Biol Blood Marrow Transplant 25 (2019) 2134–2142

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Autologous

Tandem Autologous Stem Cell Transplantation Improves Outcomes in Newly Diagnosed Multiple Myeloma with Extramedullary Disease and High-Risk Cytogenetics: A Study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation

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Article history:
Received 14 May 2019
Accepted 3 July 2019

Keywords:
Myeloma
Extramedullary disease
Autologous

A B S T R A C T

Although high-dose therapy and autologous stem cell transplant combined with novel agents continues to be the hallmark of first-line treatment in newly diagnosed transplant-eligible multiple myeloma patients, the impact of tandem autologous or autologous/reduced-intensity allogeneic transplant for patients with extramedullary disease (EMD) and high-risk cytogenetics is not yet defined. Here, we analyzed clinical and cytogenetic data from 488 adult myeloma patients with EMD undergoing single autologous (n = 373), tandem autologous (n = 84), or autologous–allogeneic transplant (n = 31) between 2003 and 2015. At least 1 high-risk abnormality was present in 41% (n = 202), with del(17p) (40%) and t(4;14) (45%) the most frequent. More than 1 high-risk abnormality was

Financial disclosure: See Acknowledgments on page 2141.

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https://doi.org/10.1016/j.bbmt.2019.07.004
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Tandem
Allogeneic
Cytogenetics

found in 54%. High-risk cytogenetics showed worse 4-year overall survival (OS) and progression-free survival (PFS) of 54% and 29%, respectively, versus 78% and 49% for standard-risk cytogenetics ($P < .001$). Co-segregation of high-risk abnormalities did not seem to affect outcome. Regarding transplant regimen, OS and PFS were 70% and 43% for single autologous versus 83% and 52% for tandem autologous and 88% and 58% for autologous–allogeneic ($P = .06$ and $P = .30$). In multivariate analysis high-risk cytogenetics were associated with worse survival (hazard ratio [HR], 2.00; $P = .003$), whereas tandem autologous significantly improved outcome versus single autologous transplant (HRs, .46 and .64; $P = .02$ and $P = .03$). Autologous–allogeneic transplant did not significantly differ in outcome but appeared to improve survival, but results were limited because of small population (HR, .31). In conclusion, high-risk cytogenetics is frequently observed in newly diagnosed myeloma with EMD and significantly worsens outcome after single autologous, whereas a tandem autologous transplant strategy may overcome onset poor prognosis.

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INTRODUCTION

For most multiple myeloma (MM) patients, plasma cell proliferation is restricted to the bone marrow. However, a subset of MM patients develops extramedullary myeloma, defined by the presence of clonal plasma cells outside the bone marrow resulting in extramedullary disease (EMD) [1]. The prevalence of EMD appears to have increased over the past 15 years, resulting in about 20% of newly diagnosed MM (NDMM) patients who had at least 1 site of extramedullary involvement (ie, because of a broader use of sensitive imaging techniques) [2,3]. The impact on outcome of EMD in NDMM is influenced by different types of involvements and by the number of involved sites [3,4]. More patients with organ involvement may present with multiple involved sites, which significantly contributes to worse outcome, whereas comparisons of patients with single sites and paraskeletal involvement after upfront transplant resulted in at least similar 3-year progression-free survival (PFS) compared with MM without EMD [3].

Studies demonstrated that MM is not only a clinically but also genetically complex and heterogeneous disease [5]. Cytogenetic alterations are considered to have an important prognostic value in MM, helping to identify high-risk patients [6,7]. Using fluorescence in situ hybridization, chromosomal changes have been observed in bone marrow plasma cells in about 90% of MM patients at initial diagnosis [8]. Several abnormalities have been identified as independent negative prognostic markers for survival of MM patients and were used by consensus panels to categorize risk groups, including tests for the presence of del(17p), t(4;14), t(14;16), t(14;20), gain (1q), and del(1p) [6,9,10]. However, stratifications were not specifically assessed for patients with NDMM EMD, whereas reports suggest that abnormalities, such as del(17p), may occur more frequently in EMD [11]. Furthermore, although autologous stem cell transplantation and the development of new agents have considerably increased the median survival of MM patients, data suggesting specific treatment options for different cytogenetic risk groups in NDMM specifically with EMD are lacking.

The aim of this study was to describe the demographic and clinical characteristics of NDMM patients with EMD in the European Society for Blood and Marrow Transplantation (EBMT) registry and available cytogenetic information who underwent either single autologous (single auto), tandem auto, or autologous/reduced-intensity allogeneic (auto–allo) stem cell transplant and to evaluate the impact of cytogenetics after different transplant strategies.

METHODS

Patients and Study Design

This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the EBMT, a nonprofit, scientific society representing more than 600 transplant centers, 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. Patients whose transplant data are reported provided informed consent to use the information for research purposes, and data are anonymized.

We analyzed 488 adult patients with NDMM and extramedullary involvement with cytogenetics available. Patients were included if they received either single auto within 12 months from diagnosis, subsequent autologous (tandem auto), or reduced-intensity conditioning (RIC) allogeneic transplant (auto–allo) within 6 months from first autograft as first-line therapy. Transplants eligible for analysis should have been performed between 2003 and 2015. Sites of involvement were defined in accordance with recent findings as paraskeletal (resulting from bone lesions), organ (resulting from hematogenous spread), and both [3,4]. Cytogenetics were initially categorized according to previously established risk groups [6,10,11]. Accordingly, high-risk cytogenetics were defined as presence of at least 1 of the following abnormalities: del(17p), t(4;14), t(14;16), t(14;20), gain(1q), and del(1p). Absence of abnormalities or other documented abnormalities (including other translocations or deletions, hyper- or hypodiploidy) were categorized together with documented standard-risk cytogenetics. Disease stage at diagnosis was determined according to the International Staging System (ISS) and renal function according to Durie and colleagues [12,13]. Performance status at transplant was assessed with the Karnofsky performance status score [14]. Data on maintenance therapy and diagnostic tools such as positron emission tomography–computed tomography or magnetic resonance imaging are not routinely documented in the EBMT registry and were thus missing.

