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Allogeneic Hematopoietic Cell Transplantation in Multiple Myeloma: Focus on Longitudinal Assessment of Donor Chimerism, Extramedullary Disease, and High-Risk Cytogenetic Features

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A B S T R A C T

Although generally not applied as first-line treatment of multiple myeloma, allogeneic hematopoietic cell transplantation (allo-SCT) can still be chosen as ultimate escalation approach in high-risk patients, preferentially within the framework of clinical trials. In this study, we investigated whether decreasing donor chimerism (DC) is predictive for relapse. In addition, we comprehensively determined the impact of several other disease- and treatment-related factors on outcome. One hundred fifty-five multiple myeloma patients whose DC status was followed serially by the short tandem repeat–based techniques at a single lab were included in this retrospective study. Outcome variables were studied in univariate and multivariable analyses. Available were 2.324 DC samples (median, 12 per patient). Loss of full DC was associated with shorter progression-free survival (PFS) (HR, 1.7; 95% CI, 1.1 to 2.6) but did not impact overall survival. Two-thirds of patients with International Myeloma Working Group–defined relapses still displayed a full DC in peripheral blood or bone marrow. Extramedullary manifestations were observed in 33% of patients, accounting for the discrepancy between DC analysis and the actual disease status. In multivariable analysis, the 2 most relevant variables for an unfavorable PFS were progressive disease before allo-SCT (HR, 3.0; 95% CI, 1.5 to 5.9) and allo-SCT at least the second relapse (HR, 2.8; 95% CI, 1.5 to 4.9), whereas for overall survival progressive disease or partial response before allo-SCT had the strongest negative effects (HR, 4.2; 95% CI, 1.9 to 9, and HR, 2.0; 95% CI, 1.0 to 3.8, respectively). Adverse cytogenetics such as del17p, t(4,14) or amp(1q21) were not associated with shorter survival after allo-SCT. Extensive DC sampling beyond robust engraftment does not appear to provide additional information helpful for disease management in most patients and is challenged by a significant incidence of extramedullary disease. In our series, allo-SCT overcame unfavorable cytogenetics.

INTRODUCTION

The impact of allogeneic hematopoietic (stem) cell transplantation (allo-SCT) in the management of multiple myeloma (MM) is still a matter of debate because randomized trials have shown inconsistent and conflicting results, with 3 studies favoring allogeneic and 4 studies showing no survival benefit [1-8]. Moreover, studies were mainly conducted in the pre–novel agent era. As a consequence, allo-SCT as a modality with considerable toxicity is generally not applied as first-line therapy for MM outside of clinical trials. Moreover, next generations of immunomodulatory drugs and proteasome inhibitors as well as the introduction of highly effective immunotherapies other than allo-SCT have dramatically changed current treatment approaches and will lead to improved disease control in most patients.

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However, even today about one-fourth of patients fail to benefit from the recent advances and relapse early, showing a median survival of less than 2 years as observed across all study groups. These *high-risk* patients had been characterized by adverse cytogenetic findings in molecular profiling or fluorescein in situ hybridization, an elevated lactate dehydrogenase, and International Scoring System III disease [9,10]. Moreover, the presence of refractory disease occurring after multiple relapses is consequently associated with poor prognosis, especially when extramedullary involvement is present [11-14]. In these situations, allo-SCT may be considered as an ultimate escalation approach, and mainly nonrandomized studies support its use particularly in *high-risk* disease or as salvage consolidation at relapse [4,15-18]. However, prospective and controlled trials are warranted to finally elucidate the role of allo-SCT in these situations.

Basically, allo-SCT takes advantage of a tumor cell-free graft along with the graft-versus-myeloma (GVM) effect targeting residual malignant plasma cells. Furthermore, allo-SCT allows for donor lymphocyte infusions (DLIs) as an additional intervention that has shown remarkable responses, clearly demonstrating the intensification of a GVM effect [19,20]. However, relapses still occur, and post-transplantation strategies such as preemptive DLIs are currently under investigation to improve and sustain the GVM effect and to prevent relapse.

One tool in monitoring the post-transplantation period is the analysis of the donor chimerism (DC) because a mixed DC was found to be associated with relapse and survival in patients suffering from acute leukemias, myelodysplastic syndrome, or chronic myelogenous leukemia [21-26]. Consequently, persistence of a mixed DC or loss of complete DC was used as a trigger for interventions such as DLI or preemptive treatment with hypomethylating agents in more recent studies [27-29]. Interestingly, data on chimerism analysis are relatively scarce for allo-SCT in MM. In a small series (n = 20), DC status was not predictive for outcome, but chronic graft-versus-host disease (cGVHD) seemed to increase the rate of patients with full DC [30]. Kröger et al. [31] used DC results of CD138 purified plasma cells as a marker for minimal residual disease and found an association of plasma cell chimerism decrease and relapse. To our knowledge, a systematic evaluation of a larger sample size has not been undertaken so far.

