamethasone; Dara, daratumumab; E, cyclophosphamide; Elo, elotuzumab; K, carfilzomib; P, prednisone; Pan, panobinostat; PLD, pegylated liposomal doxorubicin; P, pomalidomide; R, lenalidomide; T, thalidomide; V, bortezomib

prior lines	≥PR (≥VGPR), %	PFS, months	OS, months	≥grade 3 AE, %	references
3	55 (NA)	4.2	12	C 75, S 57, PN 23	21
NA	75 (36)	12	17.5	TEE 4, PN 2	24
3	75 (36)	21	35.5	N 25, PN 2, T 7, I 23, TEE 13	26
≥2	60(24CR)	NA	NR	N 30, A 8, T12, P2, F 6	89
2	50 (35)	12.8	93 at 1y	A , N, T, P	33
2	64(28)	9.6	30	N 30, T 22, L 11	40
5	31(6)	4	12.7	N 48, A 33, T 22, F 5, I 34	41
4	64.7	9.5	NR	N 52, A 24, T15	45
6	50(16)	7.2 at 26 months		F 43, N 40, A34, T 34, D 20	44
2	38(6CR)	TTP 6.22	80% at 1y	D 7, F 5, PN 8, A 10, T 30, N 14	48
≥2	44(27)	9	33	N 29, A 9, T 23, PN 3	54, 69
NA	87(56)	18.3	71% at 2y	N 11, A 8, T 17, PN 31, I 14	23
1 to 3	69(43)	16.2	26.3	A 6, T 9, N 6, PN 4, P 6	51
1 to 3	61	12	33.7	T 67, D 53, D 26	73
4	71.5(34.5)	16.5	78%	N 18, T 30, I 12, PN 8	55
1 to 3	76(54)	18.7	NA	A 14, H 9, T 8, P 7	60
2	87(70)	26.3	NR	D 4, F 8	19
1 to 3	79(4)	19.4	NA	L 77, N 34, A 19, T 19, F 8	75
1 to 3	66(36)	9.7	85% at 1y, 73% at 2y	I 21, D 8, A 7, PN 9	76
4	36	5.6	NA	P , T	78
≥1	83(59)	60.7% at 1y	NA	T 45, A 14, N 13	80
≥1	93(76)	83% at 1y, 76% at 18m	NA	N 52, T 13, A 12	81

AE, adverse events; C, constipation; CR, complete response; D, diarrhea; F, fever; I, infections; L, lymphopenia; NA, not available; NR, not reached; PN, polyneuropathy; S, somnolence; T, thrombocytopenia; TTP, time-to-progression; TEE, thromboembolic events; y, years

TABLE 5. Selected recent clinical trials in RRMM.

Trials	regimens	patients, n	≥PR (CR), %	median PFS, m	p	OS	p	≥ grade 3 AE, %	references
MM-003 Phase 3	PD	302	31 (1)	4	<0.0001	12.7 median, m		N 48, A 33, T 19	41
	D	153	10 (0)	1.9		8 median, m		N 16, A 37, T 26	
ASPIRE Phase 3	KRd	396	87 (14)	26.3	0.0001	NR (2y OS 73.3%)	0.04	D 4, F 8	19
	Rd	396	67 (13)	17.6		NR (2y OS 65%)		D 4, F 6	
ENDEAVOR Phase 3	Kd	464	77 (13)	18.7	<0.0001	2y OS 65%	0.06	A 14, H 9, T 8, P 7	60
	Vd	465	63 (6)	9.4		2y OS 72%		A10, H 3, T 9, P 8	
PANORAMA 1 Phase 3	Pan-Vd	387	61 (6)	12	<0.0001	33.7 median, m	0.26	T 67, L 53, D 26	73
	Vd	381	55 (11)	8.1		30.4 median, m		T 31, L 40, D 8	
ELOQUENT 2 Phase 3	Elo-Rd	321	79 (4)	19.4	<0.001	NA		L 77, N 34, A 19, T 19, F 8	75
	Rd	325	66 (7)	14.9				L 49, N 44, A 21, T 20, F 8	
TOURMALINE Phase 3	IRd	360	78 (12)	20.6	0.012	NA		N 23, T 19, D 6	64
	Rd	362	72 (7)	14.7				N 24, T 9, D 6	
CASTOR Phase 3	Dara-VD	251	83(19)	60.7% at 1y		NA		T 45, A 14, N 13, PN 4, D 4	80
	VD	247	63(9)	26.9% at 1y				T 33, A 16, N 4, PN 7, D 1	
POLLUX Phase 3	Dara-RD	286	93(43)	83% at 1y, 78% at 18m	<0.001	NA		N 52, T 13, A 12	81
	RD	283	76(19)	60% at 1y, 52% at 18m				N 37, T 13, A 20	

