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Development of extramedullary myeloma in the era of novel agents: no evidence of increased risk with lenalidomide–bortezomib combinations

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Summary

Proteasome inhibitors (PI) and immunomodulatory agents (IMIDs) have improved the overall survival (OS) of patients with multiple myeloma (MM), but concerns have been raised about increased incidence of extramedullary disease (EMD) after the combined use of PIs and IMIDs for upfront therapy. We evaluated whether the addition of lenalidomide to bortezomib-based front-line regimens precipitated earlier development of EMD. We reviewed the charts of 117 MM patients (median follow-up from diagnosis 6·1 years; range 0·1–10·2 years) enrolled in eight clinical trials of first-line treatment with bortezomib-based regimens, with or without lenalidomide. We assessed development of EMD as extraosseous (distant from bone) or osseous (originating from bone) plasmacytomas. The primary endpoint was time from diagnosis until development of EMD, based on imaging, biopsy and/or physical examination. Any form of EMD at progression was observed in 40 (34·2%) patients, including 21 (18%) osseous, 8 (7%) extraosseous and 11 (9%) both osseous and extraosseous. Median OS was 0·9 years (range 0·1–4·8 years) after extraosseous EMD development. Sensitivity analyses with follow-up times truncated at 5 years detected no statistically significant difference in rates of any EMD form between the two groups ($P > 0·2$ for each comparison). Therefore, we observed no evidence that bortezomib–lenalidomide-based front-line therapy precipitates earlier EMD.

Keywords: multiple myeloma, extraosseous plasmacytoma, extramedullary disease, bortezomib, lenalidomide.

Multiple myeloma (MM) is a clonal plasma cell disorder that accounts for 10% of haematological malignancies and is typically confined to the bone marrow and skeleton (Kyle & Rajkumar, 2008). Less commonly, extramedullary growth of aberrant plasma cells can occur outside of the bone marrow and can present as plasma cell leukaemia or soft-tissue plasmacytomas (Varettoni *et al*, 2010). Isolated plasmacytomas (<5% plasma cells in the bone marrow, low or no M protein) usually denote an indolent course with good response to local radiotherapy and infrequent progression to MM (Galieni *et al*, 2000). On the other hand, extramedullary plasmacytomas seen upon disease relapse behave quite differently and are often a sign of inferior survival (Madan & Kumar, 2009). Plasmacytomas can be found upon initial diagnosis in 7–17% of patients with MM or may develop during the course of the disease in 6–20% of patients (Cerny *et al*, 2008; Wu *et al*, 2009).

The introduction of proteasome inhibitors (PI) and immunomodulatory derivatives (IMID) has been associated with substantial improvement in the overall survival (OS) of patients with MM (Kumar *et al*, 2008). We have demonstrated a response rate of 100% in treatment-naive patients with MM treated with a combination lenalidomide (Revlimid), bortezomib (Velcade) and dexamethasone (RVD) in a phase I/II study (Richardson *et al*, 2010). Multi-drug regimens using combinations of a PI and an IMID have become a standard of care for upfront therapy in MM patients.

In the era of novel agents, however, there have also been concerns of an increased incidence of extramedullary disease (EMD), and of the hypothetical risk that combined use of

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PIs and IMIDs for frontline treatment might select more rapidly for aggressive clones that could precipitate faster development of EMD. It is difficult to determine the true frequency of EMD after treatment, as incidence rates may be influenced by the impact of specific therapies, as well as confounded by changes in OS, and the increased use of sensitive imaging modalities, such as computerized tomography, positron emission tomography and magnetic resonance imaging (Blade *et al*, 2011).

The primary objective of this study was to evaluate the incidence of EMD and whether the addition of lenalidomide to bortezomib-based frontline regimens precipitated the more rapid development of EMD, in the form of either extraosseous or osseous extramedullary plasmacytomas. Potential risk factors for and the prognostic impact of EMD development were also examined.