Statistical Analysis

The primary objectives of the study were overall survival (OS) and PFS within the first 4 years after first autologous transplant. OS was defined as the time between transplant and death (from any cause) or last follow-up (for censored observations). PFS was defined as the time from transplant to disease progression or death from any cause. The secondary endpoints were overall nonrelapse mortality (NRM) and cumulative incidence of relapse. NRM 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 standard EBMT criteria [15].

Categorical variables were compared with Fisher's exact test or chi-squared test. Continuous variables were analyzed using the Mann-Whitney U test for independent samples. Survival probabilities were estimated by the Kaplan-Meier method, and the log-rank test was used for univariate comparison. Median follow-up was calculated according to the reverse Kaplan-Meier method. Cumulative incidences of relapse and NRM were analyzed together in a competing risks framework. Subgroup differences in cumulative incidences were analyzed using Gray's test. All stratified analyses of outcomes, except those related to transplant strategies, were analyzed from the time of first transplant. Landmark analyses were performed to evaluate the outcomes related to transplant strategies in patients who were alive and relapse free by 6 months after first transplant. To assess the effect of multiple factors on OS and PFS, including transplant strategies, landmarked Cox proportional hazards models were used to estimate hazard ratios (HRs). The proportional hazards assumption was verified using graphic methods. Scaled Schoenfeld residuals and graphic checks proposed

by Klein and Moeschberger were performed to find evidence of violations. All estimates are reported with corresponding 95% confidence intervals (CIs), and $P < .05$ was considered statistically significant. All analyses were performed using the statistical software R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

We developed the analysis on 488 NDMM patients with EMD and available cytogenetic information after first-line single auto (n = 373), tandem auto (n = 84), and auto–allo (n = 31). At least 1 high-risk cytogenetic abnormality was present in 202 patients (41%), with del(17p) and t(4;14) the most frequent in these patients (40% and 45%, respectively). Of those 202 patients, 1 high-risk cytogenetic abnormality was found in 46%, whereas the remaining 54% had more than 1 high-risk abnormality. Paraskeletal involvement was documented in 76% of patients and organ involvement in 18% of patients. Both types of involvement were present in 6% of patients. One involved site was present in 92% of patients. Stage III, performance status < 90%, and MM subtypes other than light chain were more frequent in high-risk cytogenetics. Notably, 47% of patients with organ involvement had high-risk cytogenetics compared with 40% of patients with paraskeletal involvement.

The median follow-up was 49 months (range, 44 to 53), and median age was 59 years (range, 25 to 77). Conditioning before first transplant consisted of melphalan and was given to most patients at a dose of 200 mg/m^2, whereas 30 patients received a dose of 140 mg/m^2. All auto–allo patients received RIC and stem cells from peripheral blood. Matched related donors were used for 11 and matched unrelated donors for the remaining 20 auto–allo patients. Tandem auto and auto–allo were received more frequently by patients with high-risk cytogenetics (51% and 54%, respectively, versus 33% of all single auto; $P = .003$). More patients receiving tandem auto had disease stage II or higher according to ISS and showed less than complete remission at time of first transplant compared with single auto. Other characteristics were well balanced between single auto and tandem auto cohorts. Patients undergoing auto–allo were younger, presented more frequently with >1 involved site, and received induction containing non-bortezomib regimens more often in comparison with single auto. Patient characteristics of the total NDMM EMD cohort are listed in Table 1.

Outcome According to Cytogenetic Risk and Disease Site

First, we focused on univariable analyses on cytogenetics and EMD-specific factors. Patients with high-risk cytogenetics showed significantly worse OS and PFS of 54% (45% to 62%) and 29% (20% to 37%) versus 78% (73% to 84%), respectively, and 49% (42% to 56%) of patients with standard risk ($P < .001$; Figure 1). Cumulative incidence of relapse was 69% (61% to 78%) for high-risk versus 48% (40% to 55%) for standard-risk cytogenetics ($P < .001$). Four-year OS and PFS according to different high-risk abnormalities were del(17p), 47% and 31%; t(4;14), 55% and 33%; t(14;16), 56% and 31%; t(14;20), 56% and 26%; and gain(1q)/del(1p), 31% and 9%. The number of high-risk abnormalities categorized as isolated versus >1 high-risk abnormality showed no difference in OS and PFS, at 55% (42% to 68%) and 30% (18% to 43%) versus 53% (42% to 64%) and 27% (16% to 39%) ($P = .30$ and .20).

OS according to type of involvement was 72% (66% to 77%) for paraskeletal versus 60% (48% to 73%) for organ and 46% (23% to 69%) for both types of involvement ($P = .002$), whereas PFS was 44% (38% to 51%) versus 39% (27% to 52%). By 48

Table 1
Patient, Disease, and Transplant Characteristics (N = 488)

Characteristic	No. of Cases or Median	Percent or Range
Sex		
Female	201	41
Male	287	59
Median age, yr	59	25-77
Subtype		
IgG	231	47
IgA	106	22
Light chain	120	24
Other Ig	8	2
Nonsecretory	23	5
ISS		
I	152	36
II	140	34
III	124	30
Unknown	78	
Renal impairment		
A	361	79
B	95	21
Unknown	32	
Karnofsky performance status, %		
90-100	347	74
<90	120	26
Unknown	21	
Cytogenetic risk		
Standard	286	59
High	202	41
del(17p)	81	17
t(4;14)	90	18
gain(1q)/del(1p)	50	10
t(14;16)	13	3
t(14;20)	6	1
Disease site		
Paraskeletal	374	77
Organ	87	18
Both	27	5
No. of sites		
1	448	92
>1	40	8
Induction before first transplant		
Bortezomib-based	355	73
Nonbortezomib-based	133	27
Stage at transplant		
CR	99	20
VGPR	175	36
PR	166	34
<PR	48	10
Radiotherapy before first transplant		
No	373	77
Yes	108	22
Unknown	7	1
Median time from diagnosis to first transplant, mo	6.1	2.4-11.8
Type of transplant		
Single auto	373	77

