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Allogeneic Stem Cell Transplantation for Patients Age ≥ 70 Years with Myelodysplastic Syndrome: A Retrospective Study of the MDS Subcommittee of the Chronic Malignancies Working Party of the EBMT

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A B S T R A C T

In this retrospective analysis we evaluated the outcome of 313 patients aged ≥ 70 years in the registry of the European Group for Blood and Marrow Transplantation with myelodysplastic syndrome (MDS; n = 221) and secondary acute myeloid leukemia (n = 92) who underwent allogeneic hematopoietic stem cell transplantation (HSCT) from related (n = 79) or unrelated (n = 234) donors. Median age at HSCT was 72 years (range, 70 to 78). Conditioning regimen was nonmyeloablative (n = 54), reduced intensity (n = 207), or standard intensity (n = 52). Allogeneic HSCT for MDS patients ≥ 70 years was increasingly performed over time. Although during 2000 to 2004 only 16 patients received HSCT, during 2011 to 2013 the number of transplantations increased to 181. The cumulative incidence of nonrelapse mortality at 1 year and relapse at 3 years was 32% and 28%, respectively, with a 3-year overall survival rate of 34%. Good performance, determined by Karnofsky performance status, and recipients' seronegativity for cytomegalovirus was associated with 3-year estimated overall survival rates of 43% ($P = .01$) and 46% ($P = .002$), respectively. Conditioning intensity did not impact survival. After careful patient selection, allogeneic HSCT can be offered to patients older than 70 years with MDS.

INTRODUCTION

Myelodysplastic syndrome (MDS) defines a group of clonal hematopoietic stem cell disorders that presents with cytopenias, abnormal blast counts, and the risk of progression into acute myeloid leukemia (AML). It is diagnosed at a median age of 70 [1,2] with a peak at 80 years [1,3]. Incidence is 4 to 5 per 100.000 per year [1,4], and prevalence is 11 in 100,000 with a peak at 80 years [1-3]. The choice of treatment for MDS depends on risk stratification [5-9], transfusion needs, age, and responsiveness to specific treatment modalities. Patients with low risk scores are the treated to achieve reduction of transfusion requirements and improvement of quality of life, whereas the treatment goal for intermediate- and high-risk MDS is the reduction of the risk for transformation into AML [10]. In this situation, demethylating agents as azacitidine or decitabine provide a survival benefit [11-15].

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment option, but the decision for HSCT depends on the right timing, mental and physical fitness of the patient, available donors, comorbidities, and patient preference. Treatment guidelines recommend HSCT for intermediate-II and high-risk stages up to the age of 65 years, and reduced-intensity conditioning (RIC) regimens are commonly used up to 70 years of age. However, there is a development toward a more frequent use of HSCT for elderly patients because of increasing life expectancy in general, availability of conditioning regimens with decreased toxicity, and the observation that numerous MDS patients 70 years and older have a high performance status at time of diagnosis. To investigate outcome after HSCT in MDS patients aged ≥ 70 years, we performed a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT) registry.

METHODS

Patient Population

In this analysis we included all patients in the EBMT registry ≥ 70 years with MDS and secondary AML (sAML) with a first allogeneic transplantation between 2000 and 2013. Patients were excluded if no data on outcome, patient sex, or conditioning were available; if they had received a cord blood graft; or if they had a diagnosis of MDS/myeloproliferative disorder overlap or bone marrow failure. The remaining 313 patients were further analyzed (Table 1). Cytogenetic data were available for only 68 patients and allocated to cytogenetic risk according to the revised International Prognostic Scoring System (IPSS-R) [6].

Conditioning Regimens

We reviewed the allocation of conditioning regimen to standard (myeloablative conditioning [MAC]) or RIC as reported by the transplant center and implemented the category of nonmyeloablative (NMA) conditioning (Table 2). NMA conditioning was defined as 2 Gy total body irradiation and fludarabine [16] or 4 mg/kg busulfan alone. MAC was considered as total body irradiation > 500 cGy single dose or ≥800 cGy fractionated ± cyclophosphamide [16,17], busulfan > 9 mg/kg [17,18], melphalan > 150 mg/kg plus additional agents other than fludarabine [17] and conditioning regimens using treosulfan or thiotepa if no dose reduction ≥ 50% from standard had been applied [19]. RIC was defined as every regimen with intensity between NMA and MAC.

