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RESEARCH ARTICLE

Hematogenous extramedullary relapse in multiple myeloma - a multicenter retrospective study in 127 patients

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Abstract

The current study assesses the characteristics and outcomes of multiple myeloma (MM) patients, treated with novel agents for hematogenous extramedullary (HEMM) relapse. Consecutive patients diagnosed with HEMM between 2010-2018 were included. Patients' characteristics at diagnosis and at HEMM presentation, response to treatment, survival and factors predicting survival were recorded and analyzed. A group of 127 patients, all diagnosed with HEMM by imaging (87.3%) and/or biopsy (79%), were included. Of those, 44% were initially diagnosed with ISS3, 57% presented with plasmacytomas, and 30% had high-risk cytogenetics. Median time to HEMM was 32 months. In multivariate analysis, ISS3 and bone plasmacytoma predicted shorter time to HEMM (P = .005 and P = .008, respectively). Upfront

autograft was associated with longer time to HEMM (P = .002). At HEMM, 32% of patients had no BM plasmacytosis, 20% had non-secretory disease and 43% had light-chain disease. Multiple HEMM sites were reported in 52% of patients, mostly involving soft tissue, skin (29%), and pleura/lung (25%). First treatment for HEMM included proteasome inhibitors (50%), immunomodulatory drugs (IMiDs) (39%), monoclonal antibodies (10%), and chemotherapy (53%). Overall response rate (ORR) was 57%. IMiDs were associated with higher ORR (HR 2.2, 95% CI 1.02-4.7, P = .04). Median survival from HEMM was 6 months (CI 95% 4.8-7.2). Failure to achieve ≥VGPR was the only significant factor for worse OS in multivariate analyses (HR = 9.87, CI 95% 2.35 - 39, P = .001). In conclusion, HEMM occurs within 3 years of initial myeloma diagnosis and is associated with dismal outcome. The IMiDs might provide a higher response rate, and achievement of ≥VGPR predicts longer survival.

1 | INTRODUCTION

Hematogenous Extramedullary multiple myeloma (HEMM) is defined as the presence of soft-tissue plasmacytoma or plasma cells (PC) infiltration, in an anatomical site distant from the bone marrow[1-7] Note, HEMM is reported in 10-30% of patients during the disease course. Recent retrospective studies suggest that the administration of novel agents has not resulted in an increased risk of HEMM development, compared with chemotherapy.[4,8] Moreover, the employment of lenalidomide before allogeneic hematopoietic cell transplantation, was found to be associated with a lower risk for the development of extramedullary relapse.[9] The current study, evaluating 127 patients, all treated for HEMM relapse in the novel agent era, aimed to define the characteristics of these patients, identify factors affecting time to HEMM development, and assess the impact of patient characteristics and management at the time of HEMM relapse on treatment outcome.

2 | METHODS

The study was conducted in accordance with the Helsinki declaration and approved in all participating centers.

Myeloma databases of all 15 participating centers were searched for consecutive patients that had been diagnosed with HEMM relapse between January, 2010 and March, 2018. Patients were required to have either an imaging scan that demonstrated HEMM or a histological confirmation of HEMM. Patients with HEMM relapse involving the central nervous system (CNS) as their single HEMM site were excluded. Patients with concomitant para-skeletal plasmacytoma were included.

Data were collected from patient files, focusing on patient demographics, myeloma-related parameters at diagnosis, treatment lines prior to the development of HEMM relapse and best response to these therapies (defined by IMWG criteria at the time of treatment). Also, disease characteristics at the time of HEMM relapse (including HEMM sites and number of sites being involved), therapy administered at the time of HEMM relapse, response to therapy, progression free survival (PFS) and overall survival (OS). Factors associated with shorter duration from diagnosis, to the development of HEMM relapse, and factors predicting OS since MM diagnosis and since the development of HEMM relapse were also assessed.

2.1 | Definitions

According to the IMWG criteria,[10] measurable disease was defined as serum M-protein ≥1 g/dL and/or urine M-protein ≥200 mg/24 hours. For patients not fulfilling these criteria, (like having an oligosecretory disease), measurable disease was defined as a FLC level ≥100 mg/L (or 10 mg/dL), provided that the serum FLC ratio is abnormal.