Abbreviations: D, dexamethasone; Dara, daratumumab; Elo, elotuzumab; I, ixazomib; K, carfilzomib; Pan, panobinostat; P, pomalidomide; R, lenalidomide; T, thalidomide; V, bortezomib; A, anemia; AE, adverse events; CR, complete response; D, diarrhea; F, fatigue; HT, hypertension; L, lymphopenia; m, months; n, number; N, neutropenia; NA, not available; OS, overall survival; PFS, progression-free survival; PN, polyneuropathy; PR, partial response; T, thrombocytopenia; TTP, time-to-progression; y, years

by using subcutaneous (SC) administration.[48,49] Bortezomib can be safely administered to patients with renal failure.[50] Retreatment with bortezomib is effective if previous response lasted more than six months.[17] Triplet regimens using bortezomib as backbone in combinations with lenalidomide, cyclophosphamide, thalidomide, anthracyclines, as well as bendamustine have reported high response rates in the relapsed setting, and are well tolerated when low-dose dexamethasone and weekly subcutaneous bortezomib schedules are used (*Table 4*).[23,35,51-56]

Carfilzomib is a second generation PI, epoxyketone tetrapeptide analog with irreversible binding to the proteasome complex, approved for the treatment of RRMM

TABLE 6. Renal and hepatic dose adjustments.

	Renal	Liver
thalidomide	no dose adjustment	no dose adjustment
lenalidomide	CrCl >50ml/min : no dose adjustment	grade 3/4 toxicities judged to be related to lenalidomide, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤ grade 2
	CrCl 30-50ml/min : 10mg qd	
	CrCl <30ml/min, non dialysis dependent : 15mg every other day	
	CrCl <30ml/min, dialysis dependent : 5mg qd, on dialysis days, following dialysis	
pomalidomide	avoid in patients with a serum creatinine >3.0mg/dl	not recommended in serum bilirubin >2mg/dl and AST/ALT >3N
		stop treatment in case of elevated liver enzymes during therapy; consider a lower dose after enzymes return to baseline values
bortezomib	no dose adjustment	bilirubine >1.5N, starting dose at 0.7mg/m² in the first cycle, dose escalation to 1 mg/m² or reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability
carfilzomib	if renal toxicity develops during treatment (serum creatinine x2N, or CrCl <15ml/min, or CrCL decrease to 50% of baseline, or need for dialysis), withhold dose; if attributable to the drug, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction	liver enzymes should be monitored regularly and the dose should be reduced or withheld as appropriate (frequent increase of serum transaminases, rare cases of hepatic failure)
	if not attributable to the drug, dosing resumed at physician's discretion	
	patients under dialysis, administer the drug after dialysis	
panobinostat	no dose adjustment (no information in end stage renal failure)	bilirubine ≤1xN and AST >1.5-2xN, reduce dose to 15mg
		bilirubine >1.5-2xN, any AST >1.5-2xN, reduce dose to 10mg
		avoid in severe liver impairment
elotuzumab	no dose adjustment	no dose adjustment for mild/moderate liver impairment before therapy
		grade ≥3 transaminases elevation occurring during treatment, withhold therapy, resume after return to baseline
daratumumab	no dose adjustment	no dose adjustment for mild hepatic impairment, no data in patients with moderate to severe hepatic impairment

in patients who have received at least two prior lines of therapy including bortezomib and an IMiD. In patients refractory or intolerant to both bortezomib and lenalidomide (PX-171-003 trial), single-agent carfilzomib exhibits an ORR of 24% with a median DOR of 7.8 months, while in bortezomib-naïve patients (PX-171-004 trial), ORR is approximately 50%.[57,58] The ORR and PFS are also significantly longer for patients with standard cytogenetics compared to those with any cytogenetic abnormalities, with the exception of the translocation t(4;14) who fared as well as the patients with normal cytogenetic status.[59]

TABLE 7. Common side effects associated with MM therapy.