Statistical Analysis

Comparisons between patient characteristics in subgroups were performed by chi-square or Fisher Exact test (categorical variables) and *t*-test (continuous variables). Complete remission before HSCT was defined by marrow blast count below 5% and a normalization of peripheral blood counts for at least 4 weeks. Primary endpoints were overall survival (OS), relapse-free survival (RFS), relapse incidence, and nonrelapse mortality (NRM). OS was defined as the probability of survival since transplantation; death from any cause was considered as an event. Patients alive at time of last follow-up were censored at this date. RFS was calculated as time from HSCT to death or relapse, whatever occurred first, with patients surviving relapse-free censored at time of last follow-up. Probabilities of OS and RFS were estimated using the Kaplan-Meier product limit method, and differences in subgroups were assessed by the log-rank test. NRM was defined as any death in the absence of relapse since HSCT. Estimates of NRM and relapse incidence were calculated using cumulative incidence curves to accommodate competing risks (relapse considered a competing risk for NRM and vice versa), and comparisons among subgroups were assessed using Gray's test. Cumulative incidences of acute graft-versus-host disease (aGVHD; grades II to IV and III to IV) and chronic GVHD (cGVHD) were also analyzed in competing risks models, considering relapse and death without occurrence of relapse and GVHD (aGVHD grades II to IV and III to IV and cGVHD, respectively) as competing events. For cGVHD all cases were included independently from time of onset according to National Institutes of Health 2006 criteria. Median follow-up was calculated by means of the reversed Kaplan-Meier method.

Cox proportional hazards regression was used to assess the impact of potential prognostic factors in multivariate analyses. The impact of these factors on OS, RFS, NRM, and relapse incidence was modeled by means of (cause-specific) hazards models. The variables included in the multivariate analyses where chosen based on clinical considerations. The missing cases for Karnofsky performance status (KPS) and disease status were kept in the analysis in separate categories. Age was not included in the multivariate analysis because of a lack of significance in the univariate analysis. The impact of GVHD on outcomes was assessed by Cox models in which aGVHD grades II to IV and III to IV and cGVHD, respectively, were included as time-dependent covariates.

All P values are 2-sided, and $P < .05$ is considered significant. All analyses were performed in R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) using packages "prodlim" and "cmprsk."

RESULTS

Patient Characteristics

Median age of patients at transplantation was 72 years (range, 70 to 78), and 226 patients were men. NMA, RIC, or

Table 1
Patient and Donor Characteristics

Characteristics	Subgroup	Number
Total number of patients		313
Median follow-up, mo (range)		29.8 (26.4-37.1)
Median age at transplantation, yr (range)		71.6 (70-78)
Age groups (as used in the univariate analysis)	70-71 yr	178 (57%)
	72-73 yr	96 (31%)
	74-78 yr	39 (12%)
Gender (n = 313)	Male	226 (72%)
	Female	87 (28%)
KPS (n = 274)	90-100%	168 (61%)
	40-80%	106 (39%)
Diagnosis (n = 313)	MDS	221 (71%)
	sAML	92 (29%)
Disease status at transplantation (n = 236)	RA/RARS/del5q/RCMD-RS	34 (14%)
	RAEB/RAEB-1/RAEB-2	84 (36%)
	RAEB-t/transformed to AML	30 (13%)
	Secondary AML from diagnosis onward	88 (37%)
Cytogenetics (according to IPSS-R) (n = 72)	Very good	0
	Good	37 (51%)
	Intermediate	16 (22%)
	Poor	7 (10%)
	Very poor	8 (11%)
	"Abnormal" (not specified)	4 (6%)
Complete remission at transplant (n = 313)	Yes	110 (35%)
	No	203 (65%)
CMV serostatus in patient/donor (n = 297)	+/+	128 (43%)
	+/–	61 (21%)
	–/+	24 (8%)
	–/–	84 (28%)
Conditioning regimen (n = 313)	MAC	52 (17%)
	RIC	207 (66%)
	NMA	54 (17%)
Stem cell source (n = 313)	Bone marrow	20 (6%)
	Peripheral blood	293 (94%
Donor type (n = 313)	Related	79 (25%)
	Unrelated	234 (75%)
Engraftment (n = 309)	Yes	292 (94%)
	No	17 (6%)
Immunosuppression (n = 313)	CSA + MTX	56
	CSA + MMF	134
	Tacrolimus + MTX	3
	Tacrolimus + MMF	25
	Other regimens	105
	+ ATG	168 (54%)
	+ Campath	44 (14%)

CSA indicates cyclosporine A; MTX, methorexate; MMF, mycophenolate mofetil; ATG, antithymocyte globulin.