Patients and methods

We performed an Institutional Review Board-approved retrospective comprehensive medical chart review of 117 MM patients. Patients were eligible if they enrolled in one of eight clinical trials of first-line treatment with bortezomib-based regimens either in combination with lenalidomide: (i) RVD, (ii) RVD-cyclophosphamide, (iii) RVD-vorinostat or (iv) RVD-liposomal doxorubicin, or without lenalidomide: (i) bortezomib monotherapy, (ii) melphalan-prednisone-bortezomib (Velcade) [MPV], (iii) cyclophosphamide-bortezomib, dexamethasone and (iv) the combination of MPV-CNT0328 (an anti-interleukin 6 antibody) at the Dana Farber Cancer Institute and Massachusetts General Hospital from December 2003 to May 2012. This patient cohort was specifically selected, as systematic follow-up information was available for each participant.

Baseline patient variables were collected and included: age, gender, ethnicity, albumin, beta-2 microglobulin, lactate dehydrogenase, Durie-Salmon staging (Durie & Salmon, 1975), International Staging System (ISS) (Greipp *et al*, 2005), serum/urine M protein isotype and concentration, serum free light chain ratio, creatinine and calcium levels. Cytogenetic information was determined by interphase fluorescent *in situ* hybridization. All treatments administered to patients at diagnosis and at progression were recorded. Induction therapy was defined as the first or initial therapeutic regimen offered to a treatment-naive patient. This term also encompassed any supplementary regimens administered due to inadequate response to initial therapy. Response to induction therapy was evaluated according to the International Myeloma Working Group criteria (Durie *et al*, 2006). The development of EMD was assessed in the form of extraosseous (soft-tissue mass distant from bone) or osseous (mass originating from bone) plasmacytomas, based on radiological imaging, biopsy and/or physical examination. In this study, plasma cell leukaemia was also classified as EMD.

Statistical analysis

Patient baseline characteristics were summarized as number (%) of patients or median and range of values. The primary endpoint was time to plasmacytoma progression (osseous and extraosseous separately or the combination), defined as time from diagnosis to progression by radiographical mode, biopsy and/or physical examination. The cumulative incidence of EMD was estimated using a competing risk model, where death without occurrence of EMD was considered as a competing risk and patients were censored at last disease follow-up date for those who had not progressed or died. The Gray's test was reported for the comparison of time to occurrence of EMD by patient baseline characteristics in both univariate and multivariate analyses. The multivariate model was constructed by including all variables with $P < 0{\cdot}15$ in univariate analysis and, given its prognostic importance, the ISS stage; no formal model selection was used. To compare the rates of EMD between the two treatment groups, we conducted sensitivity analyses at truncated follow-up times of 5 and 7 years, to control for any potential bias due to shorter follow-up in patients receiving combined bortezomib-based therapy with *versus* without lenalidomide. OS was defined as time from diagnosis to death or date last known alive. Distributions of OS were estimated using the Kaplan-Meier method. The statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 2.15.2 (http://www.r-project.org/) with P-values < 0.05 considered statistically significant. Variables with P-values >0.05 and <0.1 were considered marginally significant.

Results

Overall, chart data from 117 patients who participated in bortezomib-based protocols at the Dana-Farber/Harvard Cancer Center were included in this analysis. Table I illustrates patient and disease characteristics at baseline, prior to receiving any anti-myeloma therapy. More males than females (62·4% vs. 37·6%) participated in these clinical trials at both institutions. The vast majority of patients were Caucasian (87·2%) with a minority of patients being Hispanic/Latino or African American (3·4% and 6·8%, respectively). The majority of participants were not previously known for a diagnosis of monoclonal gammopathy of unknown significance (MGUS) or smouldering MM. The most prevalent isotypes amongst participants were IgG kappa and IgG lambda (41% and 22·2%, respectively). ISS at diagnosis consisted mostly of stage I and II disease (47% and 43·6%, respectively). Durie-Salmon Staging amongst this same patient population was mainly comprised of stage IIA and IIIA disease (41·9%, and 48·7%, respectively).