Therefore, we retrospectively evaluated DC results of 155 clinically well-characterized MM patients and correlated outcome information with a set of baseline and outcome variables (primary aim of the study). In addition, we used this large number of patients to determine the impact of disease- and treatment-related factors like extramedullary disease (EMD), acute and cGVHD, and post-transplant consolidation on outcome.

METHODS

Patients

Patients whose DC status was analyzed and followed at a single lab for molecular diagnostics (Agendix GmbH, Dresden, Germany) were primarily eligible for inclusion in this retrospective study. One hundred fifty-five MM patients receiving allo-SCT at 3 large German transplant centers between January 2006 and December 2014 with availability of at least a single DC result were analyzed. Baseline characteristics are shown in Table 1.

Before allo-SCT, 45 patients had been in complete remission (CR)/very good partial remission (VGPR), 88 in PR/stable disease, and 22 had progressive disease (PD). Thirty-five patients (22%) received allo-SCT as first-line treatment, 60 (39%) at first relapse and 60 (39%) at second and subsequent relapse. Most patients had received either treosulfan/fludarabine (55%) or melphalan/fludarabine (41%) for nonablative/reduced-intensity conditioning. Thirty-seven patients received allografts from matched related donors, 86 from matched unrelated donors (MUDs), and 20 from mismatched donors.

Table 1
Patient and Transplant Characteristics

Characteristics	Missing Value	Subcharacteristics	No. of Patients	Percent
Age < 45 years at diagnosis	0 (.0)		18	11.6
MM classification	0 (.0)	IgG	82	52.9
		IgA	42	27.1
		Light chain	23	14.8
		Other Ig	1	.6
		Nonsecretory	8	5.2
Stage according to Salmon and Durie	4 (2.4)	I A/B	13	8.0
		II A/B	22	14.1
		III A/B	113	73.0
Cytogenetics	68 (43.8)	del 17p	15	9.6
		t(4;14)	13	8.3
		amp(1q21)	5	3.2
		Standard risk	54	34.8
Chimerism samples	0 (.0)	Total	2324	
		PB	2198	94.5
		BM	126	5.4
RIC conditioning	0 (.0)		155	100
		Melphalan/ fludarabine	63	40.6
		Treosulfan/ fludarabine	85	54.8
		Other	10	6.4
Immunosuppression	3 (1.9)			
		ATG	121	78
		Cyclosporine A, MTX	114	73.5
		Cyclosporine A, MMF	39	25.1
Donor type	0 (.0)			
		Matched related donors	37	23.9
		MUDs	86	55.4
		Mismatched donors	31	20
Time of allo-SCT	0 (.0)	First line	35	22.6
		Second line	60	38.7
		Third and subsequent line	60	38.7
100-Day transplant-related mortality			25	16.1

Values in parentheses are percents.
RIC indicates reduced-intensity conditioning; MTX, methotrexate; MMF, mycophenolate mofetil.

With a median follow-up of 45 months, the median progression-free survival (PFS) and overall survival (OS) were 14 months and 53 months, respectively. One hundred–day transplant-related mortality was 16%.

Chimerism Analysis

Available were 2.324 DC samples (median, 12 per patient; 126 bone marrow [BM], 2198 peripheral blood [PB]) were available. The median interval from allo-SCT to first assessment was 12 days (range, 3 to 62). Median duration of repeat chimerism sampling was 15 months (range, 0 to 92). DC analysis was performed using a fully validated multiplex short tandem repeat–PCR method (HumanType Chimera; Biotype GmbH, Dresden, Germany) on whole blood or BM [29,32]. The assay has a documented sensitivity of 1%; therefore, a chimerism status > 99% donor signal was considered as full/complete DC. In selected cases, T cell and granulocyte chimerism were assessed separately as described previously [33]. The laboratory is accredited for chimerism analysis according to the German and international standards described in the DIN/ISO 15189;2013 and participates in regular proficiency testing by United Kingdom National External Quality Assessment Service (UKNEQAS). Myeloma response assessment was performed according to the International Myeloma Working Group guidelines [34].

Statistics

The Kaplan-Meier method was used for survival analysis. PFS time was measured from allo-SCT to relapse or death in remission, whichever occurred first. OS time was defined as time from allo-SCT to death. Variables with significant

