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Allogeneic transplantation of multiple myeloma patients may allow long-term survival in carefully selected patients with acceptable toxicity and preserved quality of life

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ABSTRACT

Despite significantly improved survival and response rates in patients diagnosed with multiple myeloma, it still remains an incurable disease with a poor outcome, especially in high-risk groups. Allogeneic stem cell transplantation offers a potentially curative option but remains controversial due to considerable treatment-related toxicity. We analyzed 109 consecutive myeloma patients who had received reduced-intensity conditioning allogeneic transplantation at the Freiburg University Medical Center between 2000 and 2016. Although most patients were heavily pre-treated in high-risk constellations, the overall response rate was high with 70%, the median overall survival (OS) 39.2%, and the median progression-free survival (PFS) 14.2 months, with a median follow up of 71.5 months. Survival was significantly better in patients with response to previous therapies than in those with progressive disease (median OS 65 *vs.* 11.5 months, P=0.003; median PFS 18.4 *vs.* 5.1 months, P=0.001). Moreover, survival of patients transplanted in first-line was significantly prolonged compared to relapsed/refractory disease (median OS not reached *vs.* 21.6 months, P<0.001; median PFS 47.7 *vs.* 9.6 months, P<0.001). The non-relapse mortality was relatively low with a cumulative incidence of 12.4% at ten years. Acute graft-*versus*-host disease (GvHD) grade II-IV was observed in 25%, and moderate or severe chronic GvHD in 24%. Quality of life (QoL) assessed with the revised Myeloma Comorbidity Index before and after transplantation remained unchanged. Our data suggest that allogeneic transplantation in the context of novel immunotherapeutic approaches may enable long-term survival and even a potential cure in a carefully selected subgroup of high-risk multiple myeloma patients with acceptable toxicity and preserved QoL.

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Introduction

Despite a remarkable increase in effective treatment options, multiple myeloma (MM) still remains mostly incurable. Nevertheless, survival of patients diagnosed with MM has significantly improved over the last few years, although outcome may be poor with a median overall survival (OS) of only 2-3 years in subgroups of patients with higher stage and high-risk cytogenetics.[1,2]

Allogeneic stem cell transplantation (allo-SCT) may help to achieve long-term progression-free survival (PFS) and offers a potentially curative option due to a graft-*versus*-myeloma (GvM) effect.[3] However, allo-SCT remains controversial because of considerable toxicity, especially due to immunosuppression and subsequent infections, the risk of graft-*versus*-host disease (GvHD), and thus a potentially high non-relapse mortality (NRM).[4] Although in general allo-SCT is not routinely conducted

Table 1. Patients' characteristics.

	All n=109	Distribution according to therapeutical concept: First-line treatment n=46	Salvage situation n=63	Distribution according to time point of allo-SCT: 2000 - 2004 n=19	2005 - 2009 n=37	2010 - 2016 n=53
Median age [years] (range)	56 (30 - 70)	53 (30 - 67)	58 (42 - 70)	55 (39 - 67)	57 (43 - 70)	55 (30 - 69)
Median body weight [kg] (range)	75 (40 - 103)	72 (40 - 99)	78 (42 - 103)	71 (40 - 95)	73 (51 - 98)	78 (42 - 103)
Sex male /female n (%)	56 (51) / 53 (49)	24 (52) / 22 (48)	32 (51) / 31 (49)	9 (47) / 10 (53)	20 (54) / 17 (46)	27 (51) / 26 (49)
MM /plasma cell leukemia n (%)	106 (97) / 3 (3)	44 (96) / 2 (4)	62 (98) / 1 (2)	18 (95) / 1 (5)	36 (97) / 1 (3)	52 (98) / 1 (2)
Treatment within DSMM-trial yes / no n (%)	40 (37) / 69 (63)	34 (74) / 12 (26)	7 (11) / 56 (89)	5 (26) / 14 (74)	19 (51) / 18 (49)	16 (30) / 37 (70)
First-line treatment/ salvage situation n (%)	46 (42) / 63 (58)	46 (100) / 0 (0)	0 (0) / 63 (100)	10 (53) / 9 (47)	17 (46) / 20 (54)	18 (34) / 35 (66)
Stage according to ISS n (%)						
I / II	62 (57)	26 (57)	36 (57)	7 (37)	26 (70)	29 (55)
III β2-MG ≥ 5.5mg/L	40 (37)	20 (43)	20 (32)	12 (63)	8 (22)	20 (38)
n.e.	7 (6)	0 (0)	7 (11)	0 (0)	3 (8)	4 (7)
Cytogenetics n (%)						
Summary of all subgroups	57 (52)	20 (44)	37 (59)	2 (11)	10 (27)	45 (85)
Standard risk	20 (35*)	8 (40*)	12 (33*)	1 (50*)	2 (20*)	17 (38*)
High risk	25 (44*)	9 (45*)	16 (43*)	1 (50*)	6 (60*)	18 (40*)
Poor risk	8 (14*)	1 (5*)	7 (19*)	0 (0*)	0 (0*	8 (18*)
Ultra high risk	4 (7*)	2 (10*)	2 (5*)	0 (0*)	2 (20*)	2 (4*)
Del13-analysis only **	33 (30)	18 (39)	15 (24)	6 (31)	24 (65)	3 (6)
n.e.	19 (18)	8 (17)	11 (17)	11 (58)	3 (8)	5 (9)

MM: multiple myeloma; DSMM: German Myeloma Study Group; ISS: International Staging System; n.e.: not evaluated, β2-MG: beta-2 microglobulin. Cytogenetics: high risk: non-hyperdiploid karyotype, t(4;14), t(14;16), t(14;20), del 17p; poor risk: gain 1q, del 1p; ultra-high risk: ≥ 3 chromosomal aberrations. *% of patients with complete cytogenetic analysis. **Implemented into International Myeloma Working Group protocols.

in patients with MM, over the last decades the number of transplantations has increased.[5] However, there are few clear treatment guidelines, as it is often performed on an individual basis in relapsed/refractory MM and not in the context of clinical studies.

