Bone-independent extramedullary disease is associated with inferior overall survival in multiple myeloma patients: a single-center, real-world experience

Multiple myeloma (MM) is characterized by the accumulation of malignant plasma cells in the bone marrow resulting in lytic bone lesions, hypercalcemia and anemia.[1,2] In up to 20% of myeloma cases at diagnosis, plasma cell aggregates occur outside of the bone marrow, referred to as extramedullary disease (EMD).[3-6] Most extramedullary myeloma manifestations are contiguous with bone (paraosseous, bone-associated) but in a minority of cases, the infiltration occurs in anatomical sites independent of bone. Bone-independent extramedullary disease (BI-EMD) is thought to confer a poorer prognosis compared with paraosseous EMD[7] although this conclusion is mostly based on relatively small cohorts of patients from observational studies conducted prior to the widespread availability of novel myeloma agents. Most published studies on EMD focus on the clinical characteristics and outcomes of paraosseous EMD and only very few studies have specifically analyzed BI-EMD cases with a view to determining associations with known high-risk features. The aim of this study was to determine the incidence, clinical characteristics, association with bone disease, skeletal-related events (SRE) including pathological fractures, spinal cord compression, radiotherapy and surgical interventions, as well as response to treatment and overall survival (OS) of BI-EMD in a single-center cohort of newly diagnosed myeloma patients.

To determine the clinical characteristics and outcomes of myeloma patients presenting with BI-EMD at the time of diagnosis, we retrospectively analyzed the clinical data of symptomatic adult MM patients, as defined by the International Myeloma Working Group (IMWG) criteria, who were treated and actively followed up at University College Hospital, London, UK, between January 1, 2018 and December 31, 2022. The data cut-off date was May 3, 2023. BI-EMD in our study was defined as MM cases with plasma cell infiltration of an anatomical site distant from the bone marrow, diagnosed by whole body imaging. Patients with plasma cell leukemia and those who did not meet the criteria for MM diagnosis were excluded from the study. *P* values were calculated using logistic regression or Fisher's exact test. This study was conducted in accordance with institutional requirements and the Declaration of Helsinki. Thirty-three (33) of the 906 patients (3.6%) diagnosed with MM between 2004 and 2022 had BI-EMD at diagnosis (primary BI-EMD) while 22 (2.4%) cases were identified at relapse (secondary BI-EMD). The median duration of follow-up was 45 months (range, 1-270 months). The clinical characteristics and outcomes of the primary BI-EMD cases are summarized in Table 1. The commonest sites for primary BI-EMD were lymph nodes (45%), spleen (15%) and peritoneal nodules (9%). Other affected sites included thyroid, breast, testis, pancreas, larynx, pericardial effusion and pleural effusion. Compared with MM patients without BI-EMD, at least one skeletal-related event (SRE) was present at diagnosis in 61% of patients with primary BI-EMD *versus* 44% without BI-EMD (*P*=0.07). There was no statistically significant difference for age, sex, ethnic origin, isotype, ISS stage, high-risk cytogenetics (fluorescence *in situ* hybridization [FISH]), bone disease or first line treatment regimen between patients with or without primary BI-EMD. Of the 22 patients with secondary BI-EMD, 12 had BI-EMD at first relapse and ten at subsequent relapses. The most common secondary BI-EMD sites were lymph nodes (40%), spleen (14%), thyroid (14%), pancreas (14%), peritoneal nodules (9%), and liver (9%).

The induction treatment modalities for primary BI-EMD patients in this study were chemotherapy alone for 29 (88%) while four (12%) patients had radiotherapy in combination with chemotherapy. The majority of patients received proteosome inhibitor and immunomodulatory agents or a combination of these (72.8%). An autologous stem cell transplant (ASCT) was performed for 22 patients (67%) including three (9%) patients who received tandem ASCT. Treatment response rates were 25% complete response (CR) or very good partial response (VGPR) for the BI-EMD group compared with 30% CR plus VGPR in the patients without BI-EMD. The overall response rate (ORR) was 83.3% (95% confidence interval [CI]: 62.6-95.3) for the BI-EMD patients and 95.8% (95% CI: 93.7-97.3) for the non-BI-EMD patients (*P*=0.02). Fifteen (45%) primary BI-EMD patients relapsed during the follow-up period and at first relapse, 13 (87%) had non-EMD progression while two (13%) had bone-associated EMD progression. None of the relapses presented as BI-EMD progression.