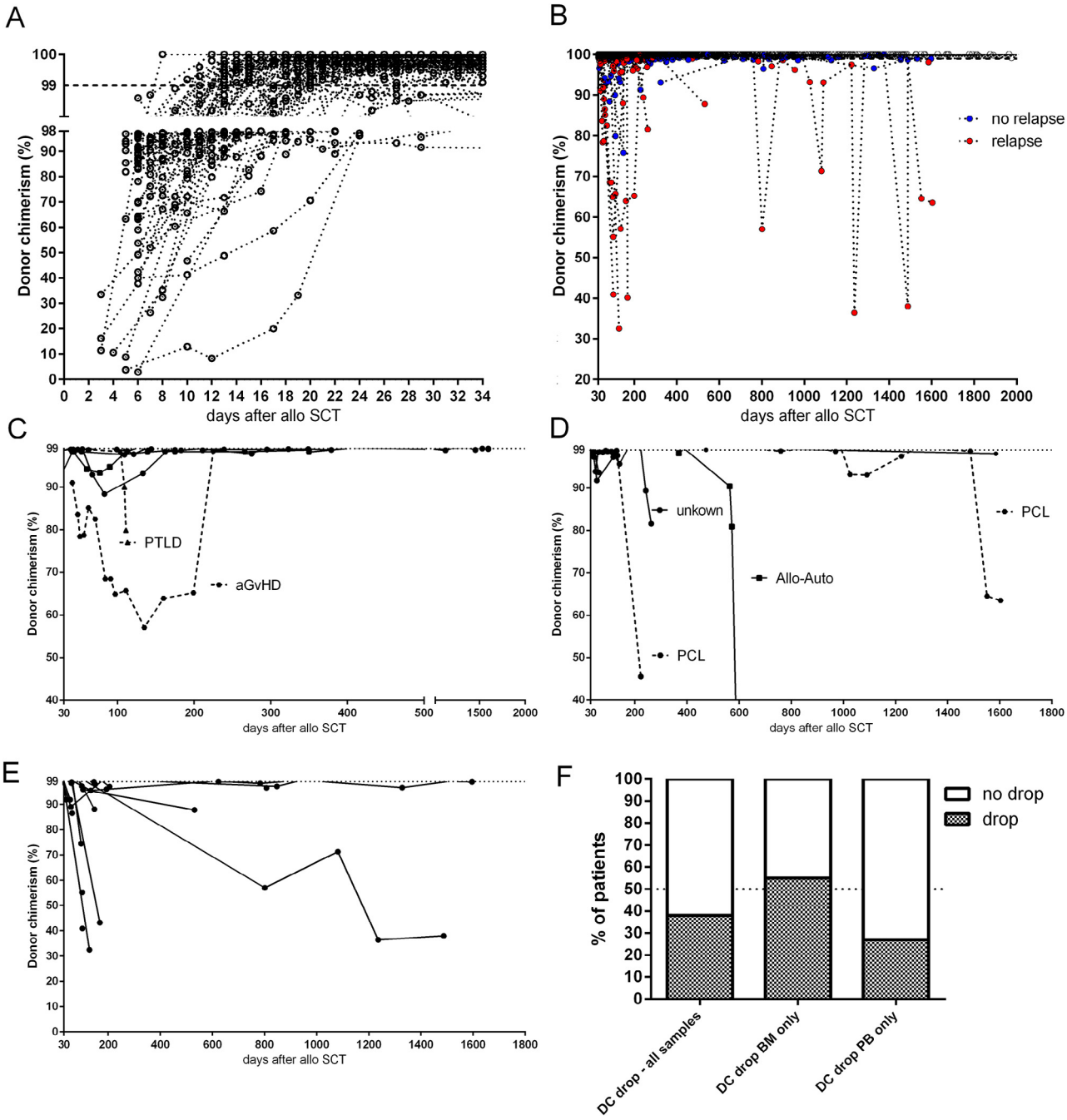

Figure 1. Donor chimerism analysis. (A) Engraftment within the first 30 days. (B) DC drops from day 30-2000. (C) DC drops in PB of patients in remission for MM. A case associated with Epstein-Barr virus triggered lymphoproliferative disease (PTLD) presenting with leukemic pattern, and another case was associated with acute GVHD. (D) DC drops in PB in relapsed patients. (E) DC drops in BM. (F) DC status at the *time point* of relapse as defined by the International Myeloma Working Group criteria.

impact on OS in univariate analysis were tested in a multivariable Cox regression model. For assessing the impact of cGVHD and preemptive DLI on outcomes, landmark analyses were performed. SPSS was used for univariate and multivariable survival analysis (IBM SPSS Statistics for Windows, version 23.0; IBM Corp., Armonk, NY), and descriptive statistics were used for DC analysis using Graph Pad Prism (version 6.07 for Windows; GraphPad Software, La Jolla CA).

RESULTS

Chimerism Analysis

We longitudinally followed DC status to determine engraftment/graft failures and the frequency of alterations in the DC level occurring in patients in remission or at disease progression.

Engraftment

Besides 2 early deaths (days 8 and 10), all patients achieved a full DC in the post-transplantation period, and no secondary graft failures occurred. In total, 575 DC results until day 30 in 126 of 155 patients were available, showing a rapid and robust engraftment with full DC in 97% of patients (Figure 1A).