Despite a high remission rate of up to 50% in retrospective analyses, early approaches in the 1980s and 1990s with high-dose myeloablative conditioning regimens were limited to younger patients with relapsed/refractory disease due to the high therapy-related toxicity, with NRM rates of 40-60%.[6] NRM could be reduced through improved supportive care and a more rigorous patient selection, but long-term survival was only achieved in 10-25% of patients.[6]

Consequently, a tandem approach was developed to separate myeloablation with maximal tumor cytoreduction achieved through high-dose chemotherapy followed by autologous (auto)-SCT, and allo-SCT with a less myelosuppressive but highly immunosuppressive regimen to reduce treatment-related organ toxicities but allow sufficient engraftment and GvM effect.[7]

In the era before the introduction of immunomodulatory drugs (IMID) and proteasome inhibitors (PI), several clinical trials were performed to analyze the combination of auto- and subsequent reduced-intensity conditioning (RIC) allo-SCT in the first-line treatment. Only two large trials with long-term follow up reached significance. In both studies, PFS and OS were superior with auto-allo-SCT compared to tandem auto-SCT.[8,9] The results suggested that high-risk cytogenetics may be overcome by allo-SCT. None of the trials showed inferiority of the auto-allo-SCT approach compared to single or double auto-SCT-study arms.[10-14]

Similarly, most retrospective studies comparing salvage allo- with a second auto-SCT in patients with relapsed MM after auto-SCT showed an improvement in PFS or a lower relapse rate after allo-SCT, but no benefit regarding OS, mostly due to high NRM.[15-18] However, in one study, after a very long follow up, PFS and OS were both superior with the allo-SCT approach.[19] There have been no prospective studies comparing allo- with auto-SCT in salvage situations.

Encouraging results were obtained with the combination of allo-SCT and immunomodulatory therapeutic approaches. The induction of a sustained anti-neoplastic effect by donor lymphocyte infusions (DLI) could be demonstrated in patients who had relapsed after allo-SCT,[3,20] also in combination with IMID and PI.[21]

Several clinical trials are currently ongoing that may help to define the role of allo-SCT, particularly in the context of new immunomodulatory approaches, emphasizing the importance of this therapeutic concept. In the light of this background, here we analyzed a substantial number of MM patients who had received RIC allo-SCT at our University Medical Center between 2000 and 2016 with regard to treatment response, survival, adverse events, and quality of life (QoL).

Table 2. Previous treatment and transplantation procedure.

Remission state at allo-SCT n (%)	
CR	13 (12)
vgPR / PR	15 (14) / 27 (25)
SD / MR	23 (21) / 1 (1)
PD	30 (28)
Median number of prior treatment lines n (range)	3 (1 - 8)
Pre-treatment with PI / IMID n (%)	54 (50) / 47 (43)
Number of prior auto-SCT n (%)	
0	9 (8)
1	74 (68)
2	26 (24)
Median time between auto- and allo-SCT [months] (range)	17.3 (1.1 - 104.2)
Median time between ID and allo-SCT [months] (range)	27.7 (4.8 - 137.4)
Interval between auto- and allo-SCT n < / > 8 months	47 / 53 of 100
HLA compatibility n (%)	
HLA-identical	92 (84)
Related / syngeneic	43 (39) / 2 (2)
Unrelated	47 (43)
HLA-non-identical unrelated	17 (16)
Donor sex male / female n (%)	71 (65) / 38 (35)
Stem cell source PB / BM n (%)	108 (99) / 1 (1)
CMV-status n (%)	
Donor positive /negative	49 (45) / 60 (55)
Patient positive / negative	67 (61) / 42 (39)

CR: complete remission; (vg)PR: (very good) partial remission; SD: stable disease; MR: minimal response; PD: progressive disease; PI: proteasome inhibitor; IMID: immunomodulatory drug; auto-SCT: autologous stem cell transplantation; ID: initial diagnosis; allo-SCT: allogeneic stem cell transplantation; HLA: Human Leukocyte Antigen; PB: peripheral blood; BM: bone marow; CMV: cytomegalovirus.

Methods

Patients' description and data source

We retrospectively analyzed 109 consecutive patients diagnosed with MM who had received RIC allo-SCT between 2000 and 2016 at the University Hospital of Freiburg. Data were analyzed as of January 2018. Patient data were retrieved from our institution's electronic medical records. Depending on the aggressiveness of their disease, patients received follow up on a regular basis. The analysis was carried out according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave their written informed consent for institutional-initiated research studies, approved by our institutional review board. Thirty-seven percent of our patients were treated in pre-emptive settings within different clinical trials of the German Myeloma Study Group (DSMM). Cytogenetic analysis was conducted in 82% of the patients. However, in 30%, FISH was only performed to detect the presence of deletion 13q14, an aberration that until recently was thought to be associated with shorter survival,[22] and therefore had been implemented into the protocols of the DSMM and International Myeloma Working Group (IMWG) trials. Remission status was defined according to IMWG criteria.[23] Relapse was defined as increase of serum paraprotein or occurrence of extramedullary disease. The Revised Myeloma Comorbidity Index (R-MCI) was determined as previously described.[24,25] Karnofsky Performance Status (KPS), age, impairment of renal and lung function, frailty, and cytogenetic risk-group had been identified as significant determinants for OS and were combined in a weighted score, allowing identification of fit (R-MCI 0-3), intermediate-fit (R-MCI 4-6), and frail patients (R-MCI 6-9) with strikingly different median OS rates of 10.1, 4.4 and 1.2 years, respectively.[24]

Conditioning regimen and graft-*versus*-host disease prophylaxis

Patients were treated with different fludarabine-containing RIC regimens (*Online Supplementary Table S1*).