Plasmacytomas at diagnosis

Soft tissue masses originating from or surrounding the axial skeleton (osseous plasmacytomas) were more common at

Table I. Patient and disease characteristics at diagnosis.

	N	%
Gender		
Male	73	62·4
Female	44	37·6
Race		
Unknown	2	1·7
Hispanic	4	3·4
White	102	87·2
Black	8	6·8
Other	1	0·9
History of MGUS		
No	109	93·2
Yes	8	6·8
History of SMM		
No	97	82·9
Yes	20	17·1
Immunofixation electrophoresis		
Unknown	1	0·9
None	6	5·1
IgG κ	48	41·0
IgG λ	26	22·2
IgA κ	18	15·4
IgA λ	8	6·8
κ	7	6·0
λ	2	1·7
IgM λ	1	0·9
Urine immunofixation electrophoresis		
Unknown	9	7·7
None	27	23·1
κ	52	44·4
λ	29	24·8
International Staging System stage at diagnosis		
Unknown	1	0·9
I	55	47·0
II	51	43·6
III	10	8·5
Durie-Salomon Stage at diagnosis		
IA	7	6·0
IIA	49	41·9
IIIA	57	48·7
IB	1	0·9
IIB	2	1·7
IIIB	1	0·9
Bone marrow cellularity at diagnosis		
Unknown	5	4·3
Hyper	65	55·6
Hypo	27	23·1
Normo	20	17·1
Number of lesions at diagnosis		
Unknown	3	2·6
0	19	16·2
1–3	40	34·2
>3	55	47·0
Plasmacytoma at diagnosis		
None	77	65·8
Osseous	38	32·5
Extraosseous	2	1·7

SMM, smouldering multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance.

diagnosis (38/117, 32·5%), while extraosseous plasmacytomas were less frequent (2/117, 1·7%).

Induction therapy

Amongst the eight bortezomib-based protocols, the RVD combination and bortezomib, as a single agent, were the most prevalent induction regimens (35% and 34·2%, respectively) (Table II). Sixteen out of 117 patients were given a second induction regimen for inadequate response to initial therapy.

Overall, 69 patients received an induction regimen containing combinations of bortezomib and lenalidomide: RVD, RVD-cyclophosphamide, RVD-liposomal doxorubicin, or RVD-vorinostat. The remaining 48 patients received bortezomib-based induction therapies without lenalidomide: bortezomib, MPV, CVD (cyclophosphamide, bortezomib, dexamethasone), and MPV-CNT0328. Throughout the follow-up period, 57 patients (48·7%) received an autologous stem cell transplant and four patients (3·4%) received an allogeneic stem cell transplant.

Response to initial therapy

Of the 117 participants, 21 patients achieved a complete remission (17·9%), 30 patients achieved a very good partial remission (25·6%) and 40 patients achieved a partial remission (PR) (34·2%). The overall response rate (PR or better) in this population was 77·7%. Only one patient (0·9%) experienced progressive disease with initial therapy. Fifty-five patients (47%) were placed on maintenance therapy following initial response; the most common maintenance agents following initial therapy were lenalidomide (36·4%) and bortezomib (43·6%). Ninety-seven patients (82·9%) eventually progressed during the follow-up period of the study.

Table II. Initial induction regimen and years of enrollment.

