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Impact of extramedullary disease in patients with newly diagnosed multiple myeloma undergoing autologous stem cell transplantation: a study from the Chronic Malignancies Working Party of the EBMT

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Abstract

We investigated extramedullary disease in newly diagnosed multiple myeloma patients and its impact on outcome following first-line autologous stem cell transplantation. We identified 3744 adult myeloma patients who received upfront single (n = 3391) or tandem transplantation (n = 353) between 2005 and 2014 with available data on extramedullary involvement at diagnosis. The overall incidence of extramedullary disease was 18.2% (n = 682) and increased per year from 6.5% (2005) to 23.7% (2014). Paraskeletal involvement was found in 543 (14.5%) and extramedullary organ involvement in 139 (3.7%). More patients with extramedullary organ involvement had multiple involved sites (≥ 2; $p < 0.001$). In patients with single sites compared to patients without the disease, upfront transplantation resulted in at least similar 3-year progression-free survival (paraskeletal: $p = 0.86$, and extramedullary organ: $p = 0.88$). In single paraskeletal involvement, this translated less clearly into worse 3-year overall survival ($p = 0.07$) while single organ involvement was significantly worse ($p = 0.001$). Multiple organ sites were associated with worse outcome ($p < 0.001$ and $p = 0.01$). First-line treatment with tandem compared with single transplantation resulted in similar survival in patients with extramedullary disease at diagnosis ($p = 0.13$, respectively).

Introduction

Multiple myeloma (MM) accounts for approximately 2% of all new cancer cases and 13% of hematological cancers with an age-adjusted incidence of 6 per 100 000 per year in the USA and Europe.[1] Autologous stem cell transplantation (ASCT) and the development of new agents have considerably increased the median survival of MM patients.[2] The disease is characterized by a clonal proliferation of malignant plasma cells with a strong dependence on the bone marrow (BM) microenvironment.[3]

However, in some MM patients, myeloma cells escape the BM resulting in extramedullary disease (EMD), which can be further characterized by two different types of involvement: 1) paraskeletal (PS), consisting of masses that arose from bone lesions and 2) extramedullary organ (EM), resulting from hematogenous spread into different organs, skin and lymph nodes.[4-5] At the time of MM diagnosis, the incidence of EM involvement in observational studies ranges from 1.7 to 4.5% using a baseline staging that includes whole-body MRI or PET-CT.[6] Paraskeletal involvement is more frequently and varies from 7 to 34.2% due to different definitions and access of sensitive imaging techniques.[7-10] Rates are also considered to be higher at relapse or after surgical interventions.[11,12] Several studies reported that EMD was associated with shorter survival rates and thus considered EMD as high-risk feature. However, the evidence of the effect of EMD at diagnosis is limited due to small populations, heterogenous patient or intervention selection, and relapse settings.[13-16] Hence, very limited data are available to assess the role of EMD at diagnosis of MM patients after upfront ASCT. This lack of evidence is striking, since ASCT is standard therapy in first-line therapy in eligible patients.[17,18]

Therefore, the objective of this study was to determine the demographic and clinical characteristics of EMD in MM patients at diagnosis and to evaluate its impact on outcome after upfront ASCT as first-line therapy. For this purpose, we analyzed 3744 patients with or without EMD at diagnosis after upfront single or tandem ASCT who had been reported to the European Society for Blood and Marrow Transplantation (EBMT) registry between 2005 and 2014.

Methods

Study design and data collection

We included adult patients with MM and available data on extramedullary involvement at time of diagnosis who received an upfront single ASCT within 12 months from diagnosis or a tandem ASCT within six months from first ASCT as first-line therapy and were reported to the EBMT registry between January 2005 and December 2014. Patients were considered eligible for analysis if there was full data on extramedullary involvement (yes or no) at time of diagnosis, its location and number of sites. This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centres mainly in Europe. Data are entered, managed, and maintained in a central database with internet access. Audits are routinely performed to determine the

accuracy of the data. Data on extramedullary involvement were extracted from the database using Med-B forms. Patients whose transplant data are reported provide informed consent to use the information for research purposes in an anonymous way.