MAC was applied in 54, 207, and 52 patients, respectively (Table 2). Median follow-up was 29.8 months. KPS was defined in 274 cases and was ≥90% in 168 patients (61%) and ≤80% in 106 patients (39%). One hundred ten patients (35.1%) were transplanted in complete remission (Table 1). Disease status at time of transplantation was refractory anemia (RA)/RA with ring sideroblasts (RARS)/deletion of chromosome 5q (del5q)/ refractory cytopenia with multilineage dysplasia with ring sideroblasts (RCMD-RS) (n = 34), RA with excess of blasts (RAEB) /RAEB-1/RAEB-2 (n = 84), RAEB in transformation (RAEB-t)/transformed to acute leukemia (n = 30), and sAML at initial diagnosis (n = 88) (Table 2). Donors were related (n = 79) or unrelated (n = 234). In our study most patients were recruited in Germany (n = 224, 71.6%), followed by Belgium (n = 23, 7.3%), Israel (n = 14, 4.5%), and Italy (n = 11, 3.5%) (Supplementary Table 1).

The number of HSCTs for MDS patients ≥ 70 years in the EBMT database increased over time. Although during 2000 to 2004 only 16 patients received allogeneic transplantation, the following 3-year periods included 27, 89, and 181 patients, respectively (Figure 1).

Table 2
Conditioning Regimens Extracted from the EBMT Database

Conditioning Regimen	No. of Patients (% of total)	No. of in vivo T cell depletion (% of regimen)
NMA	54 (17.3%)	11 (20.4%)
2 Gy TBI/Flu	54	11
RIC	207 (66.1%)	119 (57.5%)
Bu/Flu	70	42
FBM (Flu/BCNU/Mel) based	46	18
Flu/Mel (+TBI)	23	14
FLAMSA, Bu	20	16
FLAMSA + Bu/Cy; TBI/Cy; TBI; Bu/Cy; Cy; Mel	20	18
Others	28	11
MAC	52 (16.6%)	35 (67.3%)
Treo/Flu	27	24
Bu/Flu	10	5
Others	15	6
Total	313	165 (52.7%)

Allocation to NMA, RIC, and MAC was done as described in Methods. In vivo T cell depletion contained antilymphocyte globulin and/or Campath.
Bu indicates busulfan; Cy, cyclophosphamide; FLAMSA, fludarabin + amsacrine + cytarabine; Flu, fludarabine; TBI, total body irradiation; Treo, treosulfan.

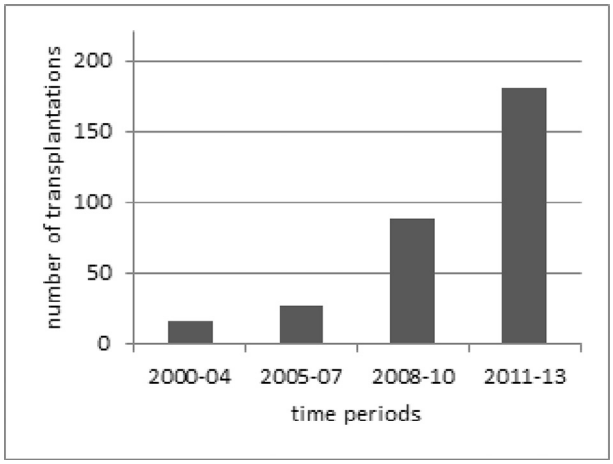

Figure 1. HSCT for MDS/sAML patients ages 70 to 79 years. The number of transplantations per year increased over time: 2000-2004, n = 16; 2005-2007, n = 27; 2008-2010, n = 89; 2011-2013, n = 181.