(*continued*)

Table 1 (*Continued*)

Characteristic	No. of Cases or Median	Percent or Range
Tandem auto	84	17
Auto–allo	31	6
Median time from first to second transplant, mo	3.0	.2-5.9

CR indicates complete response; VGPR, very good partial response; PR, partial response.

months no patients with both types of involvement were still at risk ($P = .02$). One involved site showed OS and PFS rates of 71% (66% to 76%) and 44% (38% to 50%) compared with 45% (26% to 63%) and 22% (5% to 38%) for >1 site ($P < .001$ and $P = .001$, respectively). OS stratified according to single sites of different organs was lymph nodes, 44%; central nervous system, 73%; heart or pleura, 0%; skin, 47%; gastrointestinal tract or liver, 70%; respiratory tract or lung, 100%; and kidney, 79%. Stratifying outcome of involvements according to cytogenetics, OS of standard- versus high-risk patients was 83% versus 56% for paraskeletal, 70% versus 49% for organ, and 46% versus 46% for both types of involvement.

Outcome According to Induction and Other Clinical Factors

Bortezomib-based induction regimens showed OS and PFS rates of 69% (63% to 75%) and 42% (36% to 48%) versus 64% (54% to 74%) and 34% (22% to 45%) for nonbortezomib-based regimens ($P = .44$ and $P = .12$). Rates in patients with high-risk cytogenetics were 55% and 31% versus 49% and 24%. The distribution of remission status at first transplant according to induction (bortezomib-based versus nonbortezomib) was complete remission, 21% versus 17%; very good partial remission, 38% versus 31%; partial remission, 32% versus 38%; and less than partial remission, 9% versus 14%.

Remaining clinical factors significantly associated with worse 4-year OS were impaired renal function classified according to Durie and Salmon [13] as A versus B showing 71% (66% to 77%) versus 56% (43% to 68%; $P = .006$) and radiotherapy showing 62% (51% to 72%) versus no radiotherapy resulting in 70% (65% to 76%; $P = .04$).

Factors with impact on worse PFS in univariable analyses were MM subtypes other than light chain, with PFS rates of 39% (32% to 45%) versus 50% (38% to 61%; $P = .05$), renal function B of 33% (21% to 45%) versus A of 43% (37% to 49%; $P = .02$), disease stage II or III according to ISS showing 37% (30% to 44%) versus 48% (37% to 58%; $P = .05$) in stage I, and less than complete remission at first transplant resulting in 39% (33% to 45%) versus complete remission 52% (39% to 64%; $P = .02$). PFS showed improvement over time, at 33% (19% to 48%) before 2009, 45% (48%% to 52%) between 2009 and 2012, and 49% (34% to 63%) after 2012 ($P = .03$); OS showed no difference ($P = .30$).

Outcome According to Transplant Strategies and Cytogenetic Risk

Next, we evaluated univariate effects on outcome of different transplant strategies. To address potential survivor bias in the different transplant groups, direct comparison of transplant strategies were performed in landmark analyses where included patients were alive and relapse free by 6 months. OS appeared to be influenced by transplant in univariate analysis, resulting in OS rates of 70% (63% to 76%) for single auto versus 83% (74% to 92%) for tandem auto and 88% (74% to 100%) for auto–allo ($P = .06$; Figure 2A). PFS was 43% (37% to 49%) for single auto versus 52% (40% to 64%) for tandem auto and 58% (35% to 81%) for auto–allo at 4 years ($P = .30$; Figure 2B). The cumulative incidence of NRM was 2% (0% to 4%) for single auto, 1% (0% to 4%) for tandem auto, and 10% (0% to 23%) for auto–allo ($P = .09$). The corresponding cumulative incidence of relapse was 54% (48% to 61%) for single auto, 47% (35% to 60%) for tandem auto, and 30% (8% to 52%) for auto–allo ($P = .29$).

Furthermore, we stratified results of cytogenetics according to type of transplant. After single auto, outcome was significantly different regarding both OS and PFS, resulting in 78% (71% to 85%) and 48% (40% to 56%) for standard-risk versus 41% (30% to 52%) and 22% (11% to 33%) for high-risk cytogenetics ($P < .001$; Figure 3). In contrast, tandem auto did not show