Definitions and statistical analysis

The primary end point was 3-year progression-free survival (PFS), which was defined as the time from ASCT to disease progression or death from any cause. The secondary end points were 3-year overall survival (OS), non-relapse mortality (NRM) and response. Overall survival was defined as the time from ASCT to death from any cause or last follow-up. Non-relapse mortality was defined as death without evidence of relapse or progression, with relapse or progression as competing events. Remission, progression and relapse were defined according to the standard EBMT criteria.[19]

Based on the type of extramedullary involvement, we defined three groups of myeloma patients: 1) without EMD (MM group), 2) with paraskeletal (PS group) and 3) extramedullary organ involvement (EM group). Additionally, we determined and analyzed the impact of the number of involved sites as one or multiple (≥ 2) sites. Disease stage at diagnosis was determined according to the International Staging System (ISS; I to III),[20] Salmon and Durie stages I, II or III, and additionally according to renal function A or B.[21] Performance status at ASCT was assessed with the Karnofsky score (≤ 80 indicating poor and > 80 good status).[22] Categorical variables were compared with the use of the Fisher's exact test or the χ^2 test. Continuous variables were analyzed using the Kruskal-Wallis test for independent samples.

Survival probabilities were estimated by the Kaplan–Meier method,[23] and the Log-Rank test was used for univariate comparison. Median follow-up was calculated according to the reverse Kaplan-Meier method.[24] Outcomes were artificially censored at three years. We used cumulative incidence analysis to assess NRM and labeled death from relapse as a competing event.[25,26] The proportional hazards assumption was verified using graphical methods. Scaled Schoenfeld[27] residuals and graphical checks proposed by Klein and Moeschberger[28] were performed to find evidence of violations. To minimize the effect of selection bias, we used a landmark analysis at six months whenever single and tandem ASCT were compared.

To assess the multivariate effect of factors on each end point, we used the Cox proportional hazards model to estimate hazard ratios (HR).[29] Only complete cases were included in the analysis. All tests were two-sided, with the type I error rate fixed at $\alpha = 0.05$. All analyses were performed using the statistical software R, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics 23 (SPSS, IBM Corp, Armonk, NY).

Results

Incidence and sites

Among the total of 3744 patients identified in the registry, 14.5% (n = 543) had paraskeletal involvement (PS group) and 3.7% (n = 139) extramedullary organ involvement (EM group) while 81.8% (n = 3062) had no EMD (MM group). Between 2005 and 2014, the EMD incidence per year increased from 6.5% to 23.7%.

Within the EM group, the involved sites were: kidney (27.3%, n = 38), skin (23.0%, n =32), lymph nodes (17.3%, n = 24), central nervous system (CNS; 10.1%, n = 14), lung and respiratory tract (6.5%, n = 9), gastrointestinal tract (GI) and liver (5.8%, n = 8), pleura and heart (5.0%, n = 7), and spleen, ovaries and testes (5.0%, n = 7). Most patients with EMD (93.5%, n = 639) presented with one involved site (PS1 and EM1), 5.7% (n = 36) had two sites, 0.7% (n = 5) had three sites while four and five sites were present in 0.1% (n = 1) of patients, respectively. Notably, within the PS group, all 19 patients with multiple (≥ 2) sites had only additional paraskeletal involvement (PS2) while further involvement in all 24 EM patients was also restricted to other organs (EM2).

Patient and disease characteristics

The median age at diagnosis was 59.8 years in both MM and PS, and 59.0 years in EM patients ($p = 0.59$). Among all groups were more males (57.9%) than females (42.1%). More EM patients (34.1%) had worse renal function (stage B) in comparison to PS (16.8%) and MM patients (17.3%; $p < 0.001$). Patients with EM involvement (28.3%) were more likely to have light chain disease compared to PS (22.5%) and MM patients (22.1%; $p = 0.002$). Detailed patients' characteristics are listed in Table 1.

Transplantation characteristics and responses

The source of stem cells for all patients was peripheral blood. Upfront single ASCT was applied to 3391 and tandem ASCT to 353 patients. Time to first ASCT did not differ between the groups ($p = 0.81$). Complete remission (CR) before the first ASCT was reported in 21.5% PS, 11.7% EM and 19.1% MM patients while partial remission (PR) was achieved by 72.6% PS, 79.6% EM and 74.7% MM patients ($p = 0.10$; Table 1). After ASCT, complete response was achieved by 41.6% PS, 36.1% EM and 43.9% MM patients while 54.0% PS, 51.9% EM and 49.8% MM patients showed partial response ($p = 0.001$).