Non-secretory myeloma was defined in patients with no measurable monoclonal heavy or light chains in both blood and urine (assessed by serum and urinary protein electrophoresis [SPEP/UPEP], immunofixation and free light chain tests.[11]

Bone plasmacytosis was defined in the presence of monoclonal plasma cells in the BM sample (either by using aspiration accompanied by FACS analysis or by performing a BM biopsy with immunohistochemistry staining for Kappa and Lambda). Lack of BM plasmacytosis was defined in the absence of monoclonal PC in BM aspiration and/or biopsy. Light chain MM was defined in the presence of MM characterized with an exclusive excretion of light chains, without monoclonal heavy chain by immunofixation or SPEP.

Treatment regimens were divided into conventional chemotherapies (administered mainly as multi-agent combinations) vs novel therapies, including proteasome inhibitors, immunomodulating agents and monoclonal antibodies, administered alone or in combination with another novel agent/single chemotherapeutic agent. Response to treatment was defined according to the IMWG definitions.[10]

2.2 | Statistics

Categorical variables were described as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram and Q-Q plots, and reported as mean and SD (SD), or median and interquartile range (IQR).

Since all patients had HEMM during their follow up, time from MM diagnosis to HEMM development was studied as a continuous variable. The Kruskal-Wallis test, Mann-Whitney test, and Spearman's rank correlation coefficient, were applied to assess the association between time to HEMM, categorical and continuous variables. Time to HEMM was natural logarithm transformed, and multivariate linear regression was applied. The linear regression was evaluated to meet the assumptions. Variables that were associated at a significance level of $P < 0.15$ in univariate analysis, for whom less than 10% of the data were missing, were included in the multivariate analysis. Age and sex were included in the multivariate analysis regardless of their significance in the univariate analysis.

The reverse censoring method was used to evaluate the median follow up period, and Kaplan-Meier curve was employed to estimate survival. The log-rank test was used to compare survival between categorical variables. Univariate and multivariate Cox regression models were fitted to study the association between predictors and survival. Variables detected in univariate analysis ($P < 0.05$) were included in the multivariate analysis. Age and gender were included in multivariate analysis regardless of their significance in the univariate analysis.

All statistical tests were two sided, and $P < 0.05$ was considered as statistically significant. All statistical analyses were performed using SPSS software (IBM SPSS statistics for window, version 25, IBM Corp, Armonk, NY, USA, 2017).

3 | RESULTS

3.1 | Patient characteristics at MM diagnosis

One hundred twenty-seven patients were included. Patient characteristics at diagnosis are presented in Table 1. Median age at MM diagnosis was 63 years (range 27-94). Note that 46.4% of patients had IgG MM, 24.4% had IgA, 0.8% had IgD, 23% had light chain myeloma and 5.5% had non-secretory disease. Also note 44% of the patients had ISS3, and 57.5% (n = 73) presented with plasmacytomas. At presentation, 69 individuals had bone plasmacytoma and 20 had HEMM; 16 of them (80%) had concomitant paraskeletal plasmacytoma (characteristics of patients presenting with hematogenous extramedullary plasmacytoma are presented in Table S1 in the Supplementary materials). Thirty-two percent of the patients presented with high-risk cytogenetics, including 19% that had t(4;14) and 11% that had 17p deletion. Flow cytometry analysis revealed that CD56 was expressed in 72% of cases and CD20 in 16%.

First line therapy contained proteasome inhibitors (PIs) in 55%, immunomodulating agents (IMiDs) in 55% and chemotherapy in 62%. Fifty-nine percent (n = 74) underwent an upfront autologous hematopoietic stem cell transplantation (auto HSCT) prior to the HEMM development.

3.2 | Patient characteristics at the time of HEMM relapse

Patient characteristics at the time of HEMM relapse are presented in Table 2. Median time from diagnosis to HEMM (excluding the 20 patients that presented with HEMM involvement at diagnosis) was 32 months (16-56). (Figure 1A).

In all cases HEMM was detected by biopsy and/or imaging. HEMM was demonstrated in imaging scans in 110 cases (87%), including PET/CT scans in 28% (n = 36), CT in 56% (n = 61) and MRI in 18% (n = 23). HEMM was confirmed histologically or cytologically (in cases presenting with pleural effusion) in 79% of cases (n = 100).

Median age at diagnosis of HEMM relapse was 67 years (40-101). Sixty-one percent of patients have received at least two lines of therapy prior to HEMM relapse. A group of 110 patients (87%) developed HEMM after being exposed to ImiDs. and 85 (67%) after being exposed to both IMiDs and PIs.