	N (%)	Years of enrollment
Initial induction regimen		
RVD	41 (35·0)	2006–2009
CVD	6 (5·1)	2008–2009
CRVD	10 (8·5)	2008–2009
V	40 (34·2)	2003–2006
RVD-Vorinostat	5 (4·3)	2011–2012
MPV_CNT0328	2 (1·7)	2010–2011
RVD_Doxil	9 (7·7)	2008–2009
MPV	4 (3·4)	2006

RVD, lenalidomide (Revlimid), bortezomib (Velcade), dexamethasone; CVD, cyclophosphamide, bortezomib, dexamethasone; CRVD, cyclophosphamide, lenalidomide, bortezomib, dexamethasone; V, Velcade (bortezomib); MPV, melphalan, prednisone, bortezomib; CNT0328, antibody against interleukin 6; Doxil, liposomal doxorubicin.

Plasmacytoma at follow-up

Overall, median follow-up time from diagnosis was 6·1 years (range 0·1–10·2 years) for the entire cohort; and 5·6 years (range 1·5–7·4) vs. 8·9 (range 0·1–10·2), respectively, for bortezomib-based treatment with *versus* without lenalidomide. Treatment-emergent EMD was observed in the form of osseous (n = 32, 27·4%), extraosseous (n = 19, 16·2%) or any osseous or extraosseous plasmacytoma (n = 40, 34·2%). The estimated 2-, 4-, 5- and 6-year progression rates of osseous, extraosseous and any plasmacytoma (osseous or extraosseous) in all patients can be viewed in Table III and Fig 1.

Histological evaluation was available in 7 of the 19 extraosseous plasmacytomas and in 5 of the 32 osseous plasmacytomas at progression. Biopsies were more readily obtained at diagnosis than at disease relapse, with histological tissue available in 23 of the 40 plasmacytomas at initial presentation. Only one patient had EMD in the form of plasma cell leukaemia with the diagnosis based upon evaluation of a peripheral blood smear and an absolute plasma cell count in excess of 2000.

Treatment for extraosseous plasmacytomas at progression (n = 19) consisted of radiotherapy (57·9%), bortezomib-based treatment (42·1%), lenalidomide-based treatment (21·1%), thalidomide-based treatment (31·6%) or surgical intervention (10·5%). An objective response was achieved in 36·9% of cases. Disease progression, however, occurred in the majority of cases (57·9%) despite treatment with these various therapeutic modalities.

History of previous MGUS and low haemoglobin concentration (<120 g/l) at diagnosis had a trend for shorter time to development of extraosseous plasmacytomas in univariate analyses (P = 0·06 and 0·05, respectively, Table IV). In multivariate analysis adjusted for ISS and other clinical risk factors, only history of MGUS remained a marginally significant association with time to development of extraosseous plasmacytomas (adjusted P = 0·06), but there was limited power for this analysis. For osseous plasmacytoma progression, only an elevated calcium level (≥2·5 mmol/l) predicted for poor outcome from multivariate analysis [hazard ratio (HR) = 2·9, adjusted P = 0·04]. Patients with ISS stage III had an increased risk for extraosseous progression (HR = 2·6), but the association was not statistically significant, probably due to the low incidence of ISS stage III in this population (9%).

Table III. The cumulative incidence of extramedullary disease progression (95% confidence interval) for all patients.

All patients	Osseous (%)	Extraosseous (%)	Any osseous or extarosseous plasmacytoma (%)
At 2 years	9 (4, 15)	4 (2, 9)	12 (7, 19)
At 4 years	19 (12, 26)	11 (6, 18)	25 (17, 33)
At 5 years	23 (15, 31)	15 (9, 22)	30 (21, 38)
At 6 years	29 (20, 38)	16 (10, 24)	36 (26, 45)
Total failure	32	19	40

Cytogenetic features were evaluated by fluorescence *in situ* hybridization (FISH): 15 of 94 (16%), 34 of 95 (36%), 43 out 92 (47%) and 9 of 67 (13%) evaluable patients presented with *t*(11:14), any IgH 14q32 rearrangement, del 13/13q, and del 17p, respectively. The presence of these cytogenetic features was not associated with osseous or extraosseous plasmacytoma progression ($P > 0.45$). However, we observed that all patients who had extraosseous plasmacytomas did not exhibit a *t* (11:14) by FISH (HR was not evaluable).