EMD and survival

The median follow-up was 36.3 months (range, 1 to 118.9 months) after date of ASCT. In the univariate analysis, the MM and PS groups showed similar 3-year PFS of 47.9% (95% CI, 45.8 to 50.1) vs. 50.0% (95% CI, 44.6 to 55.3; $p = 0.78$) and similar 3-year OS of 80.1% (95% CI, 78.4 to 81.8) vs. 77.7% (95% CI, 73.3 to 82.1; $p = 0.09$; Figure 1A and B). In contrast, EM patients had a significantly worse 3-year PFS of 39.9% (95% CI, 30.3 to 49.5) in comparison to MM ($p = 0.001$) and PS patients ($p = 0.007$), and a significantly worse 3-year OS of 58.0% (95% CI, 48.1 to 67.9) compared to MM and PS patients ($p < 0.001$, respectively). Within the EM group, 3-year PFS differed according to involved organs: kidney (59.5%), skin (20.1%), lymph nodes (37.6%), CNS (47.9%), lung/respiratory tract (44.4%), GI/liver (22.5%), and spleen, ovaries and testes (60.0%; Table 2).

Comparing the MM group without EMD to those with EMD, one involved site resulted in a similar 3-year PFS of 49.4% (95% CI, 44.6 to 54.3; $p = 0.36$) while multiple involved sites showed a worse PFS of 22.7% (95% CI, 5.2 to 40.2; $p = 0.001$; Figure 2A). Both one and multiple involved sites showed worse 3-year OS rates of 73.5% (95% CI, 69.2 to 77.7; $p <$

0.001) and 71.4% (95% CI, 55.1 to 87.7; p = 0.05) in comparison to patients without EMD (80.1%; Figure 2B).

By stratifying EMD groups according to one vs. multiple involved sites (PS1 vs. PS2, and EM1 vs. EM2), PS patients showed no significant difference in 3-year PFS of 50.5% (95% CI, 45.0 to 55.9%) vs. 36.0% (95% CI, 5.2 to 66.8%; p = 0.71), and OS of 77.2% (95% CI, 72.7 to 81.7%) vs. 91.7% (95% CI, 76.0 to 100; p = 0.27). In EM patients, this comparison resulted in a significantly worse 3-year PFS of multiple sites in the univariate analysis: 44.7% (95% CI, 34.1 to 55.3) vs. 13.9% (95% CI, 0 to 35.5%; p = 0.03; Figure 3A). In contrast, 3-year OS was 58.7% (95% CI, 47.9 to 69.5%) for EM1 vs. 57.5% (95% CI, 34.2 to 80.8%; p = 0.51; Figure 3B).

Tandem transplantation and survival

A landmark analysis was used to compare tandem and single ASCT, considering a total of 3139 patients who were alive at six months. In patients without EMD, the comparison of tandem vs. single ASCT resulted in similar 3-year PFS: 53.8% (95% CI, 46.7 to 60.9) vs. 51.3% (95% CI, 48.9 to 53.7; p = 0.37), and similar 3-year OS: 84.7% (95% CI, 79.6 to 89.8) vs. 81.6% (95% CI, 79.8 to 83.4; p = 0.26).

Patients with EMD showed a 3-year PFS of 59.0% (95% CI, 46.3 to 71.8) after tandem vs. 53.0% (95% CI, 47.5 to 58.6) after single ASCT (p = 0.43) while 3-year OS was 77.0% (95% CI, 66.1 to 87.9) vs. 76.9% (95% CI, 72.4 to 81.4; p = 0.91).

Within each EMD group, PS patients showed a similar 3-year PFS of 59.4% (95% CI, 45.3 to 73.6) after tandem vs. 54.3% (95% CI, 48.0 to 60.5; p = 0.44) after single ASCT and similar 3-year OS of 82.6% (95% CI, 72.3 to 92.8) vs. 80.3% (95% CI, 75.6 to 85.1; p = 0.88). Patients with EM involvement showed no significant difference in both 3-year PFS and OS after tandem vs. single transplantation: 56.2% (95% CI, 27.2 to 85.3) vs. 48.3% (95% CI, 36.6 to 60.1; p = 0.98), and 52.0% (95% CI, 20.0 to 84.0) vs. 64.9% (95% CI, 54.2 to 75.7; p = 0.39).

Role of other factors on survival and causes of death

All patients in CR before first ASCT showed a significantly better 3-year PFS of 59.8% (95% CI, 55.3 to 64.3) compared to 30.7% (95% CI, 28.2 to 33.2) in PR and 24.7% (95% CI, 17.6 to 31.8; p < 0.001) in less than PR. Three-year OS also significantly differed, with patients in CR showing 83.6% (95% CI, 80.2 to 87.0) compared to 78.8% (95% CI, 76.9 to 80.6) in patients with PR and 27.8% (95% CI, 20.8 to 34.9) in patients with less than PR (p < 0.001).