TABLE 1 Patients characteristics at MM diagnosis

Characteristic	Number of evaluable cases	Median (range) or N (%)
Age (continuous)	127	63 (27-94)
Male sex	127	76 (60%)
Myeloma type		
Heavy chain MM	127	91 (72%)
IgG		59 (46.4%)
IgA		31 (24.4%)
IgD		1 (0.7%)
Light chain MM	127	29 (23%)
Non-secretory	127	7 (5.5%)
Light chain type		
Kappa	119	69 (58%)
Lambda		50 (42%)
Albumin (g/L) (continuous)	114	37 (20-60)
Beta-2-microglobulin (μg/mL) (continuous)	110	4.2 (0.6-36.8)
ISS		
ISS1	117	35 (30%)
ISS2	117	31 (27%)
ISS3	117	51 (44%)
FISH cytogenetics		
t(4;14)	88	17 (19%)
t(14;16)	88	2 (2%)
t(14;20)	88	0 (0%)
Del17p	88	10 (11%)
Del13q	88	28 (32%)
t(11;14)	88	6 (7%)
CD56 expression on MM cells	46	33 (72%)
CD20 expression on MM cells	37	6 (16%)
Any plasmacytomas at diagnosis	127	73 (57.5%)
Bone plasmocytoma	127	69 (54.3%)
HEMM	127	20 (15.7%)

Abbreviations: Del, deletion; HEMM, hematogenous extramedullary multiple myeloma; ISS, International Staging System; MM, multiple myeloma.

TABLE 2 Patients characteristics at HEMM diagnosis

Characteristic	Number of evaluable cases	Median (range) or N (%)
Age	127	67 (40-101)
Bone marrow involvement	98	67 (68%)
PCL[a]	127	7 (5.5%)
Non-secretory MM	105	21 (20%)
Light chain MM	127	54 (43%)
Involved sites	127	
Soft tissue/skin		37 (29.1%)
Pleura and lung		32 (25%)
Lymph nodes		22 (17.3%)
Liver		15 (11.8%)
CNS[b]		14 (11%)
Gastrointestinal		10 (7.9%)
Breast		10 (7.9%)
Pancreas		3 (2.4%)
Genitourinary organs		1 (0.8%)
Gums		1 (0.8%)
Spleen		1 (0.8%)
HEMM size >5 cm (longest diameter)	90	38 (53%)
HEMM >2 sites	92	46 (52%)
Elevated LDH	127	64 (59%)
CD56 expression on MM cells	127	33 (55%)
CD20 expression on MM cells	127	8 (14%)
B2 Microglobulin (μg/mL)	63	5 (2.87-7.2)
CRP (mg/L)	97	16.7 (3.21-58.5)
Number of prior lines	127	
0 prior lines	127	13 (10%)
1 prior line		37 (29%)
≥2 prior lines		77 (61%)
Prior exposure to IMiDs	127	110 (87%)
Prior exposure to IMiDs and PIs	127	85 (67%)

[a]2 of these patients had t(11;14), one had t(4;14), one had 17p deletion and 1 had 13q deletion.
[b]CNS (central nervous system)- always in addition to another HEMM site.
Abbreviations: CNS, central nervous system; HEMM, hematogenous extramedullary multiple myeloma; IMiDs, immunomodulating agents; LDH, lactate dehydrogenase; MM, multiple myeloma; PCL, plasma cell leukemia.

Bone marrow assessment at HEMM relapse showed no evidence of plasmacytosis in 31 out of the 98 evaluable cases (32%). Non-secretory disease was reported in 21 out of 105 evaluable cases (20%) and light chain disease was reported in 54 (43%) cases. Multiple hematogenous extrameduallary sites were reported in 52%. Most commonly involved sites were soft tissue and skin (n = 37, 29.1%), followed by pleura and lung (n = 32, 25%), lymph nodes (n = 22, 17%), liver (n = 15, 12%), CNS (n = 14, 11%), gastrointestinal tract (n = 10, 7.9%), breast (n = 10, 8%), pancreas (n = 3, 2%), genitourinary organs, spleen and gums (n = 1 for each one). Of note, five patients presented also with plasma cell leukemia at the time of HEMM relapse.