For the 19 patients who developed extraosseous plasmacytomas, the median OS was 0·9 years (range 0·1–4·8 years). For the 32 patients who developed osseous plasmacytomas during the follow-up period, median OS after osseous progression was longer, at 2·47 years (0·1–8·7).

In sensitivity analyses with follow-up times truncated at 5 years (Table V), the rates of any form of EMD showed no statistically significant difference between the two treatment

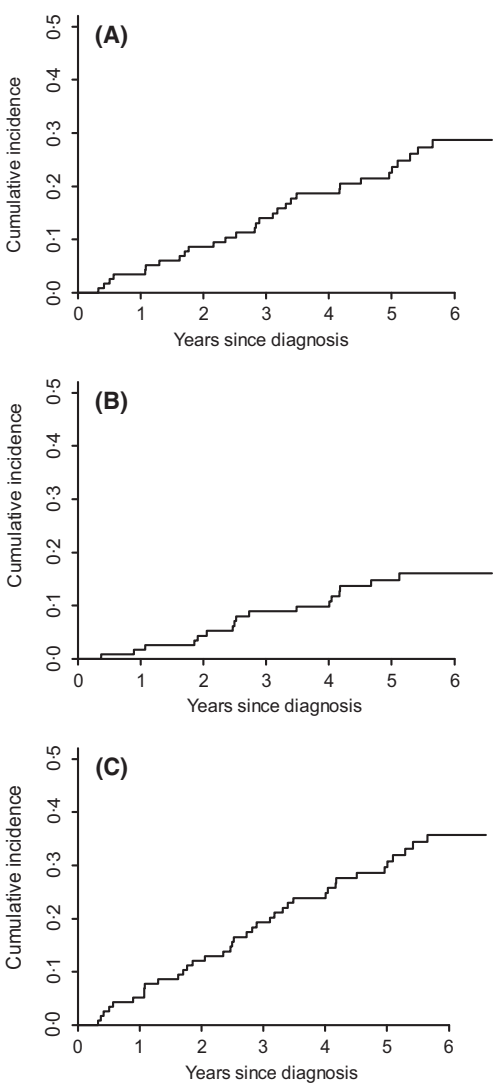

Fig 1. The cumulative incidence of development of osseous plasmacytoma (A), extraosseous plasmacytoma (B) and any plasmacytoma (C) after treatment.

Table IV. Risk factors for EMD progression.

	Osseous progressive disease				Extraossous progressive disease			
	Univariate		Multivariate*		Univariate		Multivariate*	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*
ISS		0·73	–	–		0·34	–	–
II *versus* I	0·8 (0·4, 1·6)		–	–	0·8 (0·3, 2·2)		–	–
III *versus* I	1·1 (0·3, 3·6)		–	–	2·3 (0·6, 8·5)		–	–
III *versus* I/II	1·3 (0·4, 3·9)	0·70	1·3 (0·5, 3·7)	0·61	2·5 (0·7, 8·7)	0·15	2·6 (0·7, 9·0)	0·13
DSS-III *versus* I/II	1·8 (0·9, 3·4)	0·09	1·7 (0·7, 4·2)	0·23	1·3 (0·7, 2·4)	0·45	–	–
Plasmacytoma at diagnosis	2·3 (1·2, 4·5)	0·02	1·7 (0·8, 3·7)	0·15	1·3 (0·5, 3·2)	0·60	–	–
History of MGUS	2·6 (1·0, 6·7)	0·05	2·1 (0·8, 5·4)	0·12	2·8 (0·9, 8·1)	0·06	2·7 (1·0, 7·8)	0·06
History of SMM	0·3 (0·1, 1·2)	0·08	0·4 (0·1, 2·1)	0·30	0·2 (0·03, 1·8)	0·16	–	–
B2M ≥ 3·5 mg/l	1·0 (0·5, 2·0)	0·95			0·9 (0·4, 2·4)	0·90	–	–
Hb < 120 g/l	1·6 (0·8, 3·1)	0·21			2·5 (1·0, 6·4)	0·05	2·0 (0·7, 5·1)	0·17
Calcium ≥ 2·5 mmol/l	2·2 (1·0, 4·8)	0·05	2·9 (1·1, 7·6)	0·04	2·2 (0·7, 6·3)	0·15	2·2 (0·8, 5·8)	0·13
FISH *t*(11:14)†	0·7 (0·2, 2·0)	0·45			‡	‡		
FISH *IGH* 14q32 rearrangement†	0·9 (0·4, 1·9)	0·70			1·0 (0·4, 2·6)	0·95		
FISH del 13/13q†	1·0 (0·5, 2·2)	0·96			1·3 (0·5, 3·6)	0·55		
FISH del 17p†	1·4 (0·5, 4·4)	0·54			1·4 (0·3, 6·3)	0·62		