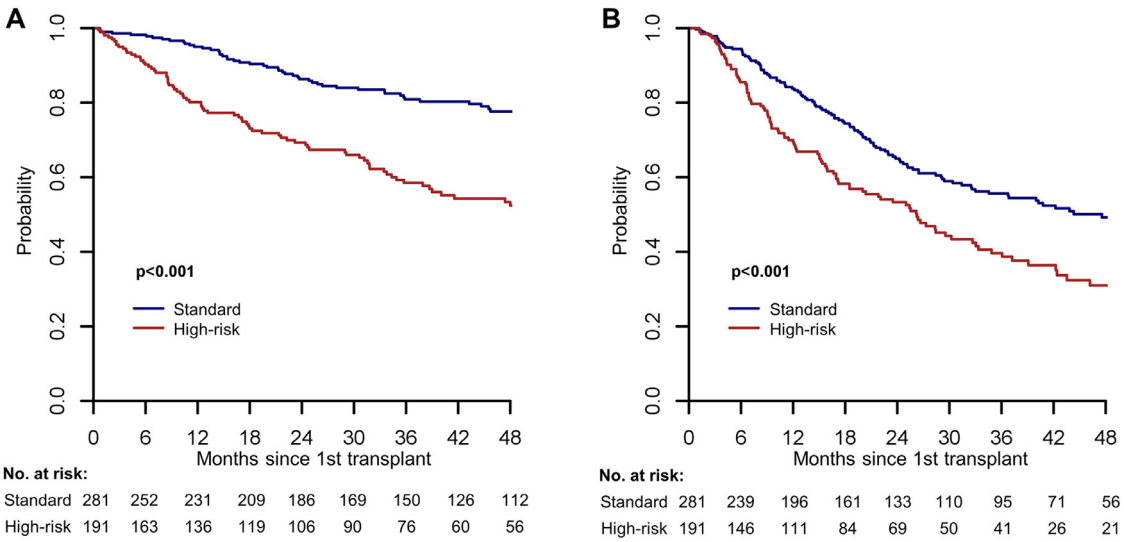

Figure 1. Post-transplant outcome by cytogenetic risk in the univariate model. Patients at risk between first autologous transplant and subsequent 48 months were included in the survival analysis of high-risk versus standard-risk cytogenetics. (A) OS was significantly affected by cytogenetics, being worse in high-risk patients ($P < .001$). (B) PFS was significantly worse in patients with high-risk cytogenetics versus standard-risk ($P < .001$).

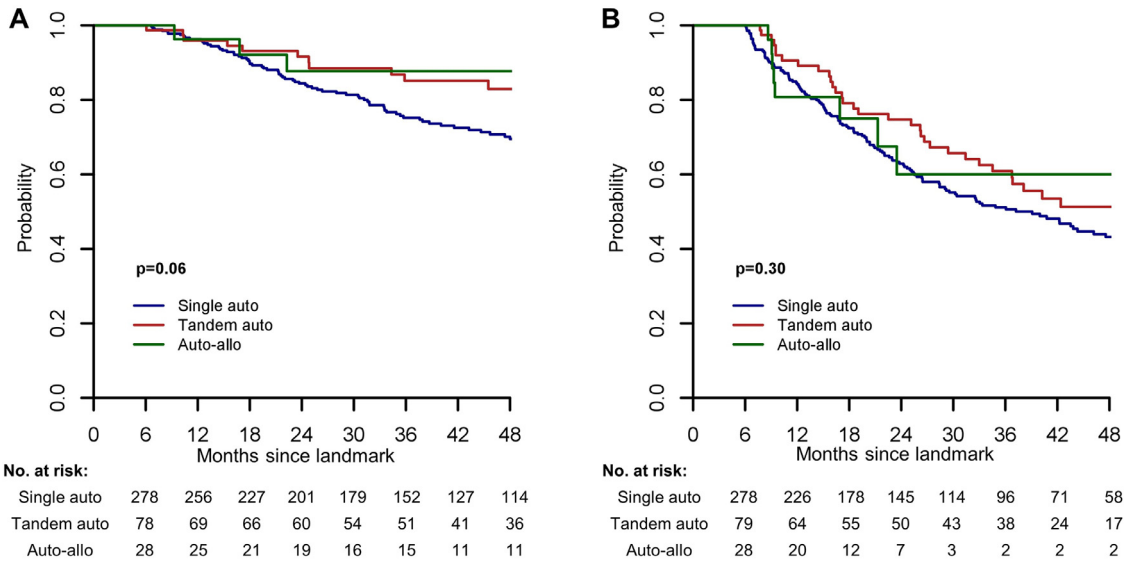

Figure 2. Post-transplant outcome by different type of transplant in the univariate landmark model. Patients at risk between months 6 and 48 after first autologous transplant were included in the survival analysis of single versus tandem autologous versus autologous–allogeneic transplant. Accordingly, patients had to be alive or relapse-free to enter analyses. (A) OS appeared to be affected by transplant, showing higher rates for tandem autologous and autologous–allogeneic transplant ($P = .06$). (B) PFS did not significantly differ between 3 transplant types ($P = .30$).

differences between standard- and high-risk cytogenetics in OS or PFS, at 82% (70% to 95%) and 56% (39% to 73%) for standard risk versus 84% (71% to 97%) and 45% (26% to 64%) for high risk ($P = .99$ and $P = .24$, respectively; Figure 4). Rates appeared to be similar for patients undergoing auto–allo, showing OS and PFS of 84% (68% to 92%) and 56% (17% to 95%) for standard-risk versus 81% (61% to 100%) and 60% (30% to 89%) for high-risk cytogenetics (Figure 5).

Multivariable Analyses on Outcome

Finally, we constructed a predefined landmarked Cox multivariable model OS and PFS (Table 2). The HRs provided by the model describe mortality risk and/or risk of progression between 6 and 48 months after first transplant. High-risk cytogenetics was associated with worse OS versus standard-risk cytogenetics, showing an HR of 2.00 (95% CI, 1.28 to 3.15; $P = .003$). Patients receiving a tandem auto or auto–allo were less likely to die than were patients who received an upfront single auto, with HRs of .46 (95% CI, .24 to .89; $P = .02$) for tandem auto and .31 (95% CI, .09 to 1.03; $P = .06$) for auto–allo. Impaired renal function B according to Durie and Salmon [13] was significantly associated with worse OS, resulting in an HR of 1.91 (95% CI, 1.09 to 3.34; $P = .02$). Light-chain MM subtype showed higher risk for death (HR, 1.69). In contrast, univariate effect of different types of involvement disappeared in the multivariate analysis when comparing paraskeletal with organ ($P = .87$) or both types of involvement ($P = .65$).