Other factors that were associated with worse PFS in patients with EMD were: older age (p = 0.04), transplantation before 2011 (p = 0.01), higher disease stage according to ISS (p = 0.01) and Salmon and Durie (p = 0.02), and lower remission status at transplantation (p < 0.001). Factors associated with worse OS in EMD patients were: transplantation before 2011 (p = 0.02), higher disease stage according to ISS (p = 0.002) and Salmon and Durie (p = 0.02), and lower remission status at transplantation (p < 0.001).

Non-relapse mortality at three years occurred in 3.0% (95% CI, 2.0 to 4.0) of MM, 3.0% (95% CI, 2.0 to 5.0) of PS patients, and 7.0% (95% CI, 2.0 to 12.0) of EM patients (p = 0.05). Main causes of death were relapse or progression (86.3%), infection (7.1%), secondary malignancy

or post-transplant lymphoproliferative disorder (3.6%), organ damage or failure (1.8%), toxicity (0.4%) and unknown in 83 patients.

Multivariate analyses

A multivariable model was constructed to examine the effect of EMD on 3-year PFS and OS after adjusting for possible prognostic factors. All factors and covariates including corresponding references are listed in Table 3. To avoid linearly dependent covariates, we merged the disease group and the new variable of the number of involved sites into a five-level variable consisting of patients without EMD (MM group) and patients with EMD according to number of involved sites (PS1, PS2, EM1 and EM2). Cox proportional hazards regression considering independent factors for worse PFS yielded significant results for EM2 with a HR of 3.40 (95% CI, 1.74 to 6.61; $p < 0.001$). Interestingly, EM1 showed no difference in PFS compared to MM with a HR of 1.03 (95% CI, 0.66 to 1.62; $p = 0.88$). The comparison of PS and MM concerning PFS revealed no difference for PS1 a HR of 1.02 (95% CI, 0.83 to 1.27; $p = 0.86$) and a less clearly HR of 2.46 (95% CI, 0.92 to 6.62; $p = 0.07$) for PS2.

In the OS analysis, EM1 and EM2 were associated with worse outcome, showing HRs of 2.30 (95% CI, 1.43 to 3.70; $p = 0.001$) and 3.64 (95% CI, 1.48 to 8.94; $p = 0.01$). Patients with one site of PS involvement did less clearly differ from patients without EMD, with a HR of 1.33 (95% CI, 0.98 to 1.83; $p = 0.07$) while PS2 resulted in similar outcome with a HR of 0.74 (95% CI, 0.10 to 5.32; $p = 0.77$).

Tandem ASCT showed similar results considering 3-year PFS and OS compared to single ASCT, with HRs of 0.83 (95% CI, 0.66 to 1.06; $p = 0.13$) and 0.74 (95% CI, 0.51 to 1.09; $p = 0.13$).

However, other factors did significantly contribute to an increased risk of worse outcome (Table 3). For PFS, these factors were: ISS stage II and III, PR and less than PR at ASCT. Overall survival was significantly influenced by stage II and III according to ISS, male sex, PR and less than PR at ASCT, and the presence of heavy and light chains.

Discussion

Extramedullary disease in patients with MM is considered as poor prognostic factor. This EBMT registry study including 682 EMD patients identified an increase per year of EMD incidence at diagnosis from 2005 to 2014. We demonstrated that first-line ASCT resulted in at least similar 3-year PFS in patients with single sites of EMD compared to patients without EMD. This did less clearly translate into worse 3-year OS in single PS involvement while single sites of EM were significantly associated with worse outcome, which became even worse if multiple sites of organs were involved. Concerning treatment options for EMD at diagnosis, we found both first-line tandem and single ASCT resulting in similar 3-year PFS and OS.

The evidence on the role of EMD at diagnosis after first-line ASCT is still limited. A retrospective single center study[30] of 27 patients concluded that ASCT might overcome onset poor prognosis compared to patients without EMD while extramedullary organ involvement was present in only four patients and could underestimate its impact on

outcome.[5] A prospective study[31] of patients in relapse with either soft-tissue or bone related involvement at a single institution found that bone-related relapses were associated with better OS, but treatments before diagnosis of extramedullary relapse significantly differed between groups. However, since different types of involvement were reported, this variable was examined closely.