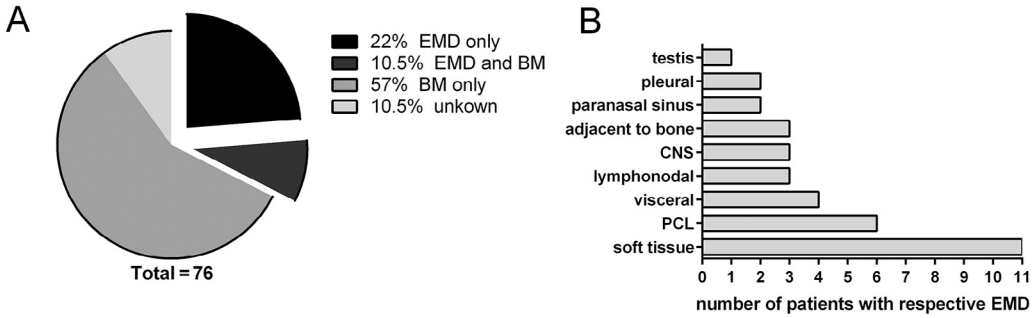

Figure 2. Extramedullary disease. (A) Relapse pattern after allo-SCT. (B) Sites with extramedullary involvement.

Overall, 44 patients (28% of all) experienced a drop in DC mainly within the first 6 months. Of those patients, most (n = 31) had a relapse or PD, whereas 13 patients had a drop in DC without signs of progression (Figure 1B). Looking at these DC drops in remission, the magnitude of chimerism decrease was mainly moderate (DC between 98% and 99%) that, however, led to tapering of immunosuppression in some patients. Four patients showed a decrease below 98%. Interestingly, all 4 patients underwent allo-SCT as part of the first-line therapy (Figure 1C).

Considering patients who lost full DC at relapse, the analyzed compartments (PB versus BM) need to be distinguished. Of 17 patients who showed a DC drop in *PB*, 5 had proven plasma cell leukemia (PCL) at relapse. These PCL patients showed a deeper DC drop, at least to <98%. Of note, a systematic screening for PCL/circulating plasma cells was not part of standard follow-up at participating centers, and therefore PCL might be under-reported. A single patient underwent an autologous SCT at relapse and consequently the DC fell to 0% (Figure 1D).

Chimerism analysis from random *BM* aspirates taken from the posterior iliac crest showed mixed DC in 19 patients, with 2 patients showing DC tiding in response to treatment (Figure 1E). In most samples the percentage of BM infiltration, as examined by immunohistochemistry, did not translate proportionally into the percentage of decrease in DC.

Chimerism status at time of relapse

We next examined whether a drop in DC is predictive for MM relapse by analyzing DC status at the time of PD according to the International Myeloma Working Group criteria within a time frame of ±50 days. This time frame was chosen because DC testing was not always performed simultaneously with serologic staging. At database lock, 76 of 155 patients relapsed or progressed. Of those, only 27 patients (36%) lost full DC, resulting in almost two-thirds of patients' PD going unrecognized by DC analysis despite serial DC measurements. DC testing from random BM aspirates was slightly more sensitive and more specific in determining relapse than PB. In summary, sensitivity and specificity was 36% and 82% from all sources, 26% and 85% from PB, and 55% and 95% from BM, respectively (Figure 1F). The positive predictive value of a mixed DC was 62% and the negative predictive value 61%. Subsequently, in an attempt to more accurately predict morphologic relapse, we modeled different area under the curve values. Although specificity could be increased by lowering DC cutoffs, positive predictive and negative predictive values were not improved. In the time frame of ±50 days, 5 patients (7%) with a drop at relapse already temporarily dropped in DC earlier, whereas another 12 patients with full DC at serologic relapse lost full DC later in their course of disease.

To understand the high proportion of relapsed patients still displaying a full DC, we analyzed these cases in more detail: Of those, 24 (32%) had an extramedullary progression without BM involvement, and in another 14% BM infiltration was ≤15%. Of note, neither BM aspiration at relapse nor appropriate imaging suitable for detecting extra- and intramedullary focal lesions was undertaken systematically in all patients, again making an under-reporting likely.

Considering outcomes, patients who lost full DC had a trend toward shorter PFS than those with sustained DC ($P = .05$). OS, however, was not different. In patients who developed disease progression, loss of DC versus sustained DC was not predictive for outcome ($P = .16$).

Relapse Pattern

Seventy-six of 155 patients relapsed after allo-SCT. When relapse patterns were analyzed, an extramedullary progression was found in one-third of patients (25/76) (Figure 2A). This includes both patients with history of EMD before allo-SCT (17/25) as well as de novo cases (8/25). Most frequently, EMD occurred at soft tissue sites (skin, muscle), followed by PCL and visceral involvement. Extensive spread with multiorgan involvement was common (10/25), and concomitant BM infiltration was present in only 7 cases. Central nervous system or testes were involved in 4 patients (Figure 2B).

Factors with Potential Impact on Outcome (Univariate Analysis)

An overview on the tested variables is summarized in Table 2 and is discussed in detail in the following paragraphs.