Regarding PFS, patients with high-risk cytogenetics were more likely to progress or die than were patients with standard-risk cytogenetics, with an HR of 1.69 (95% CI, 1.23 to

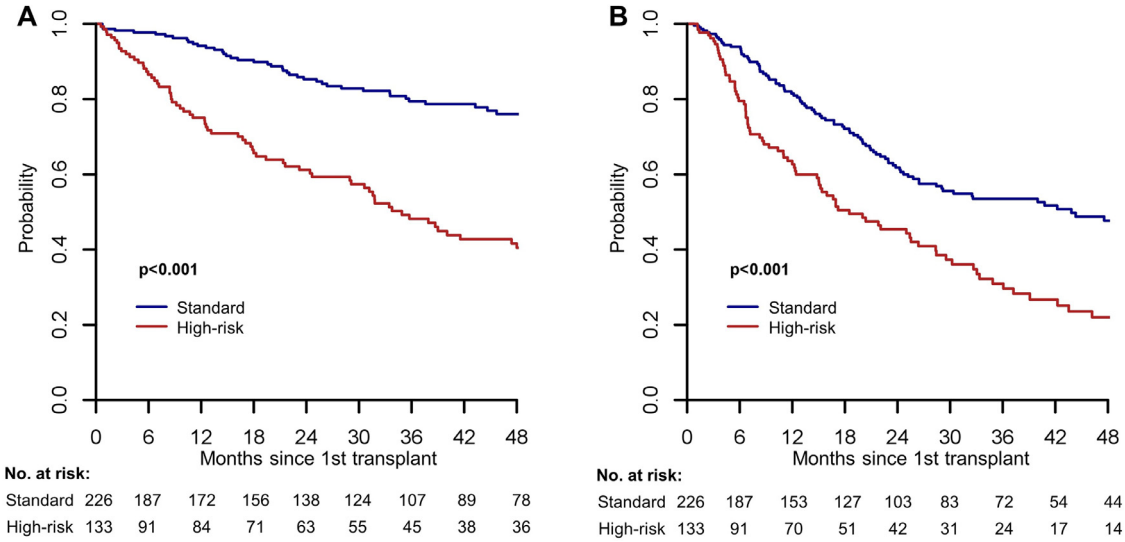

Figure 3. Post-transplant outcome by cytogenetic risk after single autologous transplant in the univariate model. Patients at risk between first autologous transplant and subsequent 48 months were included in the survival analysis of high-risk versus standard-risk cytogenetics. (A) OS was significantly affected by cytogenetics, being worse in high-risk patients ($P < .001$). (B) PFS was significantly worse in patients with high-risk cytogenetics versus standard-risk ($P < .001$).

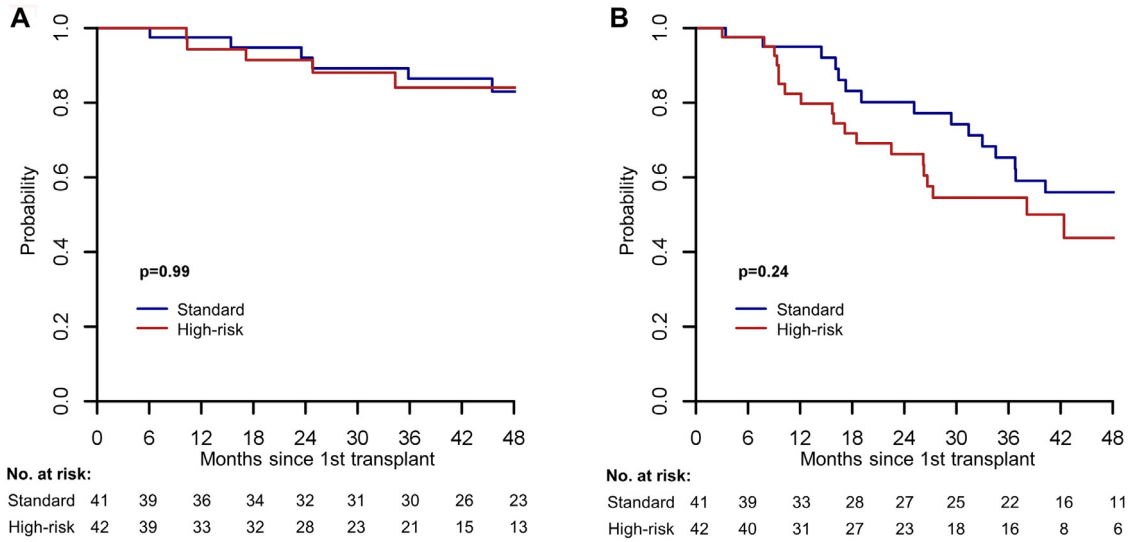

Figure 4. Post-transplant outcome by cytogenetic risk after tandem autologous transplant in the univariate model. Patients at risk between first autologous transplant and subsequent 48 months were included in the survival analysis of high-risk versus standard-risk cytogenetics. (A) OS was the same for high-risk versus standard-risk cytogenetics ($P = .99$). (B) PFS did not significantly differ between high-risk and standard-risk patients after tandem autologous transplant ($P = .24$).

2.33; $P < .001$). Tandem auto was significantly associated with better PFS versus single auto (HR, .64; 95% CI, .42 to .96; $P = .03$), whereas auto–allo resulted in similar risk for progression or death (HR, .75; 95% CI, .36 to 1.58; $P = .46$). Worse renal function (HR, 1.60), light-chain subtype (HR, 1.41), and ISS II/III (HR, 1.55) were associated with worse PFS. Similar to analysis on OS, no difference in risk for progression or death was found for comparison of paraskeletal versus organ ($P = .37$) or both types of involvement ($P = .56$). Bortezomib-based induction seemed to show better PFS versus nonbortezomib-based regimens ($P = .09$).