Engraftment and GVHD

Engraftment was achieved by most patients (n = 292, 94%). Cumulative incidence for aGVHD grades II to IV was 27% (95% confidence interval [CI], 22% to 32%) at 3 months after HSCT and for grades III to IV 13% (95% CI, 9% to 17%). Data for cGVHD were available for 195 patients. Cumulative incidence of cGVHD was 33% (95% CI, 27% to 40%) and 40% (95% CI, 33% to 47%) at 12 and 36 months after HCST, respectively. Both aGVHD and cGVHD had a significant and considerable impact on most outcomes: hazard ratios (HRs) for aGVHD grades II to IV were 2.1 for OS (95% CI: 1.4 to 3.0, $P < .001$) and 1.8 for NRM (95% CI, 1.2 to 2.8, $P = .003$); for aGVHD grades III to IV were 4.0 for OS (95% CI, 2.6 to 6.2, $P < .001$) and 3.9 for NRM (95% CI, 2.4 to 6.2, $P < .001$); for cGVHD were 2.2 for OS (95% CI, 1.3 to 3.6, $P = .003$), .4 for relapse incidence (95% CI, .2 to .9, $P = .03$), and 2.0 for NRM (95% CI, 1.1 to 3.5, $P = .02$).

Relapse and NRM

Cumulative incidence of relapse at 3 years was 28% (95% CI, 23% to 34%) and significantly lower with unrelated than related donors (23% versus 44%, $P = .002$). Disease status "RAEB-t/transformed to acute leukemia" had an increased risk of relapse compared with "RAEB/RAEB-1/RAEB-2" (49% versus 23%, $P = .015$; Figure 2), but complete remission before HSCT did not improve outcome. Cumulative incidence of NRM at 3 years was 42% (95% CI, 36% to 49%) and was lower for KPS ≥ 90% (33% versus 53%, $P = .014$), cytomegalovirus (CMV) seronegativity of the recipient (32% versus 48%, $P = .02$), and related donors (35% versus 45%, $P = .05$) (Figure 3). Reasons for death were assessable for 164 patients (Table 3). Death was mainly caused by relapse or progression (37%), infection (33%), or GVHD (16%). Other reasons were organ damage or failure (4%), secondary malignancies (3%), toxicity, or HSCT-related death (7%). For 26 patients cause of death was unknown, and 123 patients were alive at the end of their follow-up. Overall, causes of death were not significantly different between patients with and without CMV seropositivity, but numbers of lethal infections within the first 12 months after transplantation were higher for CMV-positive patients than for CMV-negative patients (n = 37, 44% of death within the first 12 months, versus n = 8, 34%, respectively).

RFS and OS

RFS at 3 years was significantly higher for patients with higher KPS (37% versus 20%, $P = .034$) and CMV-negative patients (39% versus 26%, $P = .008$). The estimated 3-year overall survival (OS) rate was 34% (95% CI, 28% to 40%) with a median follow-up of 29.8 months (95% CI, 26.4 to 37.1). In univariate analysis a significantly better 3-year OS was seen for patients with KPS ≥ 90% versus 80% or less (43% versus 23%, $P = .01$) and for CMV-negative serostatus of the patients (46% versus 29%, $P = .002$) (Figure 3, Table 4).

Analysis of Distinct Impact Factors on Outcome

Neither patient gender, choice of conditioning regimen, CMV status of the donor, nor use of T cell depletion had an impact on the primary endpoints in our analysis. In the univariate analysis age had no significant impact on outcome when compared with age groups 70 to 71 years, 72 to 73 years, and 74 to 79 years (data not shown). KPS proved to be a predictor of outcome after HSCT. Comparing patient cohorts with a high or low KPS, we found no difference regarding age at transplantation, disease status, CMV status, and conditioning regimen applied (Table 5).

To gain more detailed information concerning the impact of performance status on outcome, we further divided the patients with lower performance into different cohorts, resulting in 3 distinct groups: KPS 40% to 70% (n = 24), 80% (n = 82), and 90% to 100% (n = 168). For patients in the lowest KPS group, the rate of 1-year OS was 22% (95% CI, 13% to 43%). For the group with KPS 80%, cumulative incidence of relapse and rates of NRM, RFS, and OS at 3 years were 26% (95% CI, 15% to 36%), 53% (95% CI, 41% to 66%), 21% (95% CI, 10% to 32%), and 26% (95% CI, 14% to 38%), respectively.