In almost all patients, stem cells were harvested from the peripheral blood; only one patient received bone marrow. Forty-one percent of all transplants were conducted with a related donor, 43% with an HLA-matched unrelated donor, and 16% with an HLA-mismatched unrelated donor. Allo-SCT was performed from a male *versus* female donor in 65% *versus* 35%, respectively (Table 2). Cyclosporin A was used for GvHD prophylaxis, either in combination with alemtuzumab (37%) or mycophenolate mofetil (50%) or methotrexate (11%) with (41%) or without (59%) antithymocyte globulin (*Online Supplementary Table S1*).[26]

Statistical analysis

Data were analyzed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA). OS and PFS were calculated as time from allo-SCT to death from any cause and first observation of relapse or death. NRM was defined as death without progressive disease. Patients without observation of the event of interest at the last follow up were treated as censored observations. OS and PFS rates were estimated and reported using the Kaplan-Meier method. Relapse and NRM were considered to be competing risks. Therefore, relapse and NRM rates were estimat-

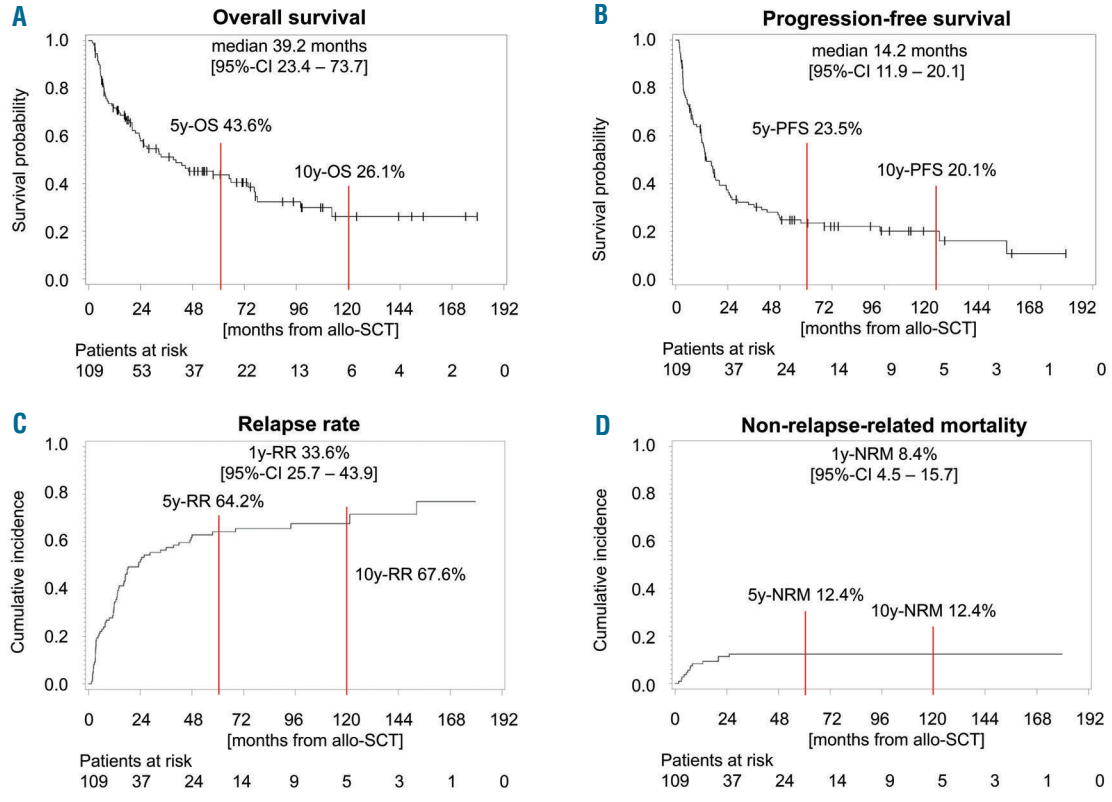

Figure 1. Outcome analysis of the entire cohort. (A) Kaplan-Meier estimates for overall survival (OS). (B) Kaplan-Meier estimates for progression-free survival (PFS). (C) Cumulative incidence of relapse rate (RR). (D) Cumulative incidence of non-relapse mortality (NRM). y: year; allo-SCT: allogeneic stem cell transplantation; CI: Confidence Interval.

ed as cumulative incidence rates using Aalen Johansen estimator[27] and compared with Fine and Gray regression models for competing risks.[28] $P<0.05$ was considered statistically significant. Prognostic factors were investigated in bivariate regression models adjusting for the time point of allo-SCT.

Results

Patients' characteristics

Median patients' age was 56 years (range 30-70) with a balanced male:female ratio. Most patients had been diagnosed with MM; 3 had plasma cell leukemia. In 42%, allo-SCT was planned as first-line treatment due to a high-risk constellation according to cytogenetic analysis, International Staging System (ISS) and/or lack of response to prior treatment,[29] mostly following a prior auto-SCT and within the DSMM protocols (87%). The majority were treated in terms of individual salvage attempts due to relapsed/refractory disease after extensive pre-treatment. A complete cytogenetic analysis was performed in 52% (57 of 109); another 30% were examined for deletion 13q14 only.

Twenty-five out of those 57 patients (44%) analyzed according to the current IMWG-consensus[30] showed high-risk cytogenetics with a non-hyperdiploid karyotype or detection of one of the following chromosomal aberrations: translocation (4;14), (14;16) or (14;20) or deletion 17p, respectively. Eight of 57 (14%) had poor risk cytogenetics due to detection of gain 1q or deletion 1p. Four of 57 (7%) were classified in the ultra-high risk-group with three or more of those chromosomal aberrations.[30]

Forty of 109 (37% of the total cohort) had high-risk disease according to the ISS with a beta (β)2-microglobulin ≥5.5 mg/L (ISS III). The risk profile according to the ISS and cytogenetics of patients treated in first-line and those with relapsed/refractory disease was similar.