	Polyneuropathy	Venous thrombo-embolic event	Thrombopenia	Neutropenia	Anemia	Infection	Pneumonia	Fatigue	Nausea	Diarrhea	Constipation	Rash	Edema
Bortezomib	X		X			X		X	X	X	X		
Carfilzomib			X	X	X		X	X	X	X			X
Thalidomide	X	X		X				X	X		X	X	X
Lenalidomide		X	X	X	X	X	X	X	X	X	X	X	X
Pomalidomide		X	X	X	X			X	X		X	X	
Cyclophosphamide			X	X	X	X			X				
Panobinostat			X	X	X		X	X		X			
Elotuzumab					X		X	X	X	X			
Daratumumab			X										

In the ENDEAVOR study, carfilzomib-dexamethasone shows a doubling of PFS compared to bortezomib-dexamethasone (18.7 months versus 9.4 months), regardless of the number of prior therapy lines or prior exposure to bortezomib or lenalidomide.[60,61] Of note, the dose of carfilzomib used is twice the FDA label dose (56mg/m^2).

Combined with lenalidomide and dexamethasone in the ASPIRE trial, carfilzomib was associated with an unprecedented PFS of 26 months compared to seventeen months in the lenalidomide-dexamethasone (Rd) control group, with a clinically relevant 31% decrease in the risk of disease progression or death. The ORR was also higher with a longer median DOR. The benefit was observed across all subgroups including patients previously exposed to bortezomib or lenalidomide and those with a high cytogenetic risk. Common adverse events were reported at a higher rate, including diarrhoea, cough, fever and hypertension, leading to treatment discontinuation in 15% of patients, but superior health-related quality of life was reported in the carfilzomib group, according to QLQ-C30.[62] The carfilzomib-lenalidomide-dexamethasone combination (KRd) is reimbursed in second line therapy since November 1st, 2016. Common carfilzomib-containing combinations are listed in *Tables 4 & 5*.

Ixazomib is a new generation PI, the first orally bioavailable, reversibly binding PI. With a molecular backbone similar to that of bortezomib, it exhibits however distinct pharmacological properties, with superior tissue penetration and higher biological activity.[63] In the TOURMALINE-MM2 trial, ixazomib combined with lenalidomide and dexamethasone improves PFS in comparison to Rd.[64] It has the advantage of a once-weekly oral administration, little neurotoxicity, but induces more gastrointestinal adverse effects compared to bortezomib (*Table 5*).

CYTOTOXIC AGENTS

Bendamustine is a bi-functional alkylating agent approved for the treatment of de novo MM that cannot be treated with thalidomide or bortezomib because of pre-existing polyneuropathy. Promising results and good tolerability have been reported in association with thalidomide, lenalidomide or bortezomib in RRMM (*Table 4*).[65-68] Cyclophosphamide or melphalan can also be combined with bortezomib, lenalidomide or pomalidomide.

TABLE 8. Reimbursement criteria: indications in RRMM.

thalidomide	no specific limitation
lenalidomide	in association with dexamethasone in RRMM patients who have already received one prior line of therapy
pomalidomide	in association with dexamethasone in RRMM patients that have already be treated by 2 lines of therapy including lenalidomide and bortezomib, and in whom disease has progressed while under therapy
bortezomib	as single-agent therapy, or in association with pegylated liposomal doxorubicin or dexamethasone, in RRMM patients that have already received one prior line of therapy, and have been treated or are ineligible to autologous stem cell transplantation
bendamustine	no access
pegylated liposomal doxorubicin	in association with bortezomib in RRMM patients who have already received one prior line of therapy, and have been treated or are ineligible to autologous stem cell transplantation
carfilzomib	reimbursed in second line of therapy in association with lenalidomide and dexamethasone since November 1st, 2016. Reimbursement pending in other indications
elotuzumab	reimbursement pending
daratumumab	reimbursed in relapsed and refractory MM, who have received at least a PI and an IMiD, and in whom disease has progressed under the last therapy, since March 1st, 2017
panobinostat	reimbursed in association with bortezomib and dexamethasone, in RRMM that have already received at least two lines of therapy including bortezomib and an IMiD, and who are in relapse or refractory to the last regimen and/or intolerant to the IMiD

Anthracyclines have marginal single-agent activity in MM. Combination of pegylated liposomal doxorubicin (PLD) with bortezomib has been reported to be superior to bortezomib alone in terms of TTP (9.3 months versus 6.5 months) in a phase III randomised trial, but long-term follow-up failed to identify any survival advantage.[54,69] PLD is however infrequently used in the treatment of RRMM given the availability of other active agents (*Table 4*).