Multivariate Analysis

In multivariate analysis (Table 6), risk of relapse was lower in all other patients compared with those with RAEB-t/transformed to acute leukemia and lowest for patients with disease status RAEB/RAEB1/RAEB2 (HR, .37; 95% CI, .16 to .84; $P = .02$). A strongly significant protective factor against NRM was KPS ≥ 90% (HR for ≤80%, 1.88; 95% CI, 1.25 to 2.85; $P < .001$), whereas CMV seropositivity of the recipient (HR, 1.88; 95% CI, 1.23 to 2.88; $P < .001$) and grafts from unrelated donors (HR, 1.63; 95% CI, 1.03 to 2.64; $P = .048$) were associated with higher NRM risk. RFS was influenced significantly by KPS (HR for ≤80%, 1.43; 95% CI, 1.04 to 1.96; $P = .03$) and CMV serostatus of the patient (HR for positive patients, 1.53; 95% CI, 1.11 to 2.12; $P = .01$). OS was lower in patients with KPS ≤ 80% (HR, 1.62; 95% CI, 1.62 to 2.27; $P = .004$) and lower in CMV-seropositive recipients (HR, 1.78; 95% CI, 1.26 to 2.50; $P = .001$).

DISCUSSION

Median age of patients receiving HSCT for MDS/AML has increased by 20 years since the 1980s [9,20]. Implementation of conditioning regimens with reduced toxicity and higher physical fitness of the elderly have enabled this development. The present investigation confirms that HSCT is a favorable treatment choice for high-risk patients with good performance status of 90% to 100%. Besides KPS, only the CMV status of the patient and disease status at time of transplantation but not age or remission status were primary parameters that had a significant impact on outcome. Differences in outcome between patients with KPS 90% to 100% and 80% reveal the difficulty of drawing ultimate conclusions from a subjective variable that can be easily influenced