As the observation period was long (17 years), summing up a heterogenous cohort due to changes in therapeutical concepts over time, we additionally compared three patient subgroups to distinguish between those with allo-SCT performed between 2000-2004, 2005-2009 or 2010-1016. There was no substantial difference in patients' characteristics between these groups; however, in the latest cohort, slightly more patients were transplanted due to relapsed/refractory disease. As expected, complete cytogenetic analyses were mainly performed in recent years. Patients' characteristics are summarized in Table 1.

At the time point of allo-SCT, 28% of the patients showed evidence of progressive disease (PD). The majority proceeded to allo-SCT after sufficient response to prior treatment: 12% complete remissions (CR), 14% very good partial remissions (vgPR), 25% PR, 21% stable diseases (SD), and 1% minimal responses (MR). Patients underwent a median of three treatment lines prior to allo-SCT (range 1-8). As we analyzed data of patients treated between 2000 and 2017, only 50% *versus* 43% received

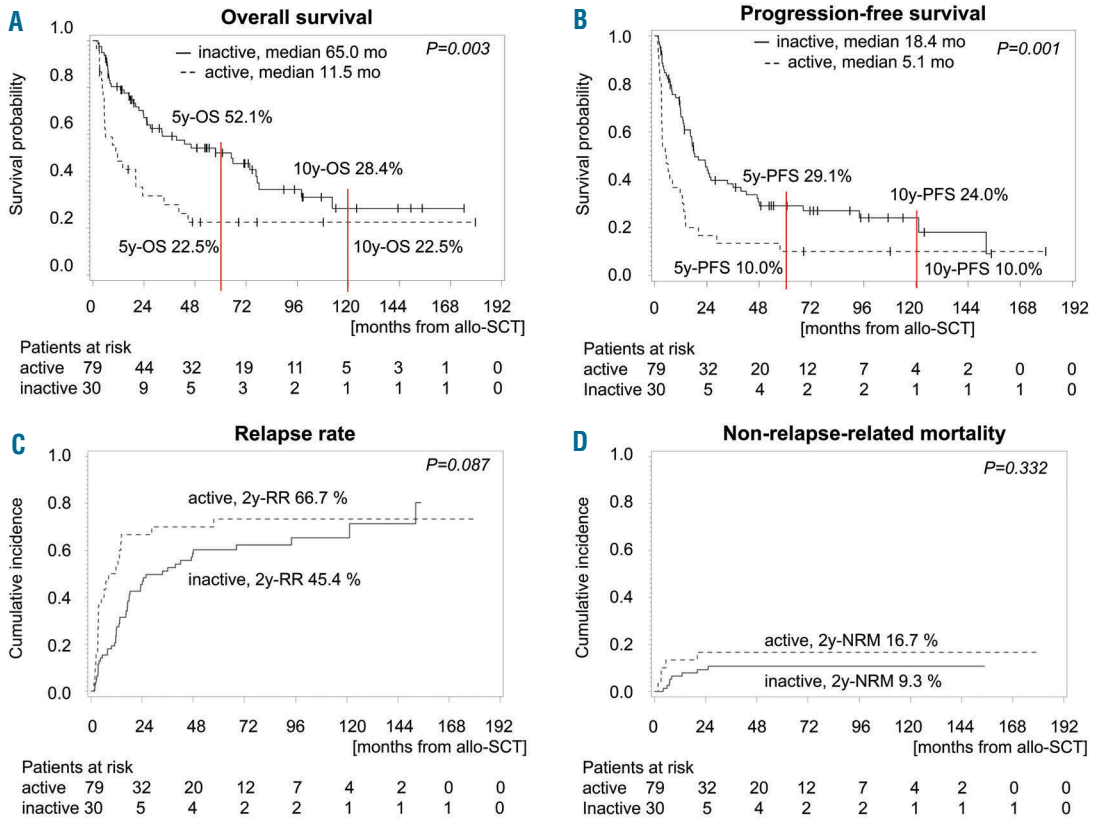

Figure 2. Subgroup analysis of disease activity prior to allogeneic stem cell transplantation (allo-SCT). Complete remission, (very good) partial remission, partial remission, stable disease or minimal response defined as inactive disease (n=79) *versus* those with progressive disease defined as active disease (n=30). (A) Kaplan-Meier estimates for overall survival (OS). (B) Kaplan-Meier estimates for progression-free survival (PFS). (C) Cumulative incidence of relapse rate (RR). (D) Cumulative incidence of non-relapse mortality (NRM); mo: months; y: year; CI: Confidence Interval.

regimens containing PI or IMID, respectively. Ninety-two percent of the cohort received prior auto-SCT, the majority of them as a single transplant; 24% had received prior auto-SCT as tandem transplant or with a second transplant in the case of relapse.[31] In 47%, the period between auto- and allo-SCT was shorter than eight months; the median interval was 17.3 months (range 1.1-104.2). Median time between initial diagnosis (ID) and allo-SCT was 27.7 months (range 4.8-137.4). Table 2 shows MM-treatment parameters before allo-SCT. Transplant data such as HLA-compatibility of the donor, stem cell source, and CMV-status are summarized in Table 2.

Graft-*versus*-host disease and engraftment

Half of the cohort did not develop any sign of acute GvHD (aGvHD). In 25%, only mild symptoms occurred corresponding to aGvHD grade I, the remaining 25% were diagnosed with aGvHD grade II-IV, of whom only 10% had grade III or IV. Symptoms occurred at a median of 47 days after allo-SCT (range 3-150). In 58% of the patients, no symptoms of chronic GvHD (cGvHD) were detected; 24% suffered from moderate or severe cGvHD (Table 3).

