Factors influencing extramedullary relapse after allogeneic transplantation for multiple myeloma

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LETTER TO THE EDITOR

Factors influencing extramedullary relapse after allogeneic transplantation for multiple myeloma

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Patients undergoing allogeneic stem cell transplantation (allo-SCT) with reduced intensity conditioning (RIC) for multiple myeloma (MM) experience a high frequency of extra-medullary relapses (EMR) (20–37%).[1–3] This study aims at determining factors predictive for EMR after allo-SCT, prognosis of EMR and efficacy of salvage therapies. We retrospectively analyzed a continuous cohort of 79 patients with MM who received allo-SCT in one single center (Montpellier University Hospital, France) between 2000 and 2010.

The median age at transplantation was 59 years (range 35–68). The median overall survival after allo-SCT was 2.6 years (0.1–12.8). Baseline characteristics of patients, previous treatments, immunological status before allo-SCT, allo-SCT modalities and post-allo immune recovery are indicated in Table 1. Allo-SCT was performed in first line of treatment (13% including 6% tandem auto allo-SCT), second line (47% including 6% of patients with primary refractory disease and 41% of patients with chemo-sensitive post auto-SCT relapse, relapse having occurred at a median of 2.1 years post auto-SCT) or third or more lines of treatment (40%). RICs used in most cases (97%) were FBS (fludarabine, intra-venous busulfan +/− thymoglobulin) ($n = 44$), FluTBI (fludarabine, total body irradiation) ($n = 17$) or Flu Cy TBI (Fludarabine, cyclophosphamide,

Table 1. Baseline characteristics of patients

	Global population N = *79*	*EMR* N = *19*	*Relapse without EM disease* N = *25*	P-*value*
Sex				
Male	30 (38%)	9 (47%)	9 (36%)	0.4474
ISS at diagnosis				
MD	22	4	8	
1	23 (40%)	5 (33%)	8 (47%)	0.7432
2	17 (30%)	5 (33%)	4 (23%)	
3	17 (30%)	5 (33%)	5 (29%)	
Plasma cell leukemia	7 (9%)	3 (16%)	3 (12%)	1.0000
Age at allo-SCT median (min–max)	55 (35–68)	54 (35–66)	58 (43–66)	0.0640
Delay between diagnosis and allo-SCT (years) median (min–max)	3.1 (0.5–17)	3.2 (0.76–17.0)	3.9 (0.9–11.3)	0.7046
Number of lines before allo-SCT				
1	10 (13%)	3 (16%)	1 (4%)	0.4868 (0–1v2–6)
2	37 (47%)	11 (58%)	12 (48%)	
3	17 (22%)	3 (16%)	7 (28%)	
4	13 (16%)	2 (11%)	3 (12%)	
6	2 (2%)	0 (0%)	2 (8%)	
Bortezomib before allo-SCT	59 (75%)	12 (63%)	19 (76%)	0.3551
Thalidomide before allo-SCT	29 (37%)	8 (42%)	11 (44%)	0.9000
Lenalidomide before allo-SCT	32 (41%)	3 (16%)	14 (56%)	**0.0067**
Number of auto-SCT before allo-SCT				
0	2 (3%)	0 (0%)	0 (0%)	0.0899
1	36 (46%)	5 (26%)	14 (56%)	
2	39 (49%)	13 (68%)	10 (40%)	
3	2 (3%)	1 (5%)	1 (4%)	
Tandem Auto-allo-SCT	12 (15%)	2 (10%)	4 (16%)	
Early allo-SCT (2000–2005)	15 (34%)	9 (47%)	6 (24%)	0.1053
Disease status at allo-SCT				
Progression	7 (9%)	1 (5%)	3 (12%)	0.4170
Stable disease	5 (6%)	1 (5%)	3 (12%)	
Partial response	21 (27%)	7 (37%)	5 (20%)	
Very good partial response	26 (33%)	3 (16%)	9 (36%)	
Near complete response	4 (5%)	1 (5%)	1 (4%)	
Complete response	16 (20%)	6 (32%)	4 (16%)	

Abbreviations: CI, confidence interval; EMR, extra-medullary relapses; ISS, international staging system; MD, missing data; OR, odds ratio. ORs are presented with a 95% CI.