High-dose chemotherapy such as DCEP and DT-PACE can be given in RRMM, but are associated with short duration responses.[70]

HISTONE DEACETYLASE INHIBITORS (HDACi)

Histone deacetylases (HDACs) are enzymes that remove acetyl groups from proteins, and have the ability to modulate oncogenesis through epigenetic activity on both histone and non-histone proteins such as tumour protein p53, heat shock protein HSP 90 and BCL-6. In MM cells, HDACi inhibit cell growth and induce apoptosis.[47]

Vorinostat was the first pan-HDAC inhibitor evaluated in clinical trials. It does not have any activity as single-agent. In the VANTAGE phase III trial, vorinostat combined with bortezomib and dexamethasone showed a PFS advantage of only one month compared to bortezomib-dexamethasone, at the cost of a low safety profile.[71]

Panobinostat, is an oral pan-HDAC inhibitor approved in 2015 for the treatment of relapsed and refractory MM, in patients who received at least two prior regimens including bortezomib and an IMiD. It blocks the aggresome pathway, an alternative route for cells to bypass the lethal effects of proteasome inhibition. The rationale to combine bortezomib and panobinostat is to simultaneously block both the proteasome and aggresome pathways.[72] In the PANORAMA phase III trial, panobinostat combined with bortezomib and dexamethasone demonstrated a significant advantage in terms of PFS (12 months versus 8.1 months in the control arm), at the cost of grade 3 diarrhoea and fatigue.[73] Patients who received prior bortezomib plus IMiD derived the greater benefit in terms of PFS (*Tables 4 & 5*).[74]

RECOMMENDATIONS

1 Before determining the treatment strategy in relapsed/refractory MM, several factors should be taken into consideration, such as disease- and patient-related factors, prior treatment response, and history of toxicities.

2 When available, patients should always be considered for enrolment in a clinical trial.

3 In patients achieving a high quality response, prolonged response (more than six months after stopping therapy) with minimal toxicity, re-administration of the agent initially proven to be effective can be considered. The duration of therapy is still a matter of debate, and depends on the drug regimen that has been previously used and the aggressiveness of the disease. In the absence of toxicity and in high-risk MM, regimens are preferably continued until progression. It might be reasonable, in some cases, to stop therapy once a stable plateau has been reached in order to limit the risk of serious toxicities.

4 In aggressive relapse, triple combinations should be used, while in selected patients with indolent relapse or frailty, double regimens can be considered.

5 *In first relapse,*

- Both **bortezomib and lenalidomide**, combined with dexamethasone, are effective. There is no specific preference between those drugs, the choice being based on response and tolerability to immediate prior therapy, co-morbidities and clinical status.
- Efficacy of **bortezomib** is increased in combination with thalidomide, lenalidomide, cyclophosphamide or pegylated liposomal doxorubicin. Patients should be carefully monitored for neuropathy, the dose and schedule is to be reduced in case of occurrence.
- **Lenalidomide** can also be combined with various agents including bortezomib and cyclophosphamide, or new agents such as carfilzomib or elotuzumab.
- **Carfilzomib** is a more active proteasome inhibitor compared to bortezomib, which has been approved in combination with either lenalidomide-dexamethasone or dexamethasone alone, for the treatment of RRMM patients who have received at least one prior line of therapy, by the European Medicines Agency (EMA). More data are needed before concluding that carfilzomib is preferred than bortezomib at relapse, especially since bortezomib is more convenient and less expensive. Carfilzomib is associated with a low incidence of PN. Physicians should be aware of serious cardiac side effects associated with carfilzomib in a small proportion of patients (5%), especially in the elderly (>75 y). The KRD regimen is reimbursed in Belgium in first relapse since November 1st, 2016.

Among other medications also approved by the EMA:

- **Panobinostat** is the first HDACi approved for the treatment of RRMM after one prior line of therapy, in combination with bortezomib and dexamethasone.
- **Elotuzumab** is a MoAb indicated, in combination with lenalidomide and dexamethasone, for the treatment of RRMM patients who have received at least one prior therapy.