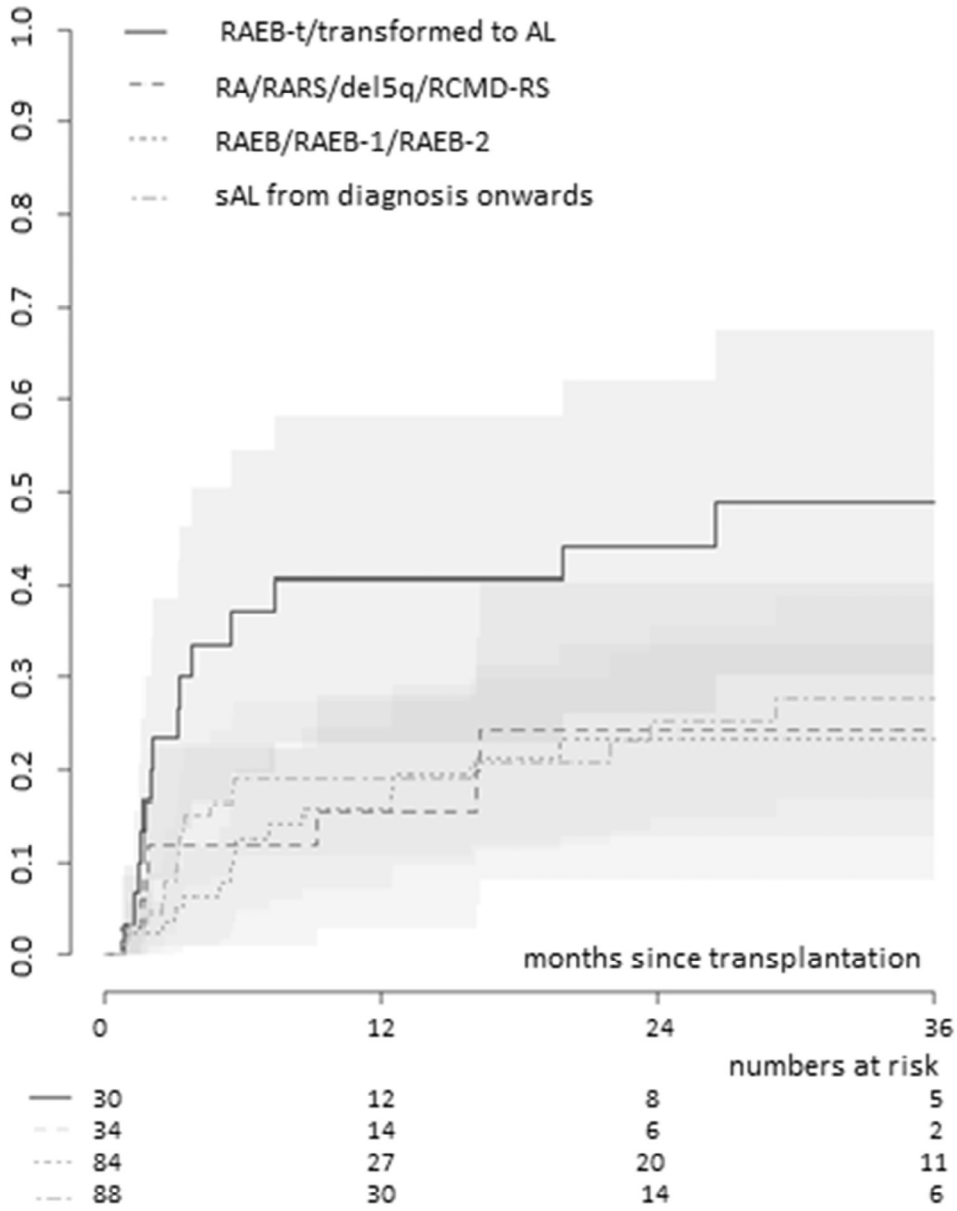

Figure 2. Relapse incidence by disease status at transplantation. Disease status "RAEB-t/transformed to AL" had a significant higher risk of relapse, compared with "RAEB/RAEB-1/RAEB-2" ($P = .04$) but not compared with the other groups. Shaded areas indicate 95% pointwise confidence intervals, and numbers below the *x*-axis correspond to number of patients at risk for the respective time points. AL indicates acute leukemia.

by the physician's preference concerning treatment choice. On the other hand, it reflects the physician's perception of his or her patient at the time of evaluation and can be administered easily. The influence of CMV positivity on survival was particularly strong in our analysis. We detected that fatal infectious complications were higher in the CMV-positive than -negative patients and might be responsible for worse outcome. A parameter not known at time of treatment choice that rapidly reduced survival probability was aGVHD and cGVHD. Its strong impact leads to the suggestion to invest time and effort to eliminate all factors favorable for GVHD development.

Median survival for IPSS-R intermediate, high, or very high risk disease is 36, 19, and 10 months, respectively [6]. In the adjusted IPSS-R for patients aged 70 to 80 years, median survival decreases to 32, 18, and 8 months, respectively. Our reported median survival of 29 months can therefore be regarded as a good outcome and can even be improved by only forwarding those patients to transplantation who have a good performance status. Despite a growing consensus that absence of comorbidities [21-24] and a good performance status [25] rather than lower age predict a favorable outcome after HSCT, especially after introduction of reduced-intensity regimens [9], age is often still taken as an independent risk factor. Hematologists today are still are quite cautious to forward an elderly patient to HSCT for good reasons, but although there are valuable conventional treatment options [11,12,14], HSCT is still the only curative treatment option. A large EBMT registry study on outcome of patients with MDS/AML did not find any significant influence of age, comparing patients aged 50 to 60 years with those older than 60 years without consideration of performance status [26]. Spyridonidis