3.3 | Factors associated with duration to the development of HEMM

Univariate analysis found an increased beta-2-microglobulin level (r = –0.296, *P* = .002), advanced ISS stage (median time: I-46 m, II-34 m, III-23 m, *P* = .01), presence of del17p (median time: 8 m vs 27 m, *P* = .006) and extramedullary plasmacytomas at MM diagnosis (median time: 27 m vs 38 m, *P* = .006), to be associated with a shorter time from MM diagnosis to HEMM relapse. In contrast, upfront auto HSCT (median time: 42 m vs 22 m, *P* = .001) and the administration of IMiD prior to the development of HEMM relapse (median time: 38 m vs 25 m, *P* = .04) were associated with longer time to HEMM.

Multivariate analysis showed that patients who presented with ISS3 (compared with ISS1) had reduction of 43.7% in time to HEMM development (95% CI = 16.5%-62.0%, *P* = .005). In addition, patients with bone plasmacytoma at diagnosis had a 35.8% shorter time to HEMM relapse (95% CI = 11.1%-53.6%, *P* = .008). In contrast, upfront autoHSCT was significantly associated with a delayed time (85%) to HEMM occurrence (95% CI = 27%-170%, *P* = .002) (Figure 1B, Table 2S).

3.4 | Treatment at HEMM relapse, response to therapy and outcome

First treatment for HEMM included PIs in 50% (n = 64), IMiDs in 39% (n = 50), MAbs (excluding checkpoint inhibitors) in 10% (n = 13) and chemotherapy in 53% (n = 67). Overall response rate (ORR) was 57%, including 17 (15%) complete remission (CRs), 15 (13%) very good partial response (VGPRs), 25 (22%) partial response (PR). A group of 59 (51%) patients failed to respond to first treatment for HEMM. When IMiDs were compared with PIs and chemotherapy, they were associated with higher response rates (OR 2.2, 95% CI 1.02-4.7, *P* = .04). Of note, most novel agents were administered as doublets or triplets. Table S3A (supplementary materials) presents specific treatment regimens. The median number of therapies administered following the development of HEMM relapse was two (range: one-three). Salvage therapy was followed by ASCT and allogeneic transplantation in five and one patients, respectively.

3.5 | Survival following the development of HEMM relapse and factors predicting survival

Median follow-up since diagnosis was 11.1 years (95% CI 7.7-15.2). The three, five and eight-year survivals from MM diagnosis were 60.8 ± 4.6%, 39.5 ± 4.7% and 28.3 ± 4.3% respectively, with a median survival of 47.7 months (3.9 years) (CI 95% 33.6-61.7) (Figure 2A). Median survival from HEMM development was 6.5 months (0.5 year) (CI 95% 5.1-7.8), with one- and three-year OS of 35.8 ± 4.7% and 17.8 ± 4.3% respectively (Figure 2B).