Hematologic recovery with an absolute neutrophil count higher than $0.5x10^9$/L and a platelet count higher than $20x10^9$/L was reached at a median of 18 days (range 10-54) and 12 days (range 5-48), respectively (Table 3).

At the time point of analysis, 42% of the patients were still alive. NRM was relatively low (13%) (Table 3). Most patients died from PD with overlapping infection and/or GvHD; GvHD was the primary cause of death in only 2 patients.

Treatment response, survival after allo-stem cell transplantation and post-transplant therapy

Overall response rate was high (70%) (Table 3). At the first response evaluation conducted on day 30 after allo-SCT, 39% of the patients showed CR, 14% vgPR, and 18% PR. SD or MR was detected in 23% *versus* 4%, respectively, while only 3% had PD. In nearly all patients, best response to treatment had already been reached at this time point. In 4 patients, follow-up examinations revealed further improvement from vgPR to CR, leading to an overall CR rate of 42%.

Thirty-two percent received DLI after allo-SCT, nearly all due to serological PD. Only one patient was treated prophylactically because of a decreasing donor chimerism, consistent with the observation that chimerism analysis probably does not provide any further information for therapy management.[32]

PI and IMID were administered in the post-transplant setting in 43% and 36%, respectively, thereof only in

Table 3. Response and treatment-related toxicity.

Alive / dead (%)				46 (42) / 63 (58)
Primary cause of death (%),	PD			49 (45)
partly overlapping	infection			19 (17)
	GvHD / GvHD only			7 (6) / 2 (2)
NRM (%)				14 (13)
Death within 100 days after allo-SCT (%)				8 (7)
Best response after allo-SCT (%)	CR	ORR	42 (39)	77 (70)
	vgPR / PR		15 (14) / 20 (18)	
	SD / MR			25 (23) / 4 (4)
	PD			3 (3)
aGvHD grade (%)	0			54 (50)
	I/ II 27			(25) / 17 (15)
	III/ IV			9 (8) / 2 (2)
aGvHD onset (range) [day after allo-SCT]				47 (3 - 150)
cGvHD (%)	no / mild			63 (58) / 13 (12)
	moderate / severe			18 (17) / 8 (7)
	n.e.			7 (6)
Median engraftment	ANC > $0.5x10^9$/L			18 (10 - 54)
[day after allo-SCT] (range)	PLT > $20x10^9$/L			12 (5 - 48)
CMV-reactivation yes / no (%)				51 (47) / 58 (53)

allo SCT: allogeneic stem cell transplantation; PD: progressive disease; GvHD: graft-*versus*-host disease; NRM: non-relapse mortality; CR: complete remission; ORR: overall response rate; (vg)PR: (very good) partial remission; SD: stable disease; MR: minimal response; PD: progressive disease; aGvHD: acute GvHD; cGvHD: chronic GvHD; n.e.: not evaluated; ANC: absolute neutrophil count; PLT: platelet count; CMV: cytomegalovirus.

32% (15 of 47) and 23% (9 of 39) as maintenance therapy without evidence of relapse, mostly within different clinical DSMM trials.

With a substantial median follow up of 71.5 months, we observed a median OS of 39.2 months (95%CI: 23.4-73.7) (Figure 1A and *Online Supplementary Table S2*). Median PFS was 14.2 months (95%CI: 11.9-20.1) (Figure 1B and *Online Supplementary Table S2*). Interestingly, Kaplan-Meier curves reached a plateau after about ten years, suggesting long-term survival in selected patients with a 10-year OS of 28.4% and 10-year PFS of 24% (Figure 1B).

The median cumulative incidence of relapse within the first year was 33.6% (95%CI: 25.7-43.9) and 67.6% in ten years (95%CI: 58.6-77.9) (Figure 1C and *Online Supplementary Table S3*). Similar to the survival curves, there was only a slight further increase in the cumulative incidence of relapse from the second year (51.4%, 95%CI: 42.6-61.9) to ten years, again pointing towards a relapse-free long-term survival.

The median cumulative incidence of NRM within the first year was relatively low with 8.4% (95%CI: 4.5-15.7) and 12.4% in ten years (95%-CI: 7.4-20.6) (Figure 1D and *Online Supplementary Table S3*). Again, there was no substantial increase in this cumulative incidence from the second year (11.4%, 95%CI: 6.7-19.4) to ten years, emphasizing the low incidence of late complications.

Subgroup analyses

To determine those patients who benefited particularly from allo-SCT, we conducted different subgroup analyses.

Disease activity prior to allo-SCT. First, we distinguished between patients with sufficient response to initial treatment reaching MR or better (inactive disease) and those with active disease and evidence of PD at the time point of allo-SCT. We observed a statistically significantly longer OS for patients responding to previous therapies compared to those with PD with a median OS of 65.0 *versus* 11.5 months, respectively (P=0.003) (Figure 2A and *Online Supplementary Table S2*). Similarly, in patients showing MR or better, median PFS was statistically significantly prolonged with 18.4 months compared to only 5.1 months in those with active disease right before allo-SCT (P=0.001) (Figure 2B and *Online Supplementary Table S2*). Similar to PFS data, the cumulative incidence of relapse differed between both groups; however, this difference did not reach statistical significance. In patients with sufficient response to prior treatment, the cumulative incidence of relapse within the first year after allo-SCT was 26.0% *versus* 53.3% in those with PD (P=0.087); similar results were obtained for longer observation periods (2, 5, 10 years) (Figure 2C and *Online Supplementary Table S3*). No significant difference in NRM was observed between these two subgroups (13.3 *vs.* 6.5% in the first year; P=0.332) (Figure 2D and *Online Supplementary Table S3*).