In our study, especially EM involvement in 139 MM patients was associated with lower rate of CR prior and after ASCT, a higher frequency of stage III according to ISS, and worse renal function. Moreover, the impact of the number of involved sites on outcome in EMD at diagnosis has not been described so far. We found 20% of all EMD patients having multiple sites of involvement, which is in line with previous reports (16%).[13] Notably, the location of further involvements was only paraskeletal in the PS group and also restricted to other organs in the EM group.[32]

The use of radiation therapy might contribute to the difference in PFS and OS of patients with single sites of EMD compared to patients without EMD, because it is considered effective by reducing progression in patients with solitary osseous and extraosseous involvements.[33,34] Especially, because reports about the efficacy of novel agents in these cohorts at diagnosis are very limited. Some results propose an induction bortezomib-based regimen followed by high-dose melphalan/ASCT for patients with paraskeletal rather than extramedullary involvement.[14,35-37] In a retrospective study[38] investigating carfilzomib alone or in combination as salvage therapy in relapse, presence of extramedullary involvement resulted in shorter duration of response compared to absent EMD, suggesting limited treatment effect. Smaller reports on the possible impact of immunomodulatory drugs showed partial efficacy regarding response rates in EMD patients.[10,39,40]

Retrospective studies highlighted an extremely poor prognosis for CNS involvement with a median OS of less than six months.[41,42] However, in addition to systemic anti-MM therapy, CNS irradiation and the use of novel combination therapies have been shown to improve the duration of response.[42] With regard to these analyses lacking transplantation settings, we investigated survival according to involved sites in EM patients, finding most of the patients having kidney, skin or lymph node involvement. After upfront ASCT, best outcomes were found in kidney and CNS involvement while skin and lymph node involvement showed worse outcome. Interestingly, our CNS cohort showed higher rates of OS compared to previous reports, which might be due to the selection of patients with CNS involvement at diagnosis while most reports evaluated patients at later phases of the disease.[41,42]

A pooled analysis of prospective studies regarding transplantation strategies suggested the superiority of tandem ASCT in patients with poor prognostic features at diagnosis.[4,43] Our landmark analyses of EMD patients who received either tandem or single ASCT as first-line therapy found no difference considering PFS and OS. However, this analysis was conducted with the use of retrospective data and is therefore subject to the attendant limitations. Regression modeling and landmark analyses were performed as a means of controlling for differences of the patients, but such adjustment cannot account for all discrepancies in clinical and diagnostic characteristics between groups. The increasing incidence of EMD

might be caused by a more frequent use of whole-body MRI or PET-CT in recent years. However, although recent evidence promotes the use of more sensitive imaging techniques,[44] data are not routinely documented nor are part of routine diagnostics yet and were thus not available in our study.[45,46] A randomized trial is the only way to overcome these challenges and to assess the definite impact of EMD in newly diagnosed MM patients after ASCT.

In conclusion, this EBMT study identified an increase of incidence per year of EMD in newly diagnosed MM patients from 2005 to 2014. We revealed that first-line ASCT in patients with single sites of EMD (PS or EM) resulted in at least similar 3-year PFS compared to patients without EMD. Nevertheless, single EM involvement was associated with worse 3-year OS, which became even worse when multiple sites of organs were involved.

Contribution

NG and NK designed the work, performed statistics, and wrote the manuscript. AB and LK collected the data from the EBMT data base, D-JE and SI performed statistics and wrote the manuscript. HN, A-MS, TM, DC, SL, MU, CC, WA, MC, AH, LX, MS, MD, PP, JAS, MI-R, MM, and LG contributed patients and collected, analyzed, and interpreted the data. All authors approved the final version of the paper.

Conflict of interests

Conflict of interests have been declared by Anne-Marie Stoppa regarding honoraria from Celgene, Janssen, Amgen, and Takeda, regarding consulting or advisory role by Celgene, Janssen, Amgen, and BMS, Celgene, Janssen, and Amgen regarding travel, accommodation, and expenses. Tamás Masszi declared COI regarding consulting or advisory role, travel accommodations, or expenses by Janssen Cilag, Novartis, BMS, Abbvie, and Takeda. William Arcese declared COI regarding travel, accommodations, or expenses by Pierre Fabre, ABN, and Merck. Michel Delforge declared COI regarding honoria from Janssen, consulting or advisory role by Amgen, BMS, Celgene, and Takeda, and research funding for his institution from Celgene and Janssen. Nicolaus Kröger received honoraria and research grants from Sanofi, Celgene and Amgen. John A. Snowden declared COI regarding honoria as well as travel, accommodations, or expenses from Sanofi. All other authors declared no conflict of interests.