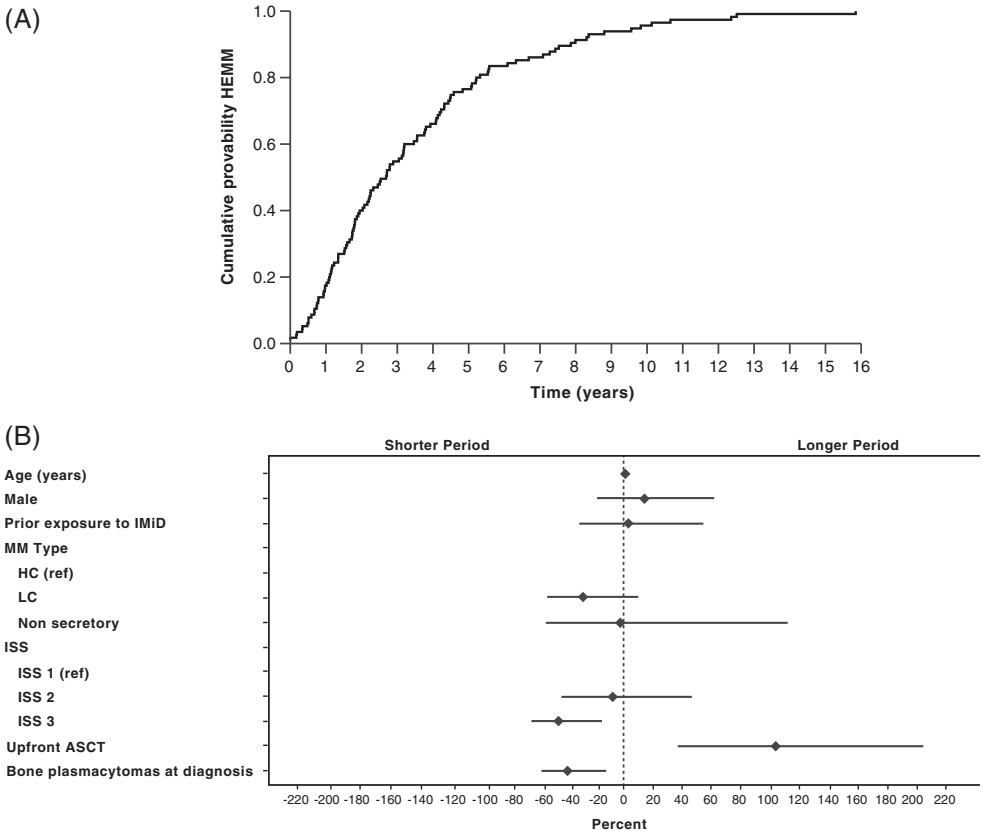

FIGURE 1 A, Time from myeloma diagnosis to hematogenous extramedullary relapse (HEMM) development. B, Factors affecting duration from diagnosis to HEMM development

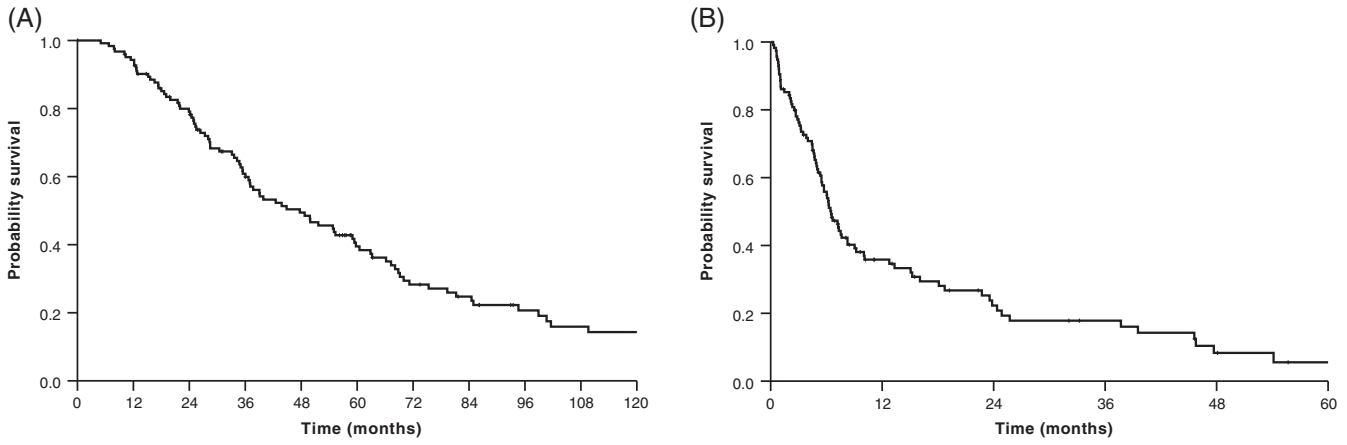

FIGURE 2 A, Overall survival from myeloma diagnosis; B, Overall survival from HEMM relapse

Univariate analysis for factors predicting shorter survival following HEMM development is presented in Table 3. The following factors were found to be associated with a significantly shorter survival from HEMM diagnosis: Translocation[11,12] in FISH (HR = 2.831, 95% CI 1.100-7.288, *P* = .03); high risk cytogenetics (HR = 2.649, 95% CI, 1.498-4.68, *P* = .001) (Figure 3A); shorter time from MM diagnosis to HEMM development (<36 months vs longer) (HR = 1.59, CI 95%, 1.04-2.43, *P* = .03) (Figure 3B); increased B2M at the time of HEMM relapse (HR = 1.064, 95% CI 1.01-1.11 *P* = .01), elevated CRP at time of HEMM relapse (HR = 1.004, 95% CI 1.001-1.008 *P* = .023), bone marrow involvement at the time of HEMM (HR = 1.8, CI 95% 1.04-3.15, *P* = .035); lung and pleura (HR = 1.9, 95% CI 1.2-3.1 *P* = .008) and CNS involvement (HR = 2.2, 95% CI 1.2-4.1 *P* = .014]). Diagnosis of HEMM based on imaging scan, particularly PET/CT and MRI, rather than histology alone, was associated with a decreased risk for death (HR 0.49, CI 0.26-0.90, *P* = .023, and HR 0.46 CI 0.28-0.77 *P* = .003 for MRI and PET/CT respectively). Failure to achieve CR or VGPR to the first treatment-line administered for HEMM relapse, was associated with shorter survival (HR = 6.029, 95% CI 0.1-0.3, *P* < 0.001) (Figure 3C). None of the treatment regimens (Table S3B, supplementary file), nor specific agents, were found to be associated with improved overall survival.