Univariate analysis showed inferior OS for MM patients with BI-EMD at diagnosis compared with those without BI-EMD; hazard ratio (HR) =4.62 (95% CI: 1.99-10.77; *P*<0.01). After adjustment for age, disease isotype and SRE at diagnosis this difference remained statistically significant (HR=3.67, 95% CI: 1.29-10.43; *P*=0.01). Kaplan-Meier analysis estimated 3-year OS rates of 87.7% (95% CI: 66.0-95.9) for the BI-EMD group and 97.9% (95% CI: 96.6-98.8) for the non-BI-EMD group (Figure 1).

Table 1. Patient characteristics with bone-independent extramedullary disease and without bone-independent extramedullary disease at diagnosis (*P* values calculated using logistic regression).

Characteristics	BI-EMD at diagnosis N=33	Without BI-EMD at diagnosis N=873	OR (95% CI)	*P*
	N (%)	N (%)		
Age in years				
<70	30 (90.9)	738 (84.5)	Reference	
70+	3 (9.1)	135 (15.5)	0.55 (0.16-1.82)	0.3
Sex				
Male	20 (60.6)	522 (59.8)	Reference	
Female	13 (39.4)	351 (40.2)	0.97 (0.47-1.97)	0.9
Ethnicity				
White	11 (50.0)	443 (68.3)	Reference	
Asian	4 (18.2)	57 (8.8)	2.83 (0.87-9.17)	
Black	5 (22.7)	98 (15.1)	2.05 (0.70-6.05)	
Chinese	0	4 (0.6)	N/A	0.3*
Mixed	0	12 (1.8)	N/A	
Other	2 (9.1)	35 (5.4)	2.30 (0.49-10.79)	
Missing	11	224		
LDH units/L				
<214	5 (45.5)	172 (68.8)	Reference	
>214	6 (54.5)	78 (31.2)	2.65 (0.78-8.93)	0.1
Missing	22	623		
Hemoglobin g/dL				
<10	4 (26.7)	160 (38.3)	Reference	
10+	11 (73.3)	258 (61.7)	1.71 (0.53-5.45)	0.4
Missing	18	455		
Adjusted Calcium mmol/L				
<2.6	7 (63.6)	295 (67.0)	Reference	
>2.6	4 (36.4)	145 (33.0)	1.16 (0.33-4.04)	0.8
Missing	22	433		
Disease isotype				
IgG	17 (60.7)	493 (59.9)	Reference	
IgA	5 (17.9)	133 (16.2)	1.09 (0.39-3.01)	
LC	5 (17.9)	194 (23.6)	0.75 (0.27-2.05)	0.2*
Other	1 (3.6)	3 (0.4)	9.67 (0.96-97.80)	
Missing	5	50		
ISS				
I	5 (27.8)	235 (42.9)	Reference	
II	7 (38.9)	181 (33.0)	1.82 (0.57-5.82)	0.4*
III	6 (33.3)	132 (24.1)	2.14 (0.64-7.13)	
Missing	15	325		
FISH				
High risk	7 (31.8)	111 (20.0)	Reference	
del(17p)	5 (22.7)	41 (7.4)	-	
t(4;14)	3 (13.6)	56 (10.1)	-	
t(14;16)	0	18 (3.2)	-	
Standard risk	15 (68.2)	444 (80.0)	1.87 (0.74-4.69)	0.2
Missing	11	318		
First line therapy				
PI	6 (18.2)	227 (26.1)	Reference	
IMiD	5 (15.2)	80 (9.2)	2.36 (0.70-7.96)	
PI and IMiD	13 (39.4)	307 (35.3)	1.60 (0.60-4.28)	
CC	0	25 (2.9)	N/A	
Anti-CD38 antibody plus PI/IMiD	4 (12.1)	88 (10.1)	1.72 (0.47-6.24)	0.7*
Immunotherapy other	0	0	1.32 (0.40-4.41)	
Other	5 (15.2)	143 (16.4)	0.03 (0.01-0.06)	
Missing	0	3		

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Characteristics	BI-EMD at diagnosis N=33	Without BI-EMD at diagnosis N=873	OR (95% CI)	*P*
	N (%)	N (%)		
Response to first line therapy				
SD	4 (16.7)	24 (4.2)	Reference	
PR	14 (58.3)	371 (65.7)	0.23 (0.07-0.74)	
VGPR	4 (16.7)	135 (23.9)	0.18 (0.04-0.76)	0.06*
CR	2 (8.3)	35 (6.2)	0.34 (0.06-2.02)	
Missing	9	308		
Overall response	83.3 (95% CI: 62.6-95.3)	95.8 (95% CI: 93.7-97.3)		0.02
SRE at diagnosis				
No	13 (39.4)	484 (55.9)	Reference	
Yes	20 (60.6)	382 (44.1)	1.95 (0.96-3.97)	0.07
Missing	0	7		