DISCUSSION

Only limited data are available regarding the optimal transplant strategy in NDMM patients with EMD and high-risk cytogenetics. A previous study in NDMM with EMD showed a slight trend toward improved outcome after tandem auto after adjusting for disease- and patient-specific variables, but inconclusive results limited interpretation and cytogenetic information was lacking [3]. In the current analysis we focused on NDMM EMD patients specifically with cytogenetics, which we could obtain from 488 patients who underwent upfront hematopoietic stem cell transplantation. We demonstrate that high-risk cytogenetics occurred in 40% of NDMM EMD patients, which resulted in worse outcome after single autograft, whereas upfront tandem auto overcame poor OS and PFS of high-risk cytogenetics.

Current consensus defines t(4;14), t(14;16), t(14;20), del (17/17p), del(1p), and gain(1q) and any non-hyperdiploid karyotype as high-risk cytogenetics in MM patients resulting in poor outcome [6]. Evaluations specifically in patients with EMD are very limited, and the incidence of high-risk

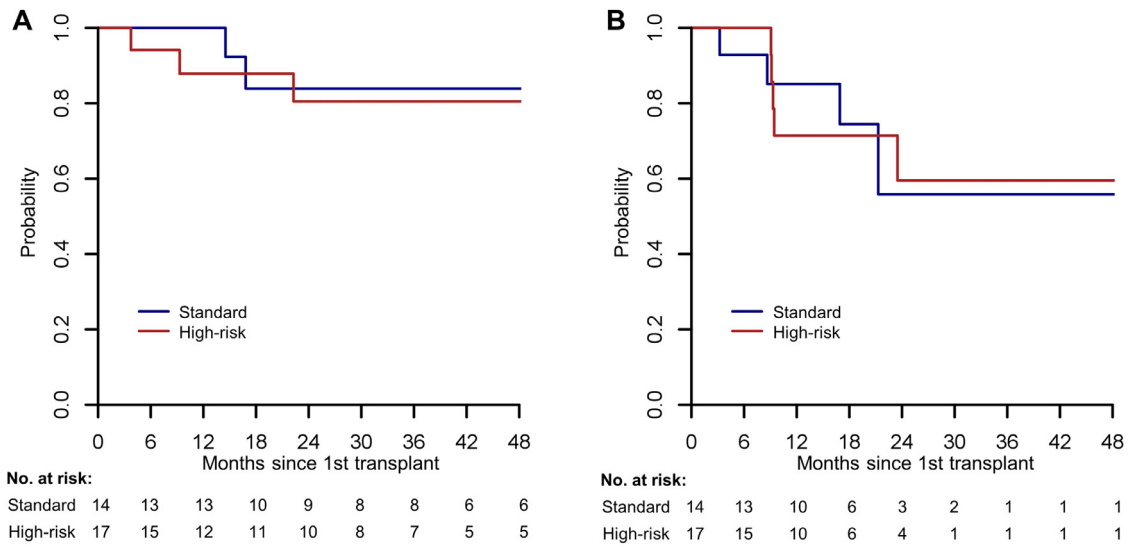

Figure 5. Post-transplant outcome by cytogenetic risk after autologous–allogeneic transplant in the univariate model. Patients at risk between first autologous transplant and subsequent 48 months were included in the survival analysis of high-risk versus standard-risk cytogenetics. *P* values are not reported because of small sample sizes. (A) OS. (B) PFS.

Table 2
Multivariable Model on OS and PFS

	OS		PFS	
Factor	HR (95% CI)	*P*	HR (95% CI)	*P*
Cytogenetics		.003		
Standard risk	Reference		Reference	
High risk	2.00 (1.28-3.15)	.003	1.69 (1.23-2.33)	.001
Transplant				
Single auto	Reference		Reference	
Tandem auto	.46 (.24-.89)	.02	.64 (.42-.96)	.03
Auto–allo	.31 (.09-1.03)	.06	.75 (.36-1.58)	.46
Involvement				
Paraskeletal	Reference		Reference	
Organ	.94 (.49-1.83)	.87	.80 (.49-1.31)	.37
Both	1.36 (.36-5.14)	.65	1.40 (.45-4.39)	.56
No. of sites				
1	Reference		Reference	
>1	2.42 (.79-7.44)	.12	1.84 (.69-4.90)	.22
Age	1.00 (.97-1.02)	.81	.99 (.97-1.01)	.17
Subtype				
Other	Reference		Reference	
Light chain	1.69 (.94-3.06)	.08	1.41 (.95-2.09)	.09
Renal impairment				
A	Reference		Reference	
B	1.91 (1.09-3.34)	.02	1.60 (1.06-2.44)	.03
ISS				
I	Reference		Reference	
II/III	1.33 (.81-2.19)	.26	1.55 (1.10-2.20)	.01
Remission status at transplant				
CR	Reference		Reference	
VGPR	1.27 (.83-1.81)	.27	1.23 (.80-1.88)	.34
PR	1.78 (1.19-2.70)	.01	1.70 (1.11-2.61)	.02
<PR	2.31 (1.35-3.93)	.002	2.17 (1.24-3.80)	.01
Induction				
Nonbortezomib-based	Reference		Reference	
Bortezomib-based	.75 (.47-1.19)	.15	.82 (.57-1.06)	.09

cytogenetic features may be influenced by sample site. In a Spanish trial including 55 NDMM patients with EMD, the proportion of patients with high-risk cytogenetics from bone marrow samples was similar in patients with and without EMD (24% versus 21%, respectively), whereas 1 retrospective multicenter study analyzing extramedullary tumor samples from 36 patients detected an overall high incidence of del(17p) in EMD with paraskeletal (32%) and organ involvement (27%) [11]. In our EMD cohort evaluating bone marrow samples, the overall incidence of high-risk cytogenetics (41%) and frequencies for del(17p) (17%) and t(4;14) (18%) were higher than previously reported for patients without EMD [16,17]. Rates according to type of involvement were 16% and 19% for paraskeletal and 21% and 17% for organ involvement. In line with previous findings, high-risk cytogenetics were more frequent in patients with organ involvement (47%) than with paraskeletal involvement (40%) [11]. In contrast to reports identifying combinations of >2 abnormalities conferring very high risk, no impact of number of cytogenetic abnormalities was identified in the present analysis [18].