TABLE 3 Univariate analysis for factors predicting OS from HEMM development

Factor	HR (95% CI)	*P*-value
Age at HEMM	0.983 (0.965-1.002)	.075
Plasmocytoma at diagnosis	1.36 (0.885-2.090)	.161
ISS at diagnosis 3 vs 1-2	1.047 (0.625-1.753)	.724
Size of HEMM mass >5 cm	0.994 (0.998-1.01)	.105
>2 HEMM lesions	1.33 (0.77-2.29)	.31
Lung and pleura	1.9 (1.2-3.1)	.008
CNS involvement	2.2 (1.2-4.1)	.014
High LDH at HEMM	2.24 (1.33-3.75)	.002
increased B2M at HEMM	1.064 (1.01-1.11)	.01
Elevated CRP at HEMM	1.004 (1.001-1.008)	.023
BM involvement at HEMM	1.8, CI 95% 1.04-3.15,	.035
Number of prior lines	1.074 (0.986-1.17)	.127
IMiD 1st Tx for HEMM	0.522 (0.24-1.1)	.172
PIs 1st Tx for HEMM	0.88 (0.58-1.33)	.55
MoAb 1st Tx for HEMM	0.94 (0.87-1.95)	.87
Chemotherapy 1st Tx for HEMM	0.85 (0.56-1.29)	.44
≤VGPR vs less	6.029 (3.018-12.047)	<.001
CR vs no response	0.15 (0.06-0.34)	<.001
VGPR vs no response	0.14 (0.05-0.34)	<.001
PR vs no response	0.53 (0.30-0.92)	.02
t(4;14)[a]	1.85 (0.984-3.497)	.05
t(14;16)[a]	7.82 (1.72-35.54)	.008
Del17p[a]	1.78 (0.78-4.02)	.16
Del13q[a]	1.24 (0.71-2.117)	.44
t(11;14)[a]	2.8 (1.1-7.3)	.03
High risk cytogenetics	2.649 (1.498-4.68)	.001
Less than 36 m from MM to HEMM relapse	1.59 (1.04-2.43)	.03
Time from last therapy	0.987 (0.972-1.002)	.097
Diagnosis of HEMM by biopsy only	1.519 (0.652-3.53)	.333
Diagnosis of HEMM by imaging scans	0.554 (0.310-0.990)	.046
Diagnosis of HEMM by PET	0.447 (0.264-0.756)	.003
Diagnosis of HEMM by MRI	0.486 (0.262-0.904)	.023

[a]All factors were at HEMM diagnosis, except cytogenetics.
Abbreviations: B2M, B2-Microglobulin; BM, bone marrow; CNS, central nervous system; CR, complete response; CRP, C-reactive protein; Del, deletion; HEMM, hematogenous extramedullary multiple myeloma; IMiDs, immunomodulary drugs; ISS, International Staging System; LCMM, light chain multiple myeloma; LDH, Lactic dehydrogenase; MM, multiple myeloma; MoAbs, monoclonal antibodies; MRI, magnetic resonance imaging; PET, positron emission tomography; PI, proteasome inhibitor; PR, partial response; t, translocation; Tx, treatment; VGPR, very good partial response.

Multivariate analysis for factors associated with shorter survival after the development of HEMM disease found that failure to achieve at least VGPR to first line therapy at the time of HEMM disease was the only predictor for OS (HR-9.87, CI 95%, 2.35 - 39, *P* = .001).

4 | DISCUSSION

The precise incidence of HEMM relapse remains unclear, ranging between 7.5% to 24%-30%.[2,4,13] These inconsistencies reflect differences in physician attentiveness, in the employment of imaging scans at disease progression, in imaging modality being selected and in the performance of biopsies, confirming the diagnosis of HEMM disease. A unique feature of our series is that most patients were diagnosed with relapsed HEMM disease based on both imaging scans with histological/cytological confirmation of HEMM relapse.

Risk factors for the development of HEMM relapse are not fully elucidated, though, high risk gene expression profile (GEP), as well as low hemoglobin and platelets levels at diagnosis were reported to be associated with an increased risk for HEMM relapse.[3]

The current study, selectively reviewing patients with an already existing HEMM relapse, was not designed to define risk factors for developing HEMM relapse.