EMD, extramedullary disease; ISS, international Staging System; DSS, Durie-Salmon stage; MGUS, monoclonal gammopathy of undetermined significance; SMM smouldering multiple myeloma; B2M, β2-microglobulin; Hb, haemoglobin concentration; FISH, fluorescence *in situ* hybridization; HR, hazard ratio.

*Includes all variables with $P < 0{\cdot}15$ from the univariate analysis and ISS stage given its prognostic importance.

†By FISH, 15 of 94 (16%), 34 of 95 (36%), 43 of 92 (47%) and 9 of 67 (13%) evaluable patients presented with *t*(11:14), IgH 14q32 rearrangement, del 13/13q, and del 17p, respectively.

‡All patients who had extraosseous progressive disease did not exhibit *t*(11:14) by FISH (HR was not evaluable). This variable was not included in the multivariate model.

groups ($P > 0{\cdot}2$ for all comparisons). Results were consistent if follow-up times were truncated at 7 years (data not shown). Of note, we did not detect a statistically significant difference between the two treatment groups in patient baseline characteristics, including ISS/Durie-Salmon stage, presence of plasmacytoma at diagnosis, history of MGUS, low haemoglobin and elevated calcium (Fisher's exact test, $P > 0{\cdot}15$, data not shown).

Discussion

This study describes the time to development of EMD in a cohort of MM patients who participated in clinical trials of bortezomib-based upfront therapy at our institutions. Until now, very few studies have focused on the incidence of EMD in the era of novel agents. The factors contributing to the perceived increase in the incidence of EMD amongst patients treated with these novel agents and combinations thereof in recent years have yet to be established. It is generally considered that EMD develops when drug-resistant clones selected for by treatment(s) also exhibit the capacity to survive and proliferate outside of the bone marrow microenvironment.

Several studies have shown that novel agents are able to disrupt the local bone marrow micro-environment (Anderson, 2001), which plays a key role in the pathogenesis of myeloma by mediating plasma cell proliferation, migration and survival. A suggested mechanism of extramedullary spread is by the loss of expression of the adhesion molecule, CD56 (Vande Broek *et al*, 2008). Chang *et al* (2005) reported two cases of patients with central nervous system involvement by plasma cells that were lacking expression of CD56 but were expressing it in the bone marrow (Chang *et al*, 2005). The development of treatment-related EMD can also be explained by the CXCL12 (SDF-1α)/CXCR4 interface, which promotes the interaction between plasma cells and the surrounding bone marrow stroma. The expression of this ligand/receptor pairing was found to be downregulated in patients previously treated with thalidomide (Oliveira *et al*, 2009).