Lines of therapy and remission status before allo-SCT

In patients who underwent allo-SCT at first or subsequent relapse, PFS and OS were significantly inferior when compared with allo-SCT as the first-line therapy ($P < .01$) (Figure 3A). A similar pattern was observed for PD before allo-SCT ($P < .0001$), whereas the best outcome was seen in patients with CR/very good PR as remission status before allo-SCT. Nevertheless, 4 patients who were transplanted with PD at allo-SCT are still in remission beyond 2 years of follow up. We have subsumed CR/very good PR because most CRs had not been biopsy-proven and PR/stable disease since minor remissions (according to European Group for Blood and Marrow Transplantation) were not assessed in the stable disease group (Figure 3B).

Table 2
Univariate Analysis

	PFS	OS
	Log Rank *P*	Log Rank *P*
Conditioning	.02	.4
EMD before allo-SCT	<.0001	<.0001
Extramedullary relapse after allo-SCT		.03
Lines of therapy before allo-SCT	<.0001	.002
Remission before allo-SCT	<.0001	<.0001
ATG (MUD only)	.02	.01
Age > 59 yr	.2	.7
Acute GVHD	.4	.3
Cytomegalovirus reactivation	.8	.5
High-risk cytogenetics	.8	.6
Gender	.5	.7
Donor (matched versus mismatch)	.8	.7
Donor–recipient AB0 match	.8	.5
Donor–recipient cytomegalovirus serostatus match	.2	.8
Donor–recipient sex match	.2	.1
Donor age > 45 yr	.5	.3

Extramedullary disease

Patients with EMD before allo-SCT had a significantly shorter PFS (median, 3 months; $P = .001$) and OS (median, 8 months; $P < .001$) when compared with patients without extramedullary manifestations (Figure 3C). A plateau at 25% survival, however, indicates allo-SCT induces long-term remissions in a subgroup of EMD patients including all subtypes of EMD such as cases with del17p or multiorgan involvement. No long-term survival was observed only in the PCL group. Considering EMD at relapse post–allo-SCT, OS in the EMD group was inferior when compared with intramedullary relapses (11 versus 56 months; $P = .03$).

Cytogenetics

Information on baseline cytogenetic abnormalities (mainly assessed by fluorescein in situ hybridization) was available in 87 patients. Of those, 33 patients showed at least 1 high-risk feature (deletion 17p, translocation (4;14), or amplification 1q), whereas 54 patients were considered to be