However, a retrospective analysis of our cohort revealed that a substantial number of these patients had initially presented with increased LDH level and high risk cytogenetics (though this should be interpreted with caution considering the high percentage of missing), features that were also reported in smaller extramedullary MM series.[2,3] In line with these "high risk features", a large proportion of our patients have also presented with plasmacytoma at diagnosis and had a highly elevated serum beta-2-microglobulin, features that are known to predict a poor outcome.[12,14]

Consistent with prior studies,[2,3,15] median time to the development of HEMM relapse was relatively short, and median number of therapeutic lines administered prior to the development of HEMM relapse was two, suggesting an important impact of disease-related factors on the development of HEMM.[15,16]

In line with prior reports, a substantial number of patients, presented with non-secretory disease and lack of bone marrow plasmacytosis at the time of HEMM relapse.[15,17] This emphasized the need for high clinical suspicion and the employment of surveillance LDH and imaging tests, which are often suggestive for the development of HEMM relapse.

Moreover, HEMM relapse had often involved "non-palpable" tissues: liver, lungs, pancreas, abdominal lymph nodes, and awareness of this complication, especially in patients that initially present with "ultra-high-risk disease", is therefore warranted. According to our analysis, diagnosis by PET and MRI predicted a better outcome compared with diagnosis relying on CT or histology only, potentially providing earlier detection of HEMM disease.[18] However, such a conclusion should be taken with caution, considering the retrospective nature of our study, and physician's discretion in selection of imaging modality, in accordance to test availability.

The potential impact of specific therapeutic agents, including novel agents, on the risk of developing HEMM remains unclear. Current evidence support that therapy itself may contribute to sub-clonal selection.[19] A complex treatment history (defined in the presence of a higher number of therapies [>2 lines] administered over ≥6 months)