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	Patients without EMD	Patients with EMD			
Characteristic	MM group	PS group	EM group	Total	*P*
No. of patients (%)	3062 (81.8)	543 (14.5)	139 (3.7)	3744	
Sex - no. (%)					
Female	1279 (41.8)	240 (44.2)	57 (41.0)	1576 (42.1)	0.55
Male	1783 (58.2)	303 (55.8)	82 (59.0)	2168 (57.9)	
Age at diagnosis in years					
Median	59.8	59.8	59.0		0.59
Range	27.4 to 77-7	26.8 to 76.8	31.8 to 72.8		
ISS - no. (%)					
I	781 (36.9)	158 (38.6)	29 (30.5)	968 (36.9)	
II	759 (35.8)	148 (36.2)	29 (30.5)	936 (35.7)	0.11
III	578 (27.3)	103 (25.2)	37 (38.9)	781 (27.4)	
Unknown	944	134	44	1122	
Renal function - no. (%)					
A	2188 (82.7)	410 (83.2)	85 (65.9)	2683 (82.1)	< 0.001
B	458 (17.3)	83 (16.8)	44 (34.1)	585 (17.9)	
Unknown	416	50	10	476	
Karnofsky score - no. (%)					
Good	1877 (67.3)	344 (67.7)	81 (62.8)	2302 (67.2)	
Poor	914 (32.7)	164 (32.3)	48 (37.2)	1126 (32.8)	0.55
Unknown	271	35	10	316	
Status at ASCT - no. (%)					
CR	580 (19.1)	115 (21.5)	16 (11.7)	711 (19.2)	
PR	2262 (74.7)	389 (72.6)	109 (79.6)	2760 (74.6)	0.10
< PR	187 (6.2)	32 (6.0)	12 (8.8)	231 (6.2)	
Unknown	33	7	2	42	
Type of myeloma - no. (%)					
Light chain only	672 (22.1)	122 (22.5)	39 (28.3)	833 (22.4)	
Non-secretory	74 (2.4)	29 (5.4)	3 (2.2)	106 (2.9)	0.002
Heavy and light chain	2292 (75.4)	389 (72.0)	96 (69.6)	2777 (74.7)	
Unknown	24	3	1	28	
Ig-type - no. (%)					
G	1648 (70.8)	282 (72.1)	72 (73.5)	2002 (71.1)	
A	634 (27.2)	101 (25.8)	22 (22.4)	757 (26.9)	0.51
D/E/M	45 (1.9)	8 (2.0)	4 (4.1)	57 (2.0)	
Unknown	735	152	41	928	
Light chain type - no. (%)					
Kappa	1853 (63.7)	327 (65.1)	73 (55.7)	2253 (63.6)	0.13
Lambda	1054 (36.3)	175 (34.9)	58 (44.3)	1287 (36.4)	
Unknown	155	41	8	204	

Number of sites - no. (%)					
0	3062 (100)			3062 (81.8)	<0.001
1		524 (96.5)	115 (82.7)	639 (17.1)	
≥ 2		19 (3.5)	24 (17.3)	43 (1.1)	
Year of ASCT - no. (%)					
< 2009	518 (16.9)	82 (15.1)	25 (18.0)	625 (16.7)	0.001
2009 to 11	1400 (45.7)	204 (37.6)	62 (44.6)	1666 (44.5)	
> 2011	1144 (37.4)	257 (47.3)	52 (37.4)	1453 (38.8)	
Time to 1st ASCT in months					
Median	6.2	6.2	6.1		0.81
Range	1.1 to 11.9	2.1 to 11.9	3.9 to 11.9		
Type of ASCT - no.					
Tandem	249	89	15	353	
Single	2813	454	124	3391	

Table 1. Patients, disease and transplantation characteristics.

Abbreviations: EMD, extramedullary disease; MM, patients without extramedullary disease; PS, paraskeletal involvement; EM, extramedullary organ involvement; No., number; ISS, International Staging System; ASCT, autologous stem cell transplantation; CR, complete remission; PR, partial remission

Site	No. of patients (%)	No. of deaths	3-year PFS in % (95% CI)	3-year OS in % (95% CI)
Kidney	38 (27.3)	7	59.5 (41.1 to 77.9)	75.3 (59.0 to 91.7)
CNS	14 (10.1)	4	47.9 (18.3 to 77.4)	64.3 (35.5 to 93.1)
Lung / respiratory tract	9 (6.5)	3	44.4 (7.4 to 81.5)	41.7 (0 to 85.1)
GI tract / liver	8 (5.8)	3	22.5 (0 to 58.8)	58.3 (22.0 to 94.7)
Pleura / heart	7 (5.0)	5	NE	NE
Spleen / ovaries / testes	7 (5.0)	2	60.0 (17.1 to 100)	60.0 (17.1 to 100)
Skin	32 (23.0)	10	20.1 (3.4 to 36.7)	53.3 (30.5 to 76.0)
Lymph nodes	24 (17.3)	10	37.6 (16.4 to 58.7)	48.2 (25.1 to 71.3)

Table 2. Involved sites in EM group and survival after ASCT.