6 *In second relapse and beyond,*

- **Pomalidomide** combined with dexamethasone is reimbursed in patients who have received at least two prior treatment regimens, including both bortezomib and lenalidomide, and have demonstrated disease progression on the last therapy. Efficacy can be increased in triplet combination using cyclophosphamide.
- **Daratumumab** has been approved in monotherapy for the treatment of RRMM patients whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and have demonstrated disease progression on the last therapy. Reimbursed in relapsed and refractory MM, who have received at least a PI and an IMiD, and in whom disease has progressed under the last therapy, since March 1st, 2017.

7 Younger fit patients, especially those with aggressive relapse, should preferably be treated with carfilzomib- or pomalidomide-based regimens. Frail patients or patients with an indolent relapse should be treated with Rd, eventually in combination with elotuzumab, or pomalidomide-dexamethasone.

8 Patients in relapse that are double refractory to bortezomib and lenalidomide should be proposed a regimen containing pomalidomide or carfilzomib, or be considered for a daratumumab-based combination, or the addition of panobinostat to a PI, or any regimen containing PLD. Access to carfilzomib, daratumumab, panobinostat is currently restricted.

9 Patients with aggressive relapse with secondary plasma cell leukaemia or EM disease require drug combinations such as VDT-PACE.

10 Salvage autologous stem cell transplantation in transplant eligible patients with relapse or progression may be considered in those that already responded to a previous HDT and achieved at least a two year PFS with no maintenance therapy. It is also indicated in transplant eligible patients that did not receive HDT and ASCT as upfront therapy.

11 Allogeneic stem cell transplantation remains a curative but experimental option to be performed in the context of clinical trials, particularly in high-risk disease and in the presence of an unfavourable karyotype during first-line treatment or at first therapy-sensitive relapse.

MONOCLONAL ANTIBODIES

Elotuzumab is a human monoclonal antibody (Moab) that targets the cell surface glycoprotein CS1 (SLAMF7, signalling lymphocytic activation molecule F7) highly expressed on MM cells but with limited expression on normal cells. Binding to this receptor mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in MM cells.

Elotuzumab (Elo) has little activity as single-agent, but has demonstrated synergistic activity when combined with lenalidomide and dexamethasone (Rd). In the ELOQUENT phase III trial, Elo-Rd demonstrated a better PFS (19.4 months versus 14.9 months) compared to Rd, with more than 80% ORR without significant toxicity.[75] Response rates were comparable in RRMM patients with poor and standard cytogenetics. Adverse reactions are primarily infusion-related that can be readily managed using premedication with corticosteroids and H1/H2 blockers. Elotuzumab has also been combined with bortezomib or thalidomide with clinical benefit (*Tables 4 & 5*).[76,77]

Daratumumab is a humanised IgG MoAb that targets CD38 on MM cells with a broad-spectrum mechanism of cell killing, including ADCC, complement-dependent cytotoxicity (CDC) and phagocytosis. Unlike elotuzumab, daratumumab does have single-agent activity.

In a phase I-II trial, daratumumab monotherapy showed encouraging efficacy in patients of whom 75% were refractory to bortezomib and lenalidomide, with an ORR of 36% at the dose of 16 mg/kg, and a median PFS of 5.6 months. In addition, 65% of patients who achieved at least a response remained free of progression at twelve months.[78] These results were confirmed in a pooled population of double refractory patients, heavily pretreated (median of five prior lines of therapy), with rapid (median time to response, one month), deep (14% with ≥ very good partial response (VGPR)), and durable responses (median DOR, 7.6 months), and a median OS of 20.1 months. Of importance, a clinical benefit was also noted in patients achieving MR or stable disease, with an OS benefit of more than twelve months.[79] Similar to other MoAb therapies, adverse reactions include hypersensitivity infusion reactions that can be mitigated by using adequate premedication. Clinical trials have been initiated using various combinations of daratumumab with other drugs. Daratumumab given in association with bortezomib and dexamethasone (DVD) or lenalidomide and dexamethasone (DRD) seems particularly efficient with significantly higher rates of ORR and longer PFS (*Tables 4 & 5*).[80,81]

OTHER EMERGING OPTIONS

Other promising agents include marizomib (a new PI), oprozomib (an oral PI related to carfilzomib), filanesib (a kinesin spindle protein inhibitor), dinaciclib (a cyclin-dependent kinase inhibitor), venetoclax (ABT-199, a selective BCL-2 inhibitor), LGH-447 (a pan-PIM kinase inhibitor), SAR650984 (an anti-CD38 MoAb), and rocilinostat (a selective HDAC6 inhibitor). Each of these agents has single-agent activity in relapsed MM.