Few studies have investigated the effect of a second autologous transplant. In the Total Therapy 3 trail, the addition of bortezomib to tandem auto improved outcome in patients with t(4;14), indicating that the effect of high-dose therapy and subsequent autologous transplant varies with induction [19,20]. A conventional meta-analysis and network meta-analysis recently found that both tandem and single transplant with bortezomib, lenalidomide, and dexamethasone were superior to single transplant alone and standard-dose therapy but no improvement in OS could be identified. Using meta-regression detected longer follow-up leading to benefit in outcome, whereas subgroup analysis according to cytogenetics was lacking [21]. The randomized phase III EMN02/HO95 study showed that a second autologous transplant was superior over single auto in terms of prolonged PFS and OS for the overall patient population and for poor prognosis subgroups of patients with advanced disease stage and high-risk cytogenetic profile. Additionally, the incorporation of bortezomib abrogated the increased risk of progression or death, particularly in del(17p) [22,23]. Collectively, although the role of single versus tandem auto for NDMM continues to be debated in the novel agent era, investigations in EMD remain scarce. We showed that tandem autologous transplant could significantly improve survival in EMD with high-risk cytogenetics. The frequency of patients receiving bortezomib-based induction was the same between single (74%) and tandem auto (71%) and did appear to improve at least PFS in comparison with nonbortezomib-based regimens. We identified improvement in PFS

over time suggesting an effect of post-transplant therapy, whereas multiple previous studies showed the benefit of maintenance therapy with lenalidomide or bortezomib after autologous transplant for MM patients [24–26]. A limitation of our study is the lack of information on specific maintenance therapy, which is not usually reported in the EBMT database, especially in EMD. Results of the largest randomized US transplant trial in upfront treatment of MM suggested that a second auto was not superior to a single auto followed by lenalidomide maintenance, even stratified according to cytogenetic risk [27]. However, more evidence regarding maintenance efficacy specific to NDMM EMD is needed in ongoing and future prospective trials.

Allogeneic transplant has been proposed as a treatment for high-risk younger patients but is still the only potential curative treatment option for MM. An analysis on 101 relapse patients treated with allogeneic transplant using fludarabine/melphalan–conditioning regimens found no influence on outcome by t(4;14), suggesting that a subset of onset poor prognosis might be overcome by this treatment [28]. In a report of 143 MM patients who underwent allogeneic transplant with mostly RIC regimens, 3-year PFS and OS did not differ for patients with or without t(4,14) or del(17) [29]. In a trial of 73 NDMM patients, auto–allo yielded similar 5-year PFS (24% versus 30%) and OS (50% versus 54%) in patients without t(4;14) or del(17p) [30]. The EBMT-NMAM2000 study showed better OS in patients treated with auto–allo receiving RIC or single auto: 49% versus 36% at 96 months [31]. Regarding EMD, a retrospective analysis including 33 patients with EMD before allogeneic transplant found significantly shorter PFS (median, 3 months) and OS (median, 8 months) versus patients without EMD. A plateau at 25% survival, however, indicated induction of long-term remissions in a subgroup of patients such as cases with del(17p) or multiorgan involvement [32]. In our NDMM EMD cohort of 31 patients receiving first-line auto–allo with RIC conditioning, OS and PFS rates were similar for patients with standard-risk (92% and 60%) versus high-risk cytogenetics (84% and 60%), which translated into a trend toward improved OS versus single auto after adjusting for other risk factors. Seventeen patients (54%) had high-risk cytogenetics versus 38% in single auto. Notably, whereas differences in outcome according to types of involvement (paraskeletal, organ, or both) remained significant in single auto, OS was similar in auto–allo with 78% (paraskeletal), 82% (organ), and 100% (both). Furthermore, lower incidences of relapse were identified after auto–allo (30%) versus single (54%) and tandem auto (47%), in contrast to previous findings [33,34]. Because this population was small, however, the therapeutic role of first-line auto–allo needs to be better defined, especially for patients with high-risk disease [35,36].

This analysis was conducted with the use of retrospective data and is therefore subject to the attendant limitations. Data on how the EMD diagnosis was assessed are not routinely documented in the EBMT registry. Another limitation of the study is the lack of information on maintenance and consolidation strategies. However, because prospective trials specific in EMD are unlikely, we used regression modeling and landmark analyses as a means of controlling for differences between cohorts in the most possible manner, but such adjustment cannot account for all discrepancies in clinical and diagnostic characteristics between patients. Thus, our results need to be interpreted in the context of the limitations of the study.

In conclusion, high-risk cytogenetics were detected in 41% NDMM patients with EMD, being more frequent in organ involvement. Tandem autologous transplant seems to improve outcomes in this high-risk cohort, suggesting superiority over single transplant, whereas results regarding auto–allo were promising but should be interpreted with caution.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Declaration of competing interest: There are no conflicts of interest to report.

Authorship statement: N.G. and N.K. designed the work, performed statistics, and wrote the manuscript. D.J.E. performed statistics and wrote the manuscript. L.K. collected data from the EBMT database. D.C., P.P., J.B.L., P.R., D.B., N.S., M.T., J.P., R.P. P., J.Y.C., M.M., X.P., G.K., M.I.-R., V.P., L.F., J.M., D.B., A.P., W.S., and L.G. contributed patients and collected, analyzed, and interpreted the data. All authors approved the final version of the manuscript.