First line therapy regimens: i) proteasome inhibitor (PI)-based - PAD: bortezomib, adriamycin and dexamethasone; ii) immunomodulatory agents (ImiD)-based - CTD: cyclophosphamide, thalidomide and dexamethasone; MPT: melphalan, prednisolone and thalidomidde; MPR: melphalan, prednisolone and lenalidomide; CRD: carfilzomib, lenalidomide and dexamethasone; DT-PACE: dexamethasone, thalidomide, cisplatin, adriamycin, cyclophosphamide, etoposide; iii) PI and ImiD - IRD: ixazomib, lenalidomide and dexamethasone; VTD: bortezomib, thalidomide and dexamethasone; iv) conventional chemotherapy (CC) – ESHAP: etoposide, methylprednisolone, high-dose cytarabine, cisplatin; VAD: vincristine, adriamycin and dexamethasone; C-VAMP: cyclophosphamide vincristine, doxorubicin and methylprednisolone; v) anti-CD38 antibody +PI/ImiD - isatuximab, pomalidomide, dexamethasone, daratumumab-VTD; vi) immunotherapy other teclistamab, talquetamab; chimerica ntigen receptor T-cell, venetoclax, daratumumab single agent). BI-EMD: bone-independent extramedullary disease; OR: odds ratio; CI: confidence interval; N/A: not applicable; LDH: lactate dehydrogenase; Ig: immunoglobulin; ISS: international staging system; FISH: fluorescence *in situ* hybridization; SD: stable disease; PR: partial response; VGPR: very good partial response; CR: complete response; LC: light chain, SRE: skeletal-related event. **P* values calculated using Fisher's exact test.

In this single-center retrospective study, the rate of BI-EMD in MM patients was similar to previous studies.[5,8] Usmani *et al.*[8] similarly analyzed newly diagnosed myeloma patients who had baseline positron emssion tomography/computed tomography (PET/CT) scans and reported EMD in 3.4% of MM patients at diagnosis. He *et al.*[3] also observed BI-EMD in 2.8% of cases by PET/CT at diagnosis. Weinstock *et al.* reported 1.2% BI-EMD at the time of diagnosis in a cohort of patients who subsequently received an ASCT or allogeneic transplant.[9] In concordance with previously published observations, BI-EMD is less common (3.2%) at the time of diagnosis compared with paraosseous EMD (13.2%) however, unlike other studies, we did not observe a higher rate of BI-EMD in relapsed MM patients with a secondary BI-EMD rate of 2.4%. The use of fluorodeoxyglucose (FDG) PET/CT scan definition for BI-EMD has a number of advantages and drawbacks. It allowed the identification of extramedullary disease in organs or tissues which would have been inaccessible to biopsy for histology. However, given the possibility of non-specific FDG uptake within certain tissues, specificity remains a challenge. It is noteworthy that histological confirmation was done in cases where biopsy was feasible. Nevertheless, correlation was observed in the resolution of extramedullary disease with overall myeloma disease response in individual patients. Interestingly, Gagelman *et al.*[5] observed from a large registry dataset, a significant increase in incidence rates of EMD from 6.5% to 23.7% between 2005 and 2014. While the authors did not specifically explore the reasons for this increase, it is possible that the recent adoption of sensitive imaging techniques such as PET/CT and PET-magnetic resonance imaging in myeloma may have contributed to this finding. In this retrospective analysis, fit MM patients with EMD were considered for treatment intensification at induction with regimens such as VTD-PACE and PET/CT imaging upstaging was essential for the identification of this group of patients. Evidently, well-designed clinical trials are needed to evaluate treatment regimens for this patient group in the current era of novel therapies including immunotherapies.

As plasma cells are usually dependent on the bone marrow microenvironment for survival, extramedullary MM occurs when malignant plasma cells evolve mechanisms to survive independent of the bone marrow stroma. Therefore, patients with BI-EMD at diagnosis (as opposed to paraosseous EMD and those without EMD) likely represent a group with unique fundamental biology. Several possible mechanisms have been postulated for the development of EMD including downregulation of chemokine receptors such as CCR1 and CXCR4 as well as decreased expression of adhesion molecules.[10] Higher rates of chromosomal aberrations have also been identified in extramedullary plasma cells compared with bone marrow plasma cells in MM patients.[11] Given the small sample size, this study was not adequately powered to determine differences in presenting characteristics but interesting trends were observed. For instance, the rate of 17p deletion was 22.7% in MM patients with BI-EMD compared with 7.4% in patients without BI-EMD and this difference was statistically significant (Fisher's exact test *P*=0.02). However, there was no significant difference when all high-risk cytogenetics were compared between the two groups (Table 1). The rate of stable disease (SD) following