Table 2. Analysis of factors related to EMR

	OR (95% CI)	P-*value*
Univariate		
Number of autografts (⩾2 vs 0–1)	3.56 (0.98; 12.96)	0.0537
Number of therapeutic lines before allo-SCT (⩾3 vs 1–2)	0.39 (0.11; 1.4)	0.1484
Lack of lenalidomide before allo-SCT	6.79 (1.57; 29.35)	0.0104
Age at allo-SCT (>56 years)	0.36 (0.10; 1.26)	0.1114
Total IgG before allo-SCT ($>7.66\ g\ l^{-1}$)	0.39 (0.11; 1.33)	0.1319
Total IgM before allo-SCT ($>0.35\ g\ l^{-1}$)	0.36 (0.10; 1.26)	0.1114
Date of allo-SCT (2006–2010 vs 2000–2005)	0.35 (0.1; 1.27)	0.1104
Multivariate		
Lack of lenalidomide before allo-SCT	6.79 (1.57; 29.35)	0.0104

Abbreviations: allo-SCT, allogeneic stem cell transplantation; CI, confidence interval; OR, odds ratio. Prognostic factors of EMR were determined using multivariate logistic regression. At a first step, a univariate analysis was performed to test each covariate of interest using logistic regression. Quantitative variables were discredited with respect to the median. Covariates that were significant at the 15% threshold in univariate analysis were then included in a multivariate logistic model. The selection method called 'backward' was used to keep only the significant variables at 5% threshold. The Wald test was used.

total body irradiation) ($n=12$). Grafts were from sibling donors (42%), matched unrelated donors (29%, including 7% with HLA 9/10 mismatches) or cord blood (29%). In case of adult donors, stem cells were collected after stem cell mobilization into the peripheral blood (PBSC) (54 grafts) or from bone marrow (2 grafts).

Patients were treated after allo-SCT at biological progression (before appearance of CRAB symptoms) or, if not preceded by biological progression, in case of EMR (biological and imaging follow-up).

EMR was defined as the presence of a pathologic soft tissue mass by imaging (computed tomography (CT)-scan, magnetic resonance imaging (MRI) or ultrasound) in patients with a detectable monoclonal component, or in case of no monoclonal component as the identification of clonal plasma cells in the biopsy or aspirate of the extramedullary lesion (soft tissue or bone adjacent tumor masses or diffuse organ infiltration by malignant plasma cells).

The median event-free survival (EFS) for the whole cohort (79 patients) was 1.34 years (0.86; 1.92). The median overall survival (OS) since diagnosis was 7.5 years (5.2; 8.8) and the median OS since allo-SCT was 2.9 years (1.6; 4.3). With a median follow-up of 4.8 years for living patients, 54% of the patients (44/79) relapsed post allo-SCT, 24% (19 patients) with EMR and 30% (25 patients) without. Extramedullary lesion occurred in the bone tissue in 15/19 patients, outside bone in three patients and in both bone and outside of bone in one patient. Soft tissue EMM was pleural or hepatic while extramedullary masses extending from bones involved mostly long bones (7/16) and crane/orbit (4/16). Histological evaluation was performed in 8/19 (42%) of EMR cases and pleural fluid cytology in one patient. In other cases, EMR was documented by MRI (47%), CT (42%) or ultrasound (10%). EMR occured at first relapse in most cases (84%). A serum monoclonal component could be detected at EMR in 10/19 patients. No bone marrow multiple myeloma cells (MMCs) was found in 79% of EMR patients and less than 10% MMCs in the remaining 21%.

The median delay for EMR occurrence was 1.28 years (0.23–7.55) post allo-SCT and was similar to that of non-EMR relapse, 1.21 years (0.07–3.41) ($P=0.3689$).

Patients relapsing with EMR have a trend to be younger at the time of allo-SCT (52 vs 55 years, $P=0.09$) (Table 1). The median duration between first treatment start and allo-SCT as well as the response rate at the time of allo-SCT was similar for patients relapsing with or without EMR (Table 1). A treatment with lenalidomide before allo-SCT significantly reduced the risk to develop post allo-SCT EMR compared with other relapses. Sixteen percent of the patients treated with lenalidomide before allo-SCT developed EMR and 56% developed non-EMR relapses. Of note, the other previous allo-SCT treatments (conventional chemotherapy, bortezomib, thalidomide, bortezomib+thalidomide, high-dose chemotherapy) did not influence the risk to develop EMR or non-EMR relapse. The allograft characteristics did not influence the rate of EMR. The post transplant immune recovery, the delay for obtaining total donor chimerism and the occurrence of acute or chronic graft versus host disease (cGvHD) were also not different between the two groups.