Allo-SCT as first-line treatment versus in relapsed/refractory MM. In the second subgroup analysis, we distinguished between patients who were allo-transplanted in first-line due to a high-risk constellation, mostly following a prior auto-SCT, and those who received allo-SCT with relapsed/refractory disease after extensive pre-treatment. Here, the differences between these two groups of patients were the most distinct. In patients allo-transplanted in first-line, the median OS was not reached, compared to 21.6 months in relapsed/refractory MM (P<0.001) (Figure 3A and *Online Supplementary Table S2*); the 5-year OS was 50.2% *versus* 5.4%, respectively. Similarly, the dif-

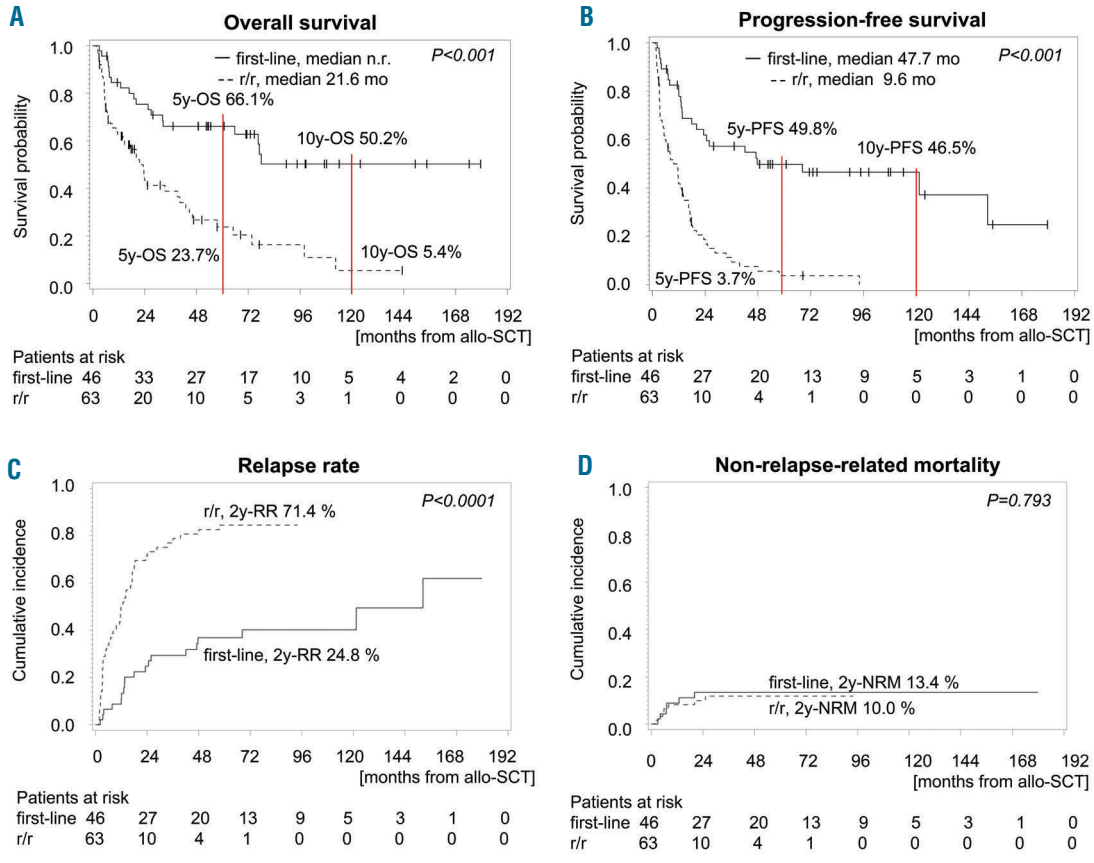

Figure 3. Subgroup analysis of therapeutic concept for patients with allogeneic stem cell transplantation (allo-SCT) within their first-line therapy (tandem approach, n=46) *versus* those with relapsed/refractory (r/r) disease (n=63). (A) Kaplan-Meier estimates for overall survival (OS). (B) Kaplan-Meier estimates for progression-free survival (PFS). (C) Cumulative incidence of relapse rate (RR). (D) Cumulative incidence of non-relapse mortality (NRM). mo: months; y: year; n.r.: not reached; CI: Confidence Interval.

ference in PFS was statistically significant with a median PFS of 47.7 months after allo-SCT in first-line *versus* 9.6 months in relapsed/refractory patients ($P<0.001$) (Figure 3B and *Online Supplementary Table S2*) and 5-year PFS was 49.8% *versus* 3.7%, respectively. The cumulative incidence of relapse was considerably lower in patients transplanted in first-line with 11.0% within the first year compared to 50.3% after allo-SCT in cases of relapsed/refractory MM ($P<0.0001$) (Figure 3C and *Online Supplementary Table S3*). Comparable to the other subgroup analyses, there was no difference in cumulative incidence of NRM (8.8 *vs.* 8.1% in the first year; $P=0.793$) (Figure 3D and *Online Supplementary Table S3*).

Disease activity after allo-SCT, HLA-compatibility and cytogenetic risk group. As expected, the remission status after allo-SCT had a substantial impact on survival, with a median OS of only a few weeks in the case of a lack of response, significantly shorter PFS, and an enhanced cumulative incidence of relapse. There was no difference in the cumulative incidence of NRM (*data not shown*).

In a subgroup analysis of HLA-compatibility, PFS and OS were impaired in patients who received allo-SCT from an HLA-non-identical donor compared to those after HLA-identical transplantation. However, the difference between the two groups did not reach statistical significance (*Online Supplementary Table S2* and *Online Supplementary Figure S1*). Likewise, there was no statistically significant difference in the cumulative incidence of relapse and NRM (*Online Supplementary Table S3* and *Online Supplementary Figure S1*).