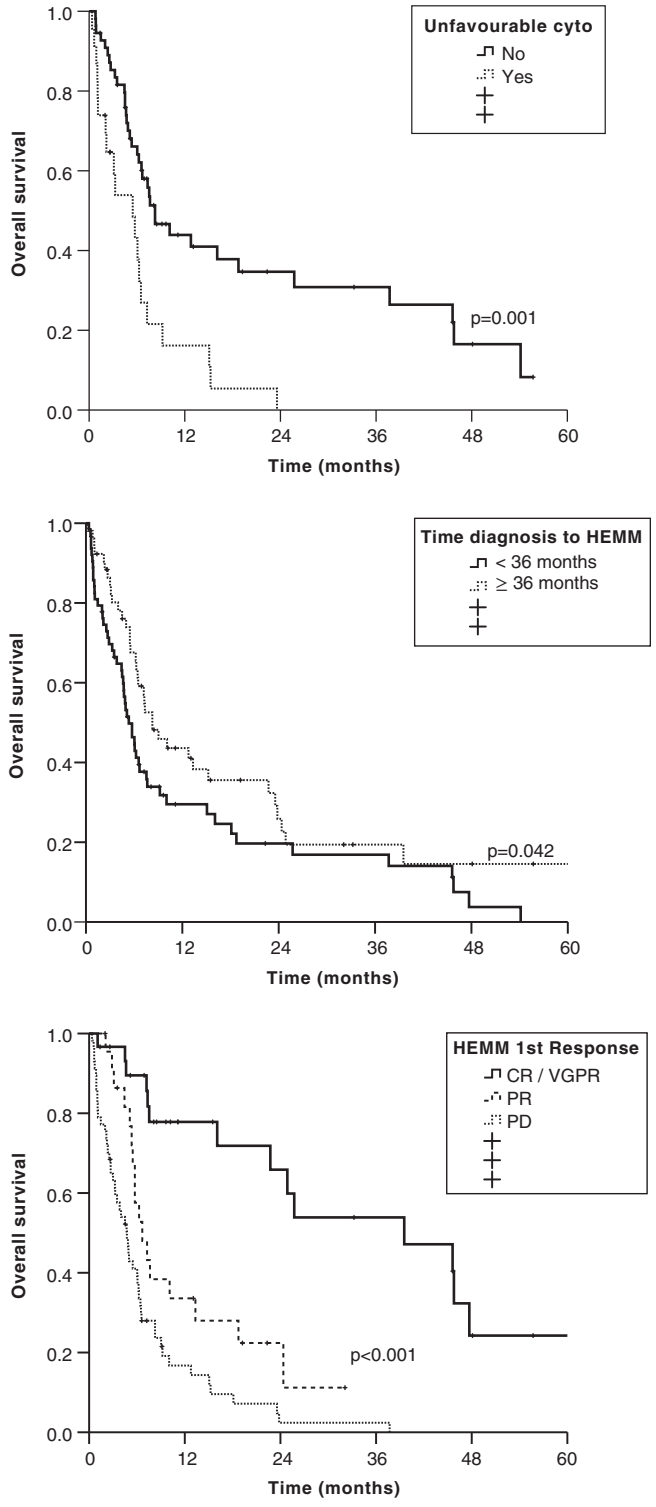

FIGURE 3 Factors affecting overall survival from HEMM diagnosis: A, Cytogenetics: high vs standard risk; B, Time from diagnosis to HEMM relapse; C, Response to 1st line therapy

has been recently reported to be associated with an increased risk for extramedullary relapse.[12] However, according to our data, the administration of IMiD-based therapy followed by auto HSCT, appeared to be associated with longer time to the development of HEMM relapse. Indeed, autologous stem cell transplantation (single rather than tandem), was shown to be valuable in patients presenting with extramedullary disease at diagnosis.[20]

The best treatment approach at the time of HEMM relapse for patients already exposed to IMiDs and PIs remains unclear. Despite the increased awareness and the introduction of novel agents over the last 15 years, in most patients treatment remains ineffective, with a median OS of 6 months.[3,13,21,22] Most patients included in our series were treated with novel triplets or combinational chemotherapy. However, due to the high variability in therapeutic regimens being used, it was impossible to define a recommended combination. An agent-oriented analysis, found IMiDs to provide a higher response rate, compared with other therapeutic regimens. Short et al,[4] reported a 31% response rate (3 out of 13) in patients, treated with pomalidomide for R/R HEMM relapse.[4] Similarly, IMiDs were also reported to be relatively active in patients experiencing HEMM following allograft,[9] interfering with MM cells and microenvironment cross talk (including cell migration and adhesion).[23] In contrast, a recent study provided by the Spanish Catalonia myeloma group, reported disappointing outcomes in patients receiving pomalidomide dexamethasone for extramedullary myeloma.[24]

Surprisingly, PIs, usually considered to be highly effective in patients with high risk disease, including in patients with extramedullary disease,[25] were not shown to be highly active. However, most of our patients received bortezomib rather than carfilzomib or ixazomib for HEMM relapse, after already being exposed to bortezomib, emphasizing the need for exploring the role of new generation PIs in this setting.

The achievement of CR was associated with a statically significant improvement in OS. Nevertheless, responses were not durable as reported in patients relapsing without having HEMM disease, emphasizing the inability of current therapies to overcome MM cells that escaped the BM niche.

The efficacy of MAbs (eg, daratumumab and elotuzumab) in HEMM has not been fully established, though few relatively small studies suggested a potential activity of daratumumab in patients with extra-medullary disease.[26] Unfortunately, the number of patients that received MAbs in our cohort was also too small to enable conclusions on this issue.

Radiotherapy, not directly addressed in our study, may still be considered to improve local disease control and analgesia. Recently, immune therapies, including bispecific T-cell engagers[27] and autologous T cells expressing a tumor-specific chimeric antigen receptor, have also shown promising responses (including a complete response) in relapsed HEMM patients.[28] Importantly, molecular characterization (eg, BRAF, RAS/RAF mutations, etc, reported in some of HEMM relapses) may help guiding therapy.[29-32] Lastly, the development of new therapies that interfere with cell homing and migration,[33] e.g. CXCR4 and CCR1 antagonists respectively[34,35] may represent a novel strategy to prevent myeloma dissemination outside the medullary niche.

In summary, HEMM relapse appears to be associated with high risk features at MM diagnosis. IMiDs and high-dose therapy, followed by autologous transplantation appears to be beneficial in these patients, delaying the development of HEMM.

A large proportion of patients with HEMM have non-secretory disease, no bone marrow involvement and the disease involves non-palpable tissues. Therefore, a high level of suspicion and use of advanced imaging (PETCT or MRI) may contribute to earlier detection. The achievement of deep responses at the time of HEMM, an accomplishment that was mainly obtained with IMiDs, was found to be the most significant factor for prolonging survival. Nevertheless, survival remains dismal and new therapeutic approaches are highly required.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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