In univariate analysis, factors associated with EMR were lack of lenalidomide before allo-SCT (OR = 6.79 (1.57; 29.35)), ⩾2 autografts before allo-SCT (OR = 3.56 (0.98; 12.96)), ⩾3 therapeutic lines before allo-SCT (OR = 0.39 (0.11; 1.4)), age at allo-SCT >56 years (OR = 0.36 (0.10; 1.26)), total IgG before allo-SCT $>7.66\ g\ l^{-1}$ (OR = 0.39 (0.11; 1.33)), total IgM before allo-SCT $>0.35\ g\ l^{-1}$ (OR = 0.36 (0.10; 1.26)) and date of allo-SCT 2006–2010 (OR = 0.35 (0.1; 1.27)).

Using a multivariate analysis, only the lack of pre-allo-SCT exposure to lenalidomide remained significantly associated with EMR (OR = 6.79 (1.57; 29.35)) (Table 2). The absence of link between exposure to lenalidomide and number of pre-allo auto-SCT was verified. In patients with EMR, only 2/19 patients had received lenalidomide in last therapeutic line before allo-SCT versus 9/25 patients who experienced non-EMR relapse. Therefore, pre-allo exposure to lenalidomide appears as a protective factor for EMR.

In this cohort, patients were treated after allo-SCT at biological progression or in case of EMR. EMR were treated mainly by lenalidomide (42%) or bortezomib (21%) +/− donor lymphocyte infusions (DLI) in case of absence of GvHD grade II or more (31%). Treatment modalities included courses of three cycles of lenalidomide or bortezomib without dexamethasone alternating with DLI (escalating doses: $1\times10E6$, $1\times10E7$, $5\times10E7$, $1\times10E8$ CD3 kg^{-1}). One patient received bendamustine and 2 received VAD (vincristine, doxorubicin, dexamethasone). These first line rescue treatments offered an overall response rate of 41% including 21% of complete responses (CR) and 20% of partial responses (PR). Interestingly, lenalidomide +/− DLI ($n=8$) induced a 61% response rate including 37% of CR. Non-EMR relapses were treated with lenalidomide (48%) or bortezomib (20%) +/− DLI (12%) with a 61% overall response rate including 33% of PR and 28% of CR. For non-EMR relapses, lenalidomide +/− DLI induced 41% of responses including 8% of CR.

The median OS (measured from the time of allo-SCT) of patients developing EMR was 4.2 years (1.1–7.9), not different from that of

patients relapsing without EMR, 3.2 years (1.5–4.4) (log-rank test: $P = 0.3138$). This holds true when the survival was measured from the time of relapse (respectively, 1.57 and 1.56 years in patients relapsing with or without EMR, $P = 0.4712$). Twenty-one percent patients with EMR survived more than 3 years after relapse.

The current cohort, comprising 79 patients, is the second largest series studying the modalities of post allo-SCT MM relapse. It confirms a high incidence of relapse (54%) including 24% of EMR (43% of post allo-SCT relapses). The median EFS and OS since allo-SCT were, respectively, 1.34 years (0.86; 1.92) and 2.9 years (1.6; 4.3). EMR occurred early, at a median of 1.2 years (0.05–2.10) after allo-SCT, mostly at first relapse (84%). The only independent protective factor for EMR observed in this study was the pre-allo exposure to lenalidomide, especially when included in last therapeutic line before allo-SCT.

A hypothesis is that EMR is driven by the expansion of a MMC subclone, which may escape immune surveillance and find a permissive microenvironment. The mechanisms of action of lenalidomide include a cereblon-dependent T-cell co-stimulation.[4] A pre-allo exposure to lenalidomide could provide a better environment for the survival and expansion of the allogenic immune repertoire and thus produce an effective graft versus myeloma effect preventing from EMR. Among the growth mechanisms that could explain local extramedullary evolution, a possibility is that MMCs in EM sites produce more autocrine survival factors (IGF1, IL6…)[5–7] and angiogenic factors,[8–10] which could make possible an autonomous growth of myeloma cells. Interestingly, lenalidomide is also an anti-angiogenic molecule and a pre-allo lenalidomide treatment could reduce angiogenesis and protect from EMR occurrence.

In this cohort, the first line rescue treatments made it possible to get an overall response rate of 41% for EMR. Looking at the association lenalidomide and DLIs, this particular option induced a 62% response rate in patients developing post allo-SCT EMR. Survival measured from the time of relapse was 1.57 years for EMR compared with 1.56 years for other relapses. Therefore, in the present study, like in others, EMR was not associated with an adverse prognosis compared with other relapses.[2,11,12]

Taking into account the high frequency of EMR, we propose to look early for EMR using imaging techniques such as all body MRI or positron-emission tomography (PET)[13] and in case of residual disease and moreover, in case of EMR, to quickly release immunosuppression and provide lenalidomide and DLI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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