When analyzing the 57 patients with complete cytogenetic analysis with respect to cytogenetic risk, a longer OS and PFS was observed in the standard risk group in comparison to patients with high risk, poor risk or ultra-high risk (*Online Supplementary Table S2* and *Online Supplementary Figure S2*). Again, there was no difference in the cumulative incidence of relapse and NRM (*Online Supplementary Table S3* and *Online Supplementary Figure S2*).

A subclassification according to cytogenetic risk of the 20 patients with available complete cytogenetic analysis transplanted in first-line showed no impact on survival. In the standard risk group, median OS was 77.2 months compared to 65.8 months in those patients with high risk, poor risk or ultra-high risk cytogenetics; 5-year OS was 100% *versus* 73.3%, respectively ($P=0.256$) (*Online Supplementary Table S2*). The median PFS was 47.7 *versus* 68.3 months, and 5-year PFS 43.8% *versus* 64.2%, respectively ($P=0.874$) (*Online Supplementary Table S2*).

Time point of allo-SCT. Over the last two decades, great improvements have been achieved in terms of anti-myeloma strategies, transplantation procedure, and supportive care. Therefore, survival may depend on the time point of allo-SCT during our long observation period of 17 years:

Table 4. Revised-Myeloma Combordity Index (R-MCI) assessment of 46 patients alive at the time point of analysis.

	ID	Prior allo-SCT	Current (last follow up)	Median change from ID to current *P*	Median change from prior allo-SCT to current *P*
Median R-MCI (range)	4 (0 - 6)	3 (0 - 5)	3 (0 - 7)	0 (-5 - 5) 0.766	0 (-3 - 5) 0.065
Median KPS [%] (range)	80 (40 - 100)	90 (60 - 100)	90 (50 - 100)	10 (-30 - 50) 0.008	0 (-20 - 40) 0.411
Moderate-severe frailty [number of patients] (%)	15 (33)	9 (20)	14 (30)	–	–
Median age [years] (range)	51 (29 - 63)	53 (29 - 67)	60 (33 - 79)	8 (2 - 20) < 0.001	6 (1 - 20) < 0.001
Median eGFR [ml/min/1.73 m²] (range)	86 (8 -121)	85 (32 - 126)	68 (16 -113)	-11 (-77 - 66) 0.028	-14 (-17 - 44) < 0.001
Moderate-severe lung function impairment [number of patients] (%)	4 (9)	0 (0)	2 (4)	–	–

ID: initial diagnosis; allo-SCT: allogeneic stem cell transplantation; KPS: Karnofsky Performance Status; eGFR: estimated glomerular filtration rate.

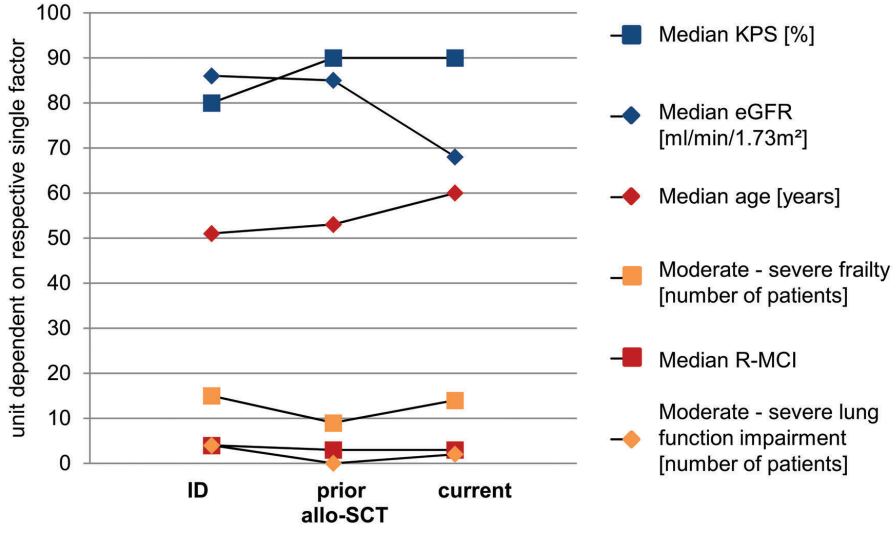

Figure 4. Quality of life (QoL) assessed with the Revised-Myeloma Comorbidity Index (R-MCI). Single factors [Karnofsky Performance Status (KPS), frailty, age, impairment of renal and lung function] are shown at initial diagnosis, the time point right before allogeneic stem cell transplantation (allo-SCT) and at the last follow up. eGFR: estimated glomerular filtration rate; ID: initial diagnosis.

2000-2004, 2005-2009 *versus* 2010-2016. Indeed, the highest cumulative incidence of NRM was observed after allo-SCT performed between 2000-2004 (*Online Supplementary Figure S3*). However, the improvement in patients transplanted more recently did not reach statistical significance, most probably due to the number of patients in the group (only 19 patients in the allo-SCT years 2000-2004). Interestingly, the lowest relapse rate was documented in the earliest transplantation period, but this fact seems to have been overturned by treatment toxicity, as OS was improved in the cohort transplanted after the year 2010 (*Online Supplementary Figure S3*). Median OS was 20.1 months (95%CI: 7.5-112.5) for patients with allo-SCT between 2000-2004, 25.6 months (95%CI: 14.0-57.6) for patients transplanted between 2005-2009, and 73.7 months (95%CI: 25.2-not reached) in the most recent cohort, respectively. Again, the difference was not statistically significant (*P*=0.190).

Survival of patients with sufficient response to initial treatment remained significantly better than survival of those with active disease when adjusting this factor for the time point of allo-SCT (*P*=0.004) (*Online Supplementary Table S4*). The same was true for the comparison of patients transplanted in first-line with those with relapsed/refractory disease (*P*<0.0001) (*Online Supplementary Table S4*).

