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%). 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  |
| 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%)                         | 0.0000  |
| 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%)                          | 0.1053  |
| Early allo-SCT (2000–2005) | 15 (34%)                 | 9 (47%)    | 6 (24%)                          |         |
| 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.
Patients 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 cranio/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 occurred 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 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)), $\geq 2$ autografts before allo-SCT (OR = 3.56 (0.98; 12.96)), $\geq 3$ 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-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 × 10E6, 1 × 10E7, 5 × 10E7, 1 × 10E8 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 of 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 EOS 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 exposure to lenalidomide, especially when included in last permissive microenvironment. The mechanisms of action of immunosuppression and provide lenalidomide and DLI.

Interestingly, lenalidomide is also an anti-angiogenic molecule could make possible an autonomous growth of myeloma cells. Adverse prognosis compared with other relapses. In the present study, like in others, EMR was not associated with an 62% response rate in patients developing post allo-SCT EMR. Looking at the 2,11,12 looking early for EMR using imaging techniques such as all body MRI.

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