Abbreviations: EM, extramedullary organ; PFS, progression-free survival; OS, overall survival; ASCT, autologous stem cell transplantation; No., number; CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; NE, not estimable

	3-year PFS		3-year OS	
Factors – reference	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Group – MM without EMD		< 0.001		< 0.001
PS1	1.02 (0.82 to 1.27)	0.86	1.33 (0.98 to 1.83)	0.07
PS2	2.46 (0.92 to 6.62)	0.07	0.74 (0.10 to 5.32)	0.77
EM1	1.03 (0.66 to 1.62)	0.88	2.30 (1.43 to 3.70)	0.001
EM2	3.40 (1.74 to 6.61)	< 0.001	3.64 (1.48 to 8.94)	0.01
Sex – male				
Female	0.86 (0.74 to 1.01)	0.06	0.71 (0.56 to 0.91)	0.01
Age in years - > 60		0.22		0.45
< 50	0.81 (0.74 to 1.03)	0.08	1.04 (0.73 to 1.48)	0.85
50 to 60	0.95 (0.80 to 1.11)	0.50	1.17 (0.91 to 1.50)	0.21
ISS – I		< 0.001		< 0.001
II	1.48 (1.23 to 1.77)	< 0.001	1.75 (1.29 to 2.37)	< 0.001
III	1.81 (1.46 to 2.24)	< 0.001	2.68 (1.92 to 3.74)	< 0.001
Renal function – A				
B	0.99 (0.79 to 1.24)	0.93	1.25 (0.92 to 1.69)	0.16
Status at ASCT – CR		< 0.001		0.02
PR	1.58 (1.26 to 1.97)	< 0.001	1.48 (1.05 to 2.08)	0.03
< PR	2.18 (1.54 to 3.10)	< 0.001	2.08 (1.22 to 3.54)	0.01
Type of myeloma - light chain		0.10		0.09
Non-secretory	0.77 (0.42 to 1.43)	0.41	1.70 (0.80 to 3.61)	0.17
Heavy and light	1.19 (0.98 to 1.46)	0.08	1.38 (1.01 to 1.88)	0.04
Year of ASCT - > 2011		0.21		0.91
< 2009	1.22 (0.97 to 1.53)	0.09	1.07 (0.75 to 1.53)	0.71
2009 to 2011	1.05 (0.88 to 1.26)	0.61	1.00 (0.76 to 1.33)	0.98
Type of ASCT - single				
Tandem	0.83 (0.66 to 1.06)	0.13	0.74 (0.51 to 1.09)	0.13

Table 3. Multivariate analysis.

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; MM, patients without extramedullary disease; PS, patients with paraskeletal involvement arisen from bone lesions; PS1, patients with paraskeletal involvement having one involved site; PS2, patients with paraskeletal involvement and multiple involved sites; EM1, patients with extramedullary organ involvement having one involved site; EM2, patients with extramedullary organ involvement and multiple involved sites; ISS, International Staging System; CR, complete remission; PR, partial remission; ASCT, autologous stem cell transplantation.

Figure legends

Figure 1. Progression-free survival (A) and overall survival (B) with numbers at risk of myeloma patients following upfront autologous stem cell transplantation according to presence of involvement: no EMD (MM), paraskeletal (PS) and extramedullary organ involvement (EM).

Figure 1A. Abbreviations: PFS, progression-free survival; MM, patients without EMD; PS, patients with paraskeletal involvement; EM, patients with extramedullary organ involvement; Tx, transplantation; N, number.

Figure 1B. Abbreviations: OS, overall survival; MM, patients without EMD; PS, patients with paraskeletal involvement; EM, patients with extramedullary organ involvement; Tx, transplantation; N, number.

Figure 2. Progression-free survival (A) and overall survival (B) with numbers at risk of myeloma patients following upfront autologous stem cell transplantation according to number of involvements: 0, 1 and ≥ 2.