Quality of life and comorbidity assessment

Since allo-SCT may cause long-term or late onset side effects that can influence patients' QoL, and due to our prior comorbidity evaluations to assess treatment tolerance, we performed the R-MCI in the 46 patients still alive at the last follow up at three different time points: at ID, right before allo-SCT, and at last follow up.[24]

At ID, the median R-MCI was 4, corresponding to the intermediate-fit risk-group; this improved to 3 prior to allo-SCT, and remained at 3 at the last follow up, thus reflecting slightly fitter patients (Table 4 and Figure 4). A comparison of R-MCI assessed at ID and right before allo-SCT to the current R-MCI assessed at the last follow up

did not reveal any significant differences (P=0.766 and P=0.065, respectively) (Table 4), but suggested that QoL under allo-SCT improved rather than deteriorated.

The R-MCI worsened from the time point of allo-SCT to the last follow up in 48% (22 of 46) of the examined patients, whereas the score improved or was unaffected in 26% each (52%). However, a decrease was caused only by aging and age-related impaired renal function in 59% (13 of 22). Only 27% (6 of 22) of the patients with decreased R-MCI after allo-SCT showed signs of (mostly moderate) GvHD. In 14% (3 of 22), the general condition was worsening due to occurrence of an independent illness (stroke, second malignancy, LKM1-positive autoimmune hepatitis). Interestingly, only 45% (10 of 22) reached CR in this cohort, whereas 58% (7 of 12) of the group with improved R-MCI were in CR at the last follow up, indicating the influence of disease activity on the patients' QoL. The cohort was too small to allow further statistical analyses.

We also assessed each of the 5 risk factors within the R-MCI and their changes upon allo-SCT separately (see Table 4 and Figure 4).

Discussion

Allo-SCT has been conducted in a large group of patients diagnosed with MM at our academic center, especially in relapsed/refractory situations in heavily pre-treated patients, mostly showing high-risk disease due to cytogenetic analysis and/or ISS. We observed a high ORR of 70%, with a median PFS of 14.2 months and a median OS of 39.2 months. Of note, only a moderate rate of high-grade GvHD occured. Survival was even better in patients with sufficient response to induction therapy (median OS, 65.0 months), and best in those treated within the first-line therapy (median OS not reached), independently of the time point of allo-SCT. As survival curves reached a plateau, and late relapses rarely occurred, a possible long-term survival or even cure may be presumed for a subgroup of MM patients. There was no statistically significant difference in survival when comparing patients transplanted in first-line with standard risk and those with high, poor or ultra-high-risk cytogenetics according to the actual IMWG-consensus.[30] Similar findings have been obtained in previous trials mostly distinguishing patients with or without detection of deletion 13q14,[22] both results suggesting that high-risk cytogenetics may be overcome by allo-SCT.[8,9,32–34]

Available data from prior retrospective trials on allo-SCT in MM are inconsistent due to divergent therapeutic concepts and heterogeneous cohorts.[4,35] Thus, comparison of survival and toxicity data is challenging.

For patients transplanted in first-line due to a high-risk constellation, mostly following a prior auto-SCT in terms of a tandem concept, the median OS reported in different studies ranges between 34 months and not reached; the best OS has been achieved with a long follow up, as in our analysis.[9-12,36] For the cohort with relapsed/refractory disease, a median OS of 13-24 months was recorded in different trials,[17,37] with our result of 21.6 months lying in the upper range of these values. Our PFS data were superior for patients with allo-SCT in first-line therapy with a median of 47.7 months compared to 19-35 months reported in the literature.[9-12,36] The median PFS reached in our cohort of relapsed/refractory patients was also quite high with 9.6 months compared to 7-10 months in previous studies.[17,37]

The therapy-associated toxicity at our center, with a cumulative incidence of NRM of 13.4% in two years after allo-SCT performed as first-line treatment, was comparable to the rates of 11-16% found in published trials.[10,12,36] We observed a relatively low NRM in relapsed/refractory MM with 10% in two years, contrary to prior analyses with rates of 11-43%.[15–18,38-40] Accordingly, the incidence of cGvHD was comparatively low, with detection of cGvHD of any grade in 36%, whereas cGvHD was observed in 32-66% of patients in other cohorts.[8,10,12,14,36,40]

In order to make an objective assessment of comorbidity and therapy-associated restrictions, we analyzed the R-MCI and its single risk factors over time. The median R-MCI of our allo-SCT cohort was 4 at ID, but improved remarkably to 3 at the assessment right before allo-SCT and at the last follow up. Formally, this increase implicates a risk-group shift from intermediate-fit (R-MCI 4-6) to fitter patients (R-MCI 0-3),[24] bearing in mind that patients had aged by almost a decade with a substantial age-related deterioration in renal function, which even under-estimated the improvement in patients' QoL. These findings suggest that QoL under allo-SCT can indeed improve or at least may not necessarily be impaired, most probably as a consequence of treatment response, as a reduction in illness-induced limitations may outweigh therapy-associated impairment.

Taken together, our data suggest that allo-SCT may enable long-term survival and a potential cure in a carefully selected subgroup of MM patients with tolerable toxicity under appropriate supportive therapy. RIC allo-SCT should preferentially be performed within clinical trials. However, it may be considered individually in younger patients with good performance status and high-risk disease in the initial course of therapy. Such an approach has the potential of achieving a significantly better survival,[35] especially in the context of novel agents and immunotherapy approaches,[41] and could improve rather than impair QoL, as shown with our R-MCI subanalyses. MRD-guided immunotherapy with DLI, IMID, PI and monoclonal antibodies may significantly improve outcome even more.[8,9,42,43] Our long-term retrospective single-center study may help to further evaluate the impact and redefine the role of allo-SCT in patients with MM in a rapidly changing treatment scenario. Future prospective trials should be designed with combinations of new drugs that allow profound cytoreduction before allo-SCT and that can enhance the efficacy of GvM through immunomodulatory effects after transplantation, thus leading to long-term disease control and survival even in high-risk MM patients.

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