Varettoni *et al* (2010) evaluated 1003 patients diagnosed with MM between 1971 and 2007 at a single institution. The incidence of plasmacytomas was increased in more recent years (2000–2007) compared to the pre-thalidomide era (1971–1999). Similar to our study, soft tissue masses extending from the axial skeleton were more prevalent at diagnosis (85%) than extraosseous soft tissue masses (15%) (Varettoni *et al*, 2010). At time of progression, however, there was an increasing rate of extraosseous plasmacytomas at 28% (Varettoni *et al*, 2010). In multivariate analysis, the risk of extramedullary spread was not associated with prior exposure to novel agents, such as thalidomide, lenalidomide, or bortezomib. In a study by Short *et al* (2011), which investigated 174 consecutive patients with relapsed refractory MM, it was reported that

Table V. Development of extramedullary disease after treatment with lenalidomide + bortezomib-based *versus* bortezomib-based (no lenalidomide) patients with follow-up times truncated at 5 years.

	t-Years progression rate (%) (95% CI)			
	Lenalidomide + bortezomib ($N = 69$)	Bortezomib-based (no lenalidomide) ($N = 48$)	*P*-value	Hazard ratio (95% CI)
Osseous				
At 2 years	7 (3, 15)	11 (4, 21)	0·663	0·84 (0·38, 1·84)
At 4 years	17 (9, 26)	22 (11, 35)		
At 5 years	22 (12, 32)	24 (13, 37)		
Total failure, *N*	14	11		
Extraosseous				
At 2 years	4 (1, 11)	4 (1, 13)	0·204	0·53 (0·20, 1·41)
At 4 years	8 (3, 16)	13 (5, 25)		
At 5 years	11 (5, 20)	20 (10, 33)		
Total failure, *N*	7	9		
Any plasmacytoma				
At 2 years	10 (4, 19)	15 (6, 27)	0·503	0·79 (0·40, 1·57)
At 4 years	23 (13, 33)	26 (14, 39)		
At 5 years	28 (17, 39)	33 (20, 47)		
Total failure, *N*	18	15		

*The reference group is the 'no lenalidomide' treatment group.

100% of patients who developed EMD in this retrospective study had previously been exposed to immunomodulatory agents (thalidomide or lenalidomide). In another retrospective single-centre study of 24 myeloma cases, Rasche *et al* (2012) demonstrated that only 8% of extramedullary relapses occurred after initial treatment, but 54% occurred after the third line of therapy. However, an important question not addressed by these studies is whether upfront therapy with combinations of a PI and an IMID predisposes patients to faster development of EMD. We therefore embarked on evaluating this question in a cohort of patients enrolled in one of 8 clinical trials of first-line treatment with bortezomib-based regimens either with or without lenalidomide.

In this retrospective study, 40 patients (34·2%) developed a plasmacytoma (osseous or extraosseous) at time of progression from their front-line therapy. Extraosseous EMD was more frequently noted at relapse than at initial diagnosis. At truncated follow-up times of 5 years and 7 years, there was no statistically significant increase in rates of any form of EMD between the two treatment groups (bortezomib with lenalidomide *versus* without lenalidomide). Based on these results, there is no evidence to suggest that combination bortezomib–lenalidomide-based front-line therapy precipitates more rapid development of EMD. Conversely, the development of extraosseous plasmacytoma was associated with poor OS (median OS 0·9 years) regardless of prior treatment. Pour *et al* (2014) similarly concluded that patients with soft tissue masses distant from bone at relapse had a dismal prognosis, with a median OS from diagnosis of EMD of 5 months. These observations emphasize the need for the development of innovative treatment strategies and in particular for these patients.

In addition, these results support the notion that the perceived increase in the incidence of EMD in recent years is related to the improved survival in this patient population: specifically, as patients are being followed-up over longer periods of time, their probability of eventually relapsing with extramedullary lesions conceivably increases. It is also plausible that the observed increase in the rate of EMD at relapse partly reflects the use of more sensitive imaging techniques. This may explain the high number of plasmacytomas at diagnosis (34·2%) reported both in our study and the study of Varettoni *et al* (2010). Our patient population consisted of clinical trial participants in tertiary care facilities, where imaging with computerized tomography, positron emission tomography and magnetic resonance imaging is more commonly requested.