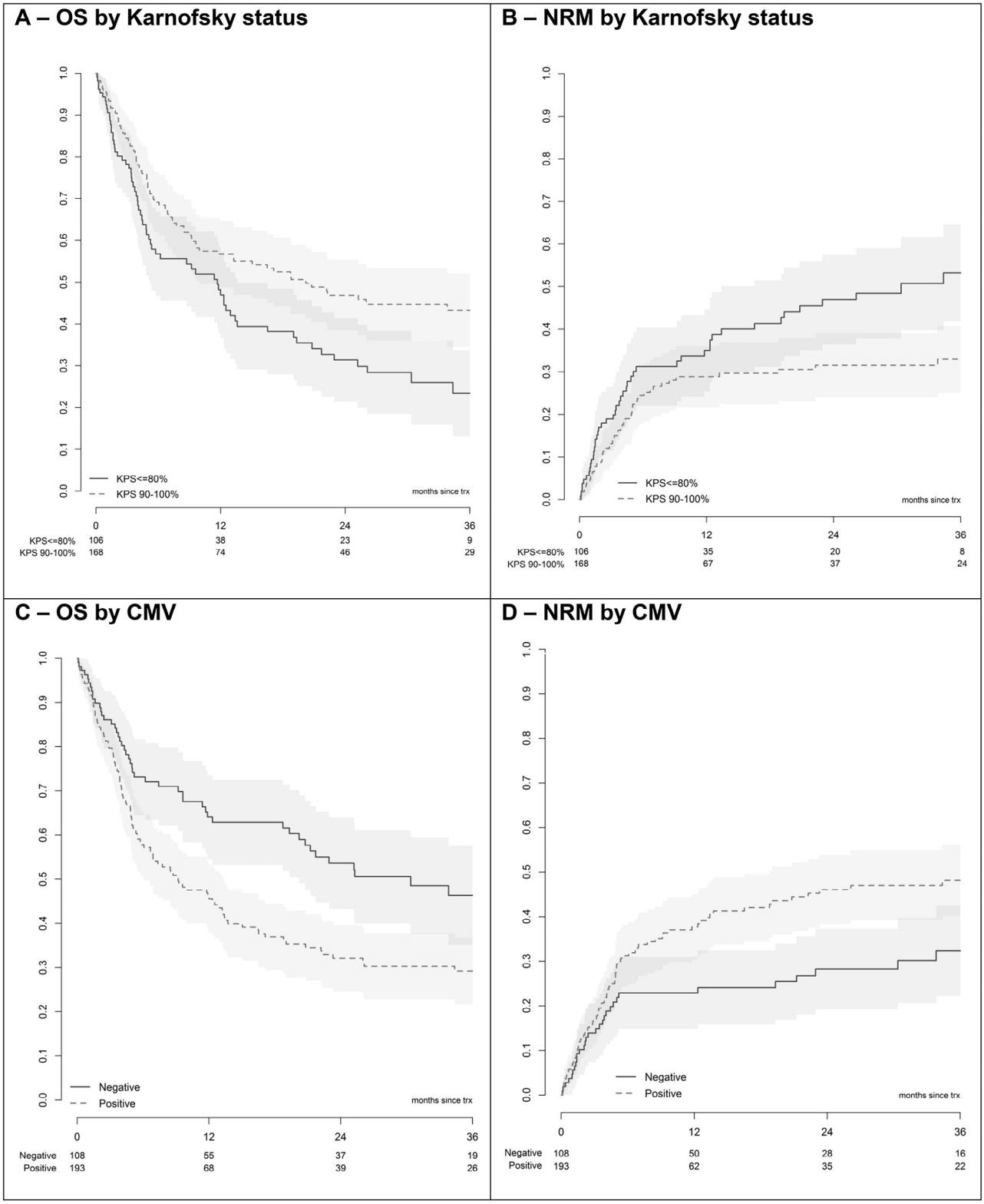

Figure 3. OS and NRM by KPS and CMV. (A) OS by KPS, $P = .01$ (B) NRM by KPS, $P = .02$ (C) OS by CMV, $P = .002$ (D) NRM by CMV, $P = .02$. In all plots, shaded areas indicate 95% pointwise confidence intervals, and numbers below the *x*-axis correspond to number of patients at risk for the respective time points.

et al. [27] (n = 35, median age 63 years, RIC) and Deschler at al [28]. (n = 160, median age 65 years, RIC) also reported good results of HSCT with a 1-year OS rates of 67% and 62%, respectively.

A retrospective analysis from the Center for International Blood and Marrow Transplant Research [29] investigated MDS patients undergoing RIC: Patients ≥ 65 years had a 2-year OS rate of 38% with no significant influence of age. However,

Table 3
Causes of Death

Cause of Death	Patients	Patients with Known CMV Status n (% of n = 156)	CMV Negative n (% of n = 48)	CMV Positive n (% of n = 108)
Relapse/progression	61	58 (37)	20 (42)	38 (35)
Secondary malignancy/PTLD	5	4 (3)	1 (2)	3 (3)
GVHD	27	25 (16)	9 (19)	16 (15)
Infection	54	53 (34)	12 (25)	41 (38)
Organ damage/failure	6	5 (3)	2 (4)	3 (3)
Toxicity	4	4 (3)	3 (6)	1 (1)
HSCT-related death	7	7 (5)	1 (2)	6 (6)
Missing	29			
Total	164	156	48	108