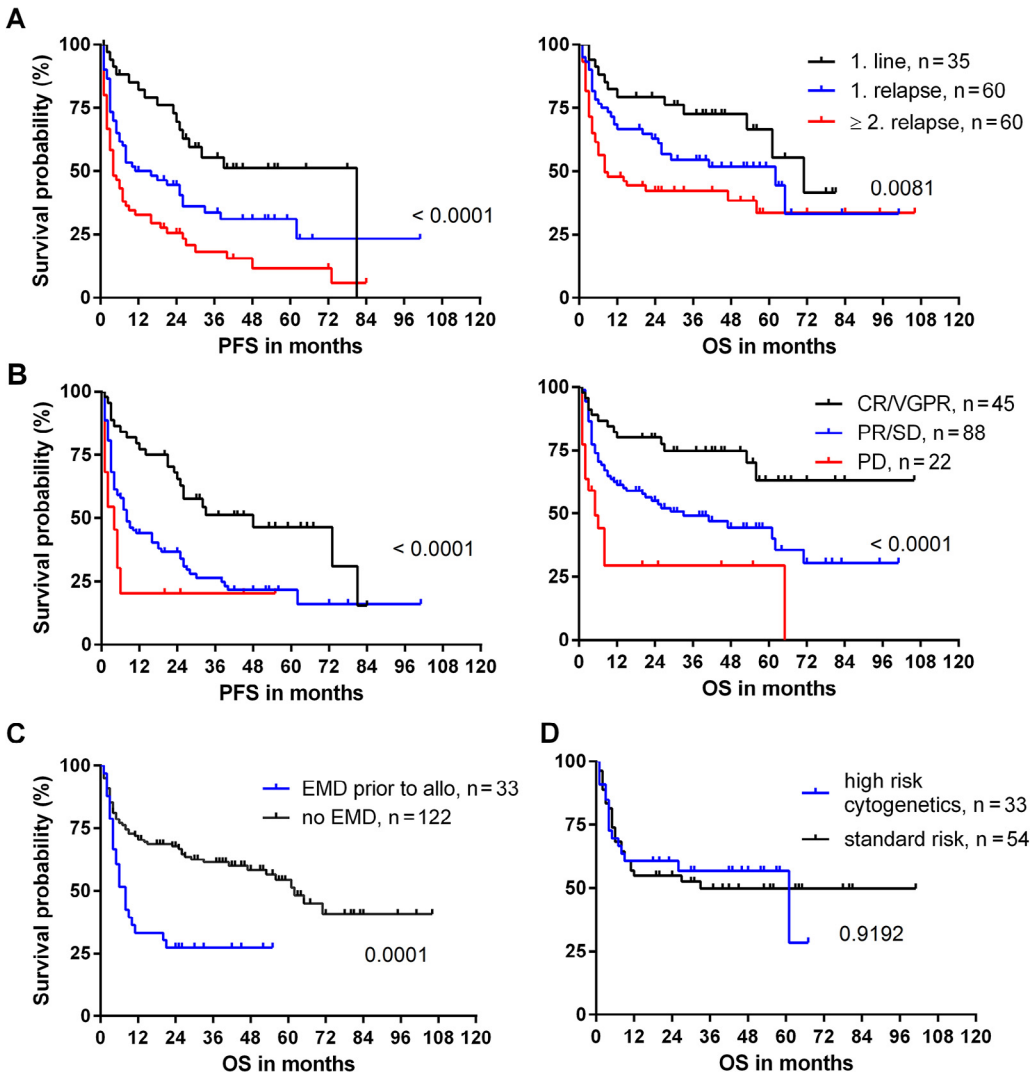

Figure 3. Factors influencing survival after allo-SCT. (A) Impact of lines of therapy before allo-SCT. (B) Impact of remission status before allo-SCT. (C) History of EMD allo-SCT. (D) Impact of cytogenetic aberrations on outcome.

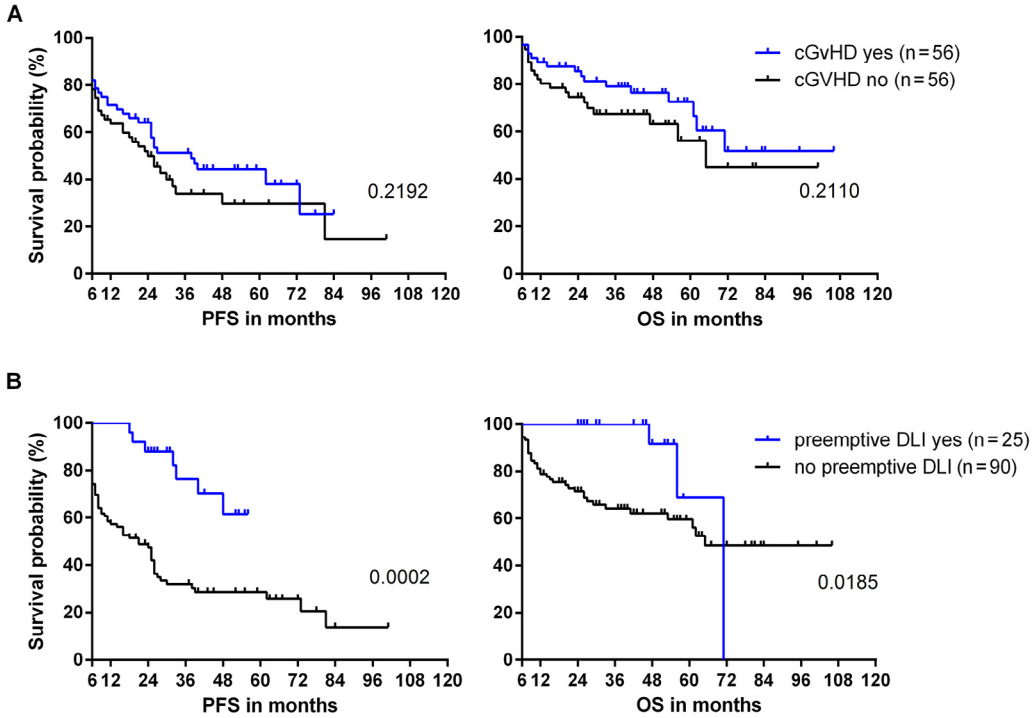

Figure 4. Landmark analysis (6 months after allo-SCT) of time-dependent variables. (A) Impact of cGVHD on PFS and OS. (B) Impact of preemptive DLI on PFS and OS.

standard risk. No statistical differences in PFS and OS were found (Figure 3D). Of note, median OS in the high-risk group was 61 months from allo-SCT, although most patients underwent allo-SCT as salvage therapy (24/33).

Conditioning regimen with antithymocyte globulin

Patients treated with melphalan/fludarabine had a more favorable early post–allo-SCT course in terms of PFS. However, melphalan/fludarabine was preferentially used in first-line treatment (50%). Furthermore, the survival curves crossed at about 5 years. MUD-transplanted patients, having received antithymocyte globulin (ATG) as a part of the conditioning, had a significant superior OS (median, 47 versus 5 months; $P = .01$) when compared with MUD patients having not received ATG. Moreover, all deaths in the group of MUD patients not receiving ATG were due to disease progression (and not GVHD). However, the number of MUD patients not receiving ATG was small (n = 13).