HIGH DOSE THERAPY WITH AUTOLOGOUS AND ALLOGENEIC STEM CELL TRANSPLANTATION

Autologous stem cell transplantation remains an option in transplant eligible patients with relapse or progression, particularly if they did not receive HDT and ASCT at diagnosis. After a previous autograft, several reports on salvage ASCT suggest a clinical benefit with an approximate ORR of 65%, and PFS and OS approaching twelve and 32 months, respectively. These studies are limited by being mainly retrospective, having patient selection bias and not using new drugs induction therapies.[82] In a phase III trial, salvage ASCT compared to conventional chemotherapy alone appears to improve PFS but not OS. Patients with adverse cytogenetic risk profile did not benefit from the procedure.[14] Patients that already responded to a previous HDT and achieved at least a two year PFS appear to benefit the most, even in more advanced age.[14,16,83,84] At relapse, ASCT remains an option in transplantation-eligible patients that did not receive HDT and ASCT at diagnosis. Post-ASCT strategies are under investigation.

Allogeneic stem cell transplantation (alloSCT) could be a therapeutic option for some MM patients, but its role and timing is still a subject of debate. Myeloablative conditioning results in long-term PFS but is challenged by its high treatment-related morbidity and mortality. Reduced intensity allogeneic transplantation has been developed in order to still allow a graft-versus-myeloma effect while reducing conditioning-related toxicities.

Young high-risk patients with an early relapse after first-line treatment (i.e. cytogenetics, EM disease, plasma cell leukaemia) who achieved a good quality response with salvage therapy, could be considered for alloSCT, preferably in the context of clinical trials, using bortezomib or newer agents for graft modulation post-transplant.[16,82] Physicians should balance the risk of graft-versus-host disease, increased susceptibility to infections and the gain in disease control.

HIGH RISK SITUATIONS

RENAL FAILURE

Renal dysfunction is common in RRMM, particularly in the elderly, either in relation to disease progression or co-morbidities (diabetes, hypertension, use of nephrotoxic drugs), and may have an impact on treatment decisions. Several drugs do not require dose adjustments: PIs, thalidomide, cyclophosphamide, PLD and pomalidomide. Lenalidomide does require dose adaptations. Recommended dose adjustments are listed in *Table 6*.

HIGH-RISK CYTOGENETICS

In RRMM patients with high-risk cytogenetics such as t(4;14) and del(17p), decision making on salvage therapy is difficult because of the absence of prospective trials. Current data on newer agents indicate that they may partly overcome the deleterious impact of high-risk abnormalities in this setting. Lenalidomide-dexamethasone is a suboptimal regimen unable to overcome the negative impact of del(17p), and probably t(4;14) (conflicting results).[11,85] In contrast, pomalidomide is the first drug to have shown an increase activity in del(17p), but not in t(4;14) MM patients.[42,56] Deeper responses have been observed in heavily pretreated high-risk MM patients, when pomalidomide is associated with bortezomib and dexamethasone.

SUPPORTIVE CARE

Patients with RRMM are more at risk of frequent infections, bone disease or anaemia.

Infections with encapsulated germs should be managed proactively, and patients should be vaccinated against influenza, haemophilus influenza and pneumococcus. Intravenous bisphosphonates should be started or restarted at relapse, in combination with calcium and vitamin D supplementation. Local radiation therapy (20-40 Gy) may be required for local bone lesions in case of pain or imminent fracture. Anaemia should be treated with EPO (erythropoietin 40.000 UI per week, or darbepoetin 500 μg per three weeks) or transfusion.[86]

Prevention of polyneuropathy and thrombosis should follow the published guidelines.[87]

Common side effects observed with current myeloma drugs are reported in *Table 7*.

Carfilzomib has been associated with cardiac adverse events (congestive heart failure and cardiac arrest) that have led to treatment discontinuation in a small proportion of patients; electrocardiogram, pulmonary function tests, echocardiography should be recommended prior to carfilzomib treatment.[88]

It is important to draw attention to the fact that daratumumab interferes with routine blood-compatibility testing. Daratumumab in patient plasma directly binds to CD38 on reagent red cells used in the blood bank, causing a false positive antibody screen. Neutralising procedures have been developed.

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

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