REFERENCES

1. Bladé J, Fernández de Larrea C, Rosiñol L, Cibeira MT, Jiménez R, Powles R. Soft-tissue plasmacytomas in multiple myeloma: incidence, mechanisms of extramedullary spread, and treatment approach. *J Clin Oncol*. 2011;29:3805–3812.
2. Cavo M, Terpos E, Nanni C, et al. Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. *Lancet Oncol*. 2017;18:e206–e217.
3. Gagelmann N, Eikema DJ, Iacobelli S, et al. 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. *Haematologica*. 2018;103:890–897.
4. Pour L, Sevcikova S, Greslikova H, et al. Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extramedullary relapse. *Haematologica*. 2014;99:360–364.
5. Manier S, Salem KZ, Park J, et al. Genomic complexity of multiple myeloma and its clinical implications. *Nat Rev Clin Oncol*. 2016;14:100–113.
6. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127:2955–2962.
7. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33:2863–2869.
8. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome Genetic abnormalities and survival in multiple of the Intergroupe Francophone du Myelome. *Blood*. 2007;109::3489–3495.
9. Fonseca R, Bergsagel PL, Drach J. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia*. 2009;23:2210–2221.
10. Chng WJ, Dispenzieri A, Chim CS. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014;28:269–277.
11. Billecke L, Murga Penas EM, May AM, et al. Cytogenetics of extramedullary manifestations in multiple myeloma. *Br J Haematol*. 2013;161:87–94.
12. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23:3412–3420.
13. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. 1975;36:842–854.
14. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma—with particular reference to bronchogenic carcinoma. *Cancer*. 1948;1:634–656.
15. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*. 1998;102:1115–1123.
16. Rosiñol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pre-transplantation therapy in multiple myeloma: results of a randomized phase III PETHEMA/GEM study. *Blood*. 2012;120:1589–1596.
17. Fonseca R, Blood E, Rue M, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood*. 2003;101:4569–4575.
18. Boyd KD, Ross FM, Chiecchio L, NCRI Haematology Oncology Studies Group. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. *Leukemia*. 2012;26:349–355.
19. Usmani SZ, Crowley J, Hoering A, et al. Improvement in long-term outcomes with successive Total Therapy trials for multiple myeloma: are patients now being cured? *Leukemia*. 2013;27:226–232.

20. Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma. *Blood*. 2015;125:3085–3099.
21. Dhakal B, Szabo A, Chhabra S, et al. Autologous transplantation for newly diagnosed multiple myeloma in the era of novel agent induction: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4:343–350.
22. Cavo M, Gay FM, Patriarca F, et al. Double autologous stem cell transplantation significantly prolongs progression-free survival and overall survival in comparison with single autotransplantation in newly diagnosed multiple myeloma: an analysis of phase 3 EMN02/HO95 Study. *Blood*. 2017;130; abstr 401.
23. Sonneveld P, Goldschmidt H, Rosiñol L, et al. Bortezomib-based versus nonbortezomib based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. *J Clin Oncol*. 2013;31:3279–3287.
24. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol*. 2017;35:3279–3289.
25. Goldschmidt H, Lokhorst HM, Mai EK, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. *Leukemia*. 2018;32:383–390.
26. Gay F, Jackson G, Rosiñol L, et al. Maintenance treatment and survival in patients with myeloma: a systematic review and network meta-analysis. *JAMA Oncol*. 2018;4:1389–1397.
27. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Comparison of autologous hematopoietic cell transplant (autoHCT), bortezomib, lenalidomide (Len) and dexamethasone (RVD) consolidation with Len maintenance (ACM), tandem autohct with Len maintenance (TAM) and autohct with Len maintenance (AM) for up-front treatment of patients with multiple myeloma (MM): primary results from the randomized phase III trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702–StaMINA Trial). *Blood*. 2016;128. LBA-1.
28. Schilling G, Hansen T, Shimoni A, et al. Impact of genetic abnormalities on survival after allogeneic hematopoietic stem cell transplantation in multiple myeloma. *Leukemia*. 2008;22:1250–1255.
29. Roos-Weil D, Moreau P, Avet-Loiseau H. Impact of genetic abnormalities after allogeneic stem cell transplantation in multiple myeloma: a report of the Société Française de Greffe de Moelle et de Thérapie Cellulaire. *Haematologica*. 2011;96:1504–1511.
30. Kröger N, Badbaran A, Zabelina T, et al. Impact of high-risk cytogenetics and achievement of molecular remission on long-term freedom from disease after autologous-allogeneic tandem transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:398–404.
31. Gahrton G, Iacobelli S, Björkstrand B, EBMT Chronic Malignancies Working Party Plasma Cell Disorders Subcommittee. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. *Blood*. 2013;121:5055–5063.
32. Rasche L, Röllig C, Stuhler G, et al. Allogeneic hematopoietic cell transplantation in multiple myeloma: focus on longitudinal assessment of donor chimerism, extramedullary disease and high risk cytogenetic features. *Biol Blood Marrow Transplant*. 2016;22:1988–1996.
33. Vincent L, Ceballos P, Plassot C, et al. Factors influencing extramedullary relapse after allogeneic transplantation for multiple myeloma. *Blood Cancer J*. 2015;5:e341.
34. Perez-Simon JA, Sureda A, Fernandez-Aviles F, et al. Reduced-intensity conditioning allogeneic transplantation is associated with a high incidence of extramedullary relapses in multiple myeloma patients. *Leukemia*. 2006;20:542–545.
35. Maffini E, Storer BE, Sandmaier BM, et al. Long term follow-up of tandem autologous-allogeneic hematopoietic cell transplantation for multiple myeloma. *Haematologica*.
36. Malek E, El-Jurdi N, Kröger N, de Lima M. Allograft for myeloma: examining pieces of the jigsaw puzzle. *Front Oncol*. 2017;7:287.