Variables without impact on outcome

There was no significant difference in outcome between matched related donors, MUDs, and mismatched donors. Acute GVHD, cytomegalovirus reactivation, age, and gender had no significant impact on PFS and OS. Furthermore, no impact was observed for donor–recipient AB0 match, cytomegalovirus serostatus, sex match, or donor age > 45 years, respectively.

Time-Dependent Variables

Because of the retrospective nature of this study, data on the exact onset date of cGVHD and the date of delivery of preemptive DLI were not available. Thus, a time-dependent analysis was not possible. Instead, we performed a landmark analysis at 6 months after allo-SCT to distinguish the effects of acute from cGVHD (day 100) and at the same time include a relevant number of patients to study the impact of cGVHD on survival.

Chronic graft-versus-host disease

Of 155 patients 112 (72%) were alive at 6 months after allo-SCT. Of those, 56 (49%) had developed cGVHD up to that time point. In the landmark analysis, PFS and OS of patients with cGVHD compared with no cGVHD were not statistically different (median PFS, 38 versus 24 months; $P = .2$; and median OS, not reached versus 65 months; $P = .2$) (Figure 4A).

Donor lymphocyte infusion

Preemptive DLI had been administered in a subgroup of patients with anticipated high risk of relapse (n = 25) mainly as part of a post-allogeneic concept including other drugs as well. PFS and OS in this group were superior at 6 months (undefined versus 21 months and 71 versus 65 months, respectively) and also at later landmarks of 1 and 2 years (Figure 4B). Of note, 6 patients with high-risk cytogenetic abnormalities were in sustained CR beyond 2 years of follow up.

Multivariable Analysis

Variables with significant impact on PFS and OS in univariate analysis were included in a multivariable analysis. Lines of prior therapies, PD before allo-SCT, history of EMD, and loss of full DC significantly impaired PFS ($P = .001$, $P = .001$, $P = .012$, and $P = .01$, respectively), whereas OS was significantly inferior in patients with PR or PD before allo-SCT ($P = .02$ and $P = .0001$, respectively) and EMD history ($P = .02$) (Figure 5).

DISCUSSION

To the best of our knowledge, this is the largest study of serial DC analysis in MM and one of the largest series investigating outcome variables in a cohort of clinically well-characterized

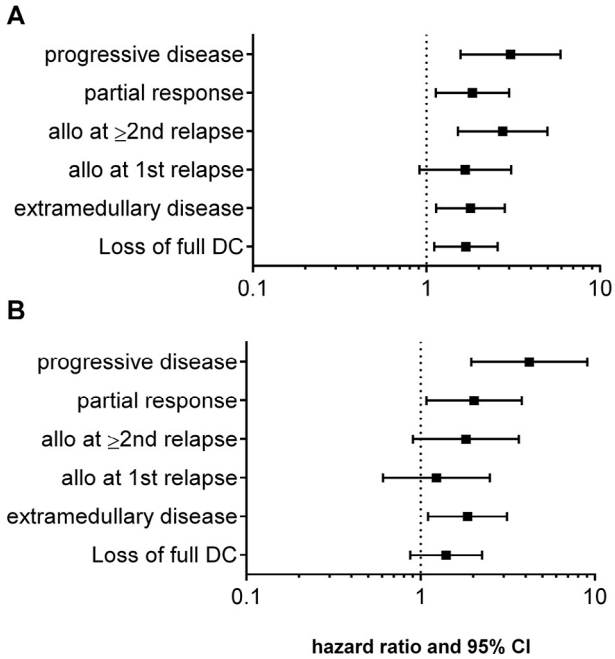

Figure 5. Multivariable analysis: Forrest plot shows hazard ratios and 95% confidence intervals (CI) for PFS (A) and OS (B). Reference category for remission state was CR/VGPR before allo-SCT, whereas for first and second relapse it was allo-SCT at initial diagnosis, no signs of EMD for proven extramedullary involvement, and full DC to "loss of full DC," respectively.

MM patients who received an allo-SCT. The close monitoring of 126 patients' DC within the first 30 days post-transplantation showed rapid engraftment in 97%, with only 5 patients whose full engraftment was achieved beyond 30 days. Of note, delayed engraftment was not associated with adverse outcome. Graft rejections are to be expected in about 2% to 5% of reduced-intensity conditioning–transplanted patients [35] but were not seen in any case. This robust engraftment in all patients and the lack of graft rejections indicate the significant immunosuppression in MM due to pretreatment and underlying disease as was observed before [36,37].

Forty-four patients (28%) experienced a DC drop to less than 99% at some point during their post-transplant period. In most of these patients (70%), disease progression caused the drop in DC. However, 13 of 44 patients lost full DC while in remission, which led to tapering of immunosuppression in some cases. Other clinical decisions such as administration of preemptive DLI were not solely based on DC results, which were aggregated with numerous clinical parameters but on a range of clinical triggers such as cytogenetic risk and the presence of GVHD.