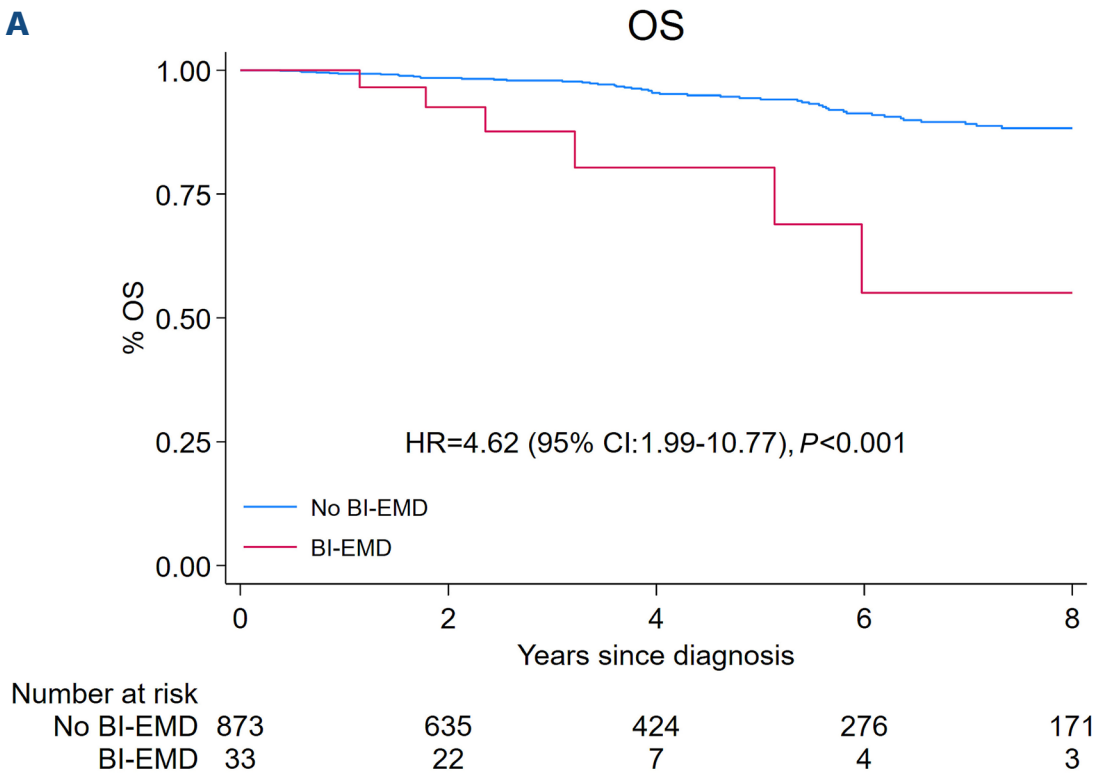

Figure 1. Survival outcomes of myeloma patients with bone-independent extramedullary disease compared with those without bone-independent extramedullary disease. (A) Overall survival (OS). (B) Progression-free survival (PFS). BI-EMD: bone-independent extramedullary disease; HR: hazard ratio; CI: confidence interval.

induction chemotherapy was also relatively higher in BI-EMD patients (16.7% *vs.* 4.2%).

The presence of EMD regardless of the type is associated with inferior OS and a poor prognosis.[3,4,8] Furthermore, findings from another single-center study reported inferior survival for MM patients with BI-EMD compared with paraosseous EMD.[7] Our single-center retrospective analysis showed inferior ORR and OS for BI-EMD patients despite the majority of patients receiving novel anti-myeloma agents (proteasome inhibitors, immumomodulatory drugs, IMid, anti-CD38 antibodies). PFS analysis was however limited due to the relatively short duration of follow-up in this study. Evidently, investigation of novel agents is required to improve outcomes in EMD. A recent early-phase trial of mezigdomide, a cereblon E3 ligase modulator, in a heavily pretreated group of MM patients showed an overall response rate of 30% in a subgroup with EMD.[12] The activity of regimens with novel therapeutic agents including peptide-drug conjugates such as melflufen[13] similarly need to be evaluated in myeloma patients with BI-EMD, particularly earlier in the disease course.

In summary, despite treatment advancements in MM,[14] primary BI-EMD remains a poor prognostic feature conferring inferior overall treatment response and OS. Data from this single-center study suggests PET/CT scans allow the identification of BI-EMD thereby enabling the possibility of intensifying treatment. More studies including translational studies and clinical trials are needed to elucidate the unique biology of BI-EMD and in developing targeted therapies for this group of MM patients.

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Contributions

KX designed the study. KX and CA wrote the paper. WW performed the data analysis. NK collected the data. KX and CK were the supervising authors. All authors critically reviewed the manuscript.

Data-sharing statement

Data is available on request.

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