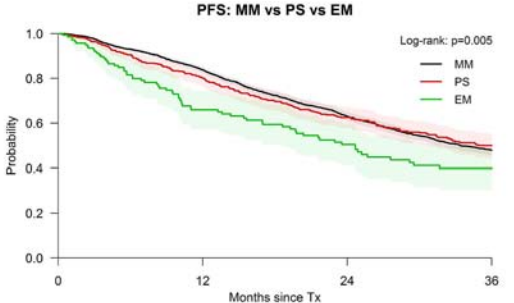
Figure 2A. Abbreviations: PFS, progression-free survival; Tx, transplantation; N, number.

Figure 2B. Abbreviations: OS, overall survival; Tx, transplantation; N, number.

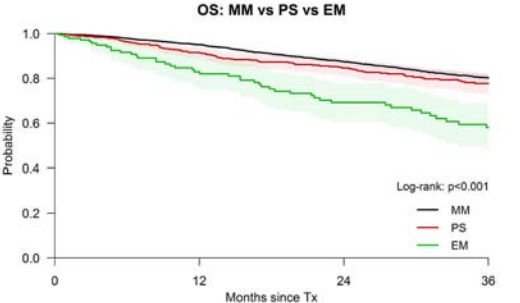
Figure 3. Progression-free survival (A) and overall survival (B) with numbers at risk of myeloma patients with extramedullary organ involvement following upfront autologous stem cell transplantation according to number of involvements: 1 and ≥ 2.

Figure 3A. Abbreviations: PFS, progression-free survival; EM, patients with extramedullary organ involvement; EM1, patients with one site of EM; EM≥2, patients with two or more sites of EM; Tx, transplantation; N, number.

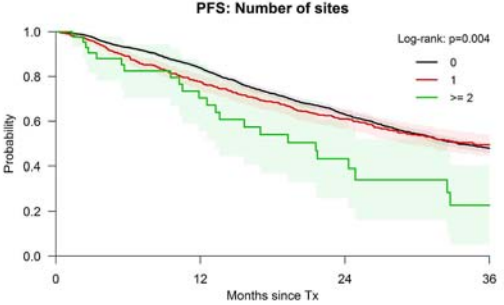
Figure 3B. Abbreviations: OS, overall survival; EM, patients with extramedullary organ involvement; EM1, patients with one site of EM; EM≥2, patients with two or more sites of EM; Tx, transplantation; N, number.



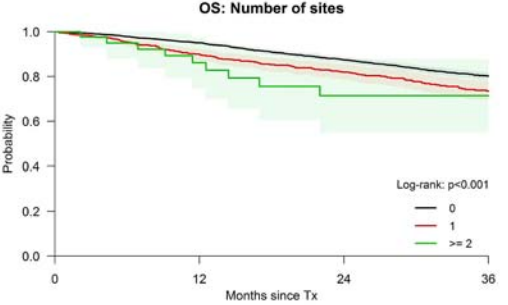
N at risk				
MM	3062	2059	1288	778
PS	543	335	199	114
EM	139	73	49	30



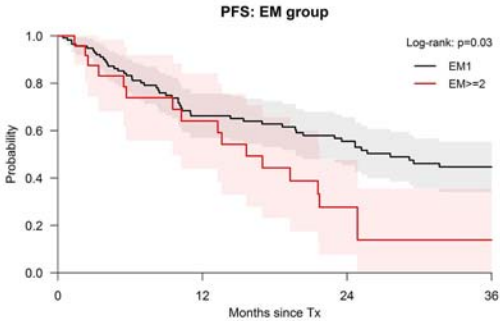
N at risk				
MM	3062	2329	1766	1277
PS	543	382	268	176
EM	139	91	67	42

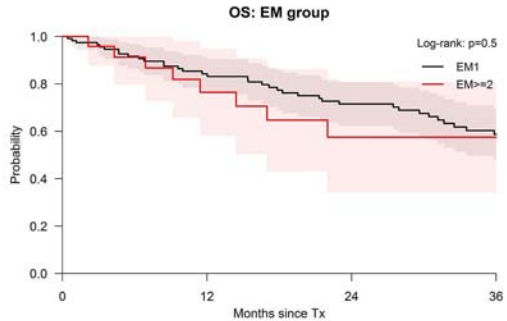


N at risk				
0	3062	2059	1288	778
1	639	385	237	140
>= 2	43	23	11	4



N at risk				
0	3062	2329	1766	1277
1	639	446	319	205
>= 2	43	27	16	13


PFS: EM group
Log-rank: p=0.03
EM1
EM>=2
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months since Tx
N at risk
EM1 115 60 45 29
EM>=2 24 13 4 1


OS: EM group
Log-rank: p=0.5
EM1
EM>=2
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months since Tx
N at risk
EM1 115 77 60 37
EM>=2 24 14 7 5