Molecular cytogenetic data from extramedullary lesions has been documented in small case series. Lopez-Anglada *et al* (2010) documented a case of relapsed EMD with a newly acquired *TP53* (*p53*) deletion in the soft tissue lesion, but wild type *TP53* in the bone marrow. Another group performed immunostains for TP53 on both bone marrow and plasmacytoma biopsies from 12 cases of MM and found an increased nuclear accumulation of TP53 in the extramedullary tissues (Sheth *et al*, 2009). In a retrospective study, Rasche *et al* (2012) identified 24 patients with relapsed extramedullary plasmacytomas, 19 of which had available molecular data. Cytogenetics at initial MM diagnosis revealed 13q deletion in 11 of 19 cases, *t*(4,14) in 10 of 19 (52%) and deletion 17p in 4 of 19 (21%) (Rasche *et al*, 2012). These incidences are significantly higher when compared to medullary MM. Using gene expression profiling (GEP), Usmani *et al* (2012) determined that the cumulative

incidence of EMD was significantly increased in patients who had GEP-defined high-risk disease, such as *MAF* and *MAFB* over-expression, usually associated with *t*(14;16) and *t*(14;20) translocations, respectively. In our study, del13/13q by FISH was the most common cytogenetic abnormality at diagnosis, followed by *IGH* 14q32 rearrangement (26%), *t*(11;14) (17%) and finally, del 17p (6%). Statistically, the presence of these cytogenetic findings at diagnosis did not predict for the development of plasmacytoma at progression. Interestingly, all patients who did develop extraosseous soft tissue masses at progression did not exhibit a *t*(11;14) by FISH at diagnosis. In a study by Bink *et al* (2008), 38 cases of primary extramedullary plasmacytomas were analysed by FISH and compared to data found in systemic MM. Cytogenetically, extramedullary lesions and MM were closely related, but only *t*(11;14) translocations were absent from the extramedullary group (Bink *et al*, 2008). These findings raise the question about a possible protective role associated with the presence of a *t*(11;14) translocation at diagnosis against the development of extraosseous disease at progression. A larger patient population is needed to further confirm this hypothesis.

This study was limited by the relatively limited number of patients and the retrospective nature of the data collection. Due to the different follow-up times for the various protocols, we had to use sensitivity analysis to formally compare the rate of development of EMD between the two treatment groups. Furthermore, while the use of clinical trial data provided us with systematic follow-up information, the patients participating in these trials do not necessarily reflect patients with MM on a global scale. For these reasons, further confirmation of our findings with extended follow-up, as well as studies of treatment effect and correlative studies (incorporating both genotypic and phenotypic features), as well as outcome of EMD are warranted. Nonetheless, the results of this study indicate that there is no evidence, at this point, to suggest that upfront therapy based on combinations of bortezomib and lenalidomide in newly diagnosed MM patients are associated with faster development of EMD. These results also underscore the importance of combination therapy and the value of synergism between IMID and PI in the frontline treatment of patients with MM as well as the importance of rational combination therapy as part of treatment strategies across the course of the disease as a whole (Lonial *et al*, 2011).

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Author contributions

C.V. performed the medical chart review, analysed data and participated in the writing of the paper. W.X. provided input in the design of the study, analysed data and participated in the writing of the paper. J.L., I.M., E.K.O'D, C.P.-P., M.W., D.W., R.S., N.C.M, N.R., and K.C.A. contributed to clinical follow-up of patients, as well as analysis and interpretation of data. M.E.M contributed to data collection. E.W. provided input in the design of the study, analysed data and participated in the writing of the paper. C.S.M. designed the research study, and participated in the interpretation of data and writing of the paper. P.G.R. contributed to the design of the study and participated in the interpretation of data, writing of the paper and clinical follow up of patients.

Disclosures

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