DC testing has been reported as a tool for measuring disease burden and to predict or detect relapse in leukemic and lymphoid diseases [33,38-40]. In this study 76 of 155 patients experienced PD. Only 27 of 76 cases (36%) of PD were detected with serial DC analysis. It is noteworthy that 45% of patients with full DC at relapse/progression had EMD and/or BM infiltration by MM cells of less than 15%.

Our results suggest that serial DC analysis in recipients of allografts for MM are of limited importance for disease management beyond the achievement of full DC early in the post-transplant period. However, this effect may be because a decreasing DC was not defined as the trigger for DLI in this study. In our series the only clinical guidance triggered by DC was tapering of immunosuppression in some cases. For improving disease control and/or triggering post-transplant consolidation using ether DLI and/or conventional consolidation (eg, bortezomib/dexamethasone, immunomodulatory drugs, etc.), the determination of minimal residual disease status may be a more promising approach and should be performed after allo-SCT, preferentially in the context of a clinical trial. Prospective studies should use validated minimal residual disease measurements, such as multiparameter flow or molecular methods from patients' BM, as previously demonstrated [41,42].

Considering high-risk features, it is an important observation that cytogenetic aberrations usually associated with an unfavorable prognosis in MM patients receiving standard therapies lose their negative impact after an allo-SCT. This finding is in line with previous reports suggesting allo-SCT can overcome adverse cytogenetic features, clearly justifying a further clinical evaluation of this modality in high-risk disease [4,8,15,43]. Of note, cytogenetic data were not available in 43% of patients, limiting the statistical power of this analysis. In contrast, resistance to chemotherapy as documented by PD before allo-SCT and the number of previous lines of therapy negatively influenced outcome in multivariable analysis. The latter was previously observed in a single-center study from the Mayo Clinic [44]. Molecular profiling is warranted to further elucidate the genetic background of these findings. Interestingly, OS was particularly impaired in patients who failed to respond to reinduction therapy and had PD before allo-SCT, which may also translate into poor response to salvage regimens after allo-SCT, explaining in part the impact of this variable.

A clinical condition typically associated with resistance to all available therapies is EMD, especially when occurring at relapse [14,45]. We found a high incidence of EMD relapses of around 33%, which in line with the incidence reported by others that varied between 20% and 37% [46-49]. The frequent spread of myeloma to extramedullary sites can be interpreted as an escape to more immuno-deprived regions as compared with BM, and indeed 4 patients in our series experienced central nervous system or testicle involvement. However, post-allogeneic concepts including DLI and lenalidomide have recently shown response rates around 60% in EMD patients, and survival was not inferior to intramedullary relapses [46]. In our cohort OS in the EMD relapse group was impaired when compared with intramedullary relapses. Considerably worse, however, was the outcome of patients with pre-existing EMD before allo-SCT bearing a median OS of only 8 months. Nevertheless, a subgroup of 25% of patients showed long-term survival, which is significant even in the era of novel immunotherapies. In the SIRIUS MMY2002 trial [50], the CD38 targeting antibody daratumumab led to an overall response rate of 21% in EMD patients, indicating at least some activity at extramedullary sites. A comprehensive strategy using allo-SCT as the platform for novel immunotherapies including DLI, immunomodulatory drugs, and monoclonal antibodies should be considered to improve the outcome of this difficult-to-treat population.

Concerning the impact of cGVHD, we cannot confirm without uncertainty the protective effect as it was reported by others before [44,51]. At a landmark follow-up of 6 months, outcome of patients with cGVHD was superior (median OS, not reached versus 65 months), but the difference was not statistically significant. This is in line with previous findings that showed GVHD was not significantly associated with decreased hazard ratios for relapse in plasma cell disorders [52]. In contrast, preemptive DLI significantly improved PFS

and OS, supporting the positive results of post-allogeneic concepts as previously observed by others [53,54]. However, prospective trials with standardized treatment are warranted to finally elucidate the potential of preemptive DLI.

In this retrospective analysis, the primary selector for inclusion was the availability of serial chimerism results, which may bias the rate of survival because early deaths occurring before DC sampling might be under-reported. On the other hand, it reflects real-life data from 3 German transplant centers indicating efficacy of allo-SCT in difficult-to-treat conditions such as high-risk cytogenetics or EMD.

In conclusion, serial chimerism monitoring beyond acute engraftment seems to be of limited value for the disease management of MM after allo-SCT because routine monitoring of myeloma parameters is able to detect significant progression, and DLI may be triggered based on status of immunosuppression and potential signs of GVHD rather than on DC changes. Taking the retrospective nature of our analysis into account, allo-SCT in this series may indeed overcome the negative prognostic impact of unfavorable cytogenetic markers and may therefore be considered for such patients. Controlled trials are warranted to find strategies to safely use the GVM effect in addition to the novel therapies to improve outcomes in future patients with MM.

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