Reported causes of death for CMV-negative and -positive patients as well as for the total cohort.
PTLD indicates post-transplant lymphoproliferative disorder.

for the complete study cohort of MDS/AML patients, KPS < 80% had a significant influence on 1-year NRM as well as on 2-year OS. A later Center for International Blood and Marrow Transplant Research study [17] identified both age and KPS as independent risk factors for outcome, whereas different conditioning intensities led to similar 5-year OS rates for MAC, RIC, or NMA of 34%, 33%, and 26%, respectively. NRM in all groups was similar ($P = .49$). Patients in the MAC group were significantly younger than those in the other groups ($P < .001$) and more often presented with KPS ≥ 90% ($P < .001$). Significant covariates in multivariate analysis (among others) were age (≥40 versus <40 years) and KPS (≥90 versus <90%) for NRM, treatment failure (inverse of RFS), and mortality (inverse of OS). Brand et al. [30] compared the outcome of patients registered in transplant and nontransplant registries and found that elderly patients in both groups seemed to have a similar outcome in terms of OS survival, whereas Platzbecker et al. [15] showed that OS is higher after HSCT compared with treatment with 5-Azacytidine in patients with higher risk MDS/sAML aged 60 to 70 years (2-year OS: 39% versus 23%, respectively). Eastern Cooperative Oncology Group 1 to 2 was associated with a 3- to 4-fold higher risk of mortality, compared with physically unrestricted patients. Koreth et al. [31] found HSCT with RIC regimens in intermediate-II to high-

Table 4
Univariate Analysis of Outcome

	OS		RFS		RI		NRM	
	% (95% CI)		% (95% CI)		% (95% CI)		% (95% CI)	
1-year outcomes	52.1 (46.2-58.1)		47.0 (41.1-52.9)		20.6 (15.9-25.4)		32.4 (26.9-37.8)	
2-year outcomes	38.6 (32.5-44.7)		33.2 (27.3-39.1)		27.1 (21.6-32.5)		39.7 (33.8-45.7)	
3-year outcomes	34.3 (28.1-40.5)		29.3 (23.3-35.2)		28.3 (22.8-33.9)		42.5 (36.2-48.7)	
	OS		RFS		RI		NRM	
3-year outcomes	% (95% CI)	*P*	% (95% CI)	*P*	% (95% CI)	*P*	% (95% CI)	*P*
Karnofsky status		.01		.03		.7		.014
90-100%	43.3 (34.5-52.1)		36.5 (27.9-45.1)		30.5 (22.5-38.5)		32.9 (25.0-40.8)	
40- 80%	23.4 (13.1-33.7)		20.0 (10.3-29.7)		26.8 (17.3-36.2)		53.2 (41.6-64.8)	
Age		.7		.7		.4		.3
70-71 yr	32.6 (24.6-40.7)		28.6 (20.9-36.3)		24.6 (17.7-31.4))		46.9 (38.5-55.2)	
72-73 yr	34.0 (22.3-45.8)		26.9 (15.3-38.4)		37.5 (25.7-49.3)		35.7 (24.0-47.3)	
74-78 yr	41.0 (23.9-58.0)		37.3 (21.1-53.5)		24.7 (10.3-39.2)		38.0 (21.6-54.3)	
Donor type		.4		.6		.002		.05
Related	34.1 (22.0-46.1)		21.0 (9.8-32.1)		44.3 (31.6-56.9)		34.8 (22.4-47.1)	
Unrelated	34.6 (27.4-41.8)		32.3 (25.2-39.2)		22.5 (16.6-28.5)		45.2 (38.0-52.5)	
Remission status		.2		.4		.3		1.0
CR	38.7 (27.4-49.9)		30.9 (20.1-41.7)		23.7 (14.7-32.8)		45.3 (34.0-56.7)	
No CR	32.3 (25.0-39.6)		28.5 (21.4-35.6)		30.5 (23.5-37.6)		40.9 (33.5-48.3)	
CMV status (patient)		.002		.008		1		.02
CMV negative	46.3 (35.1-57.6)		38.5 (27.6-49.4)		29.2 (19.5-38.9)		32.3 (22.0-42.5)	
CMV positive	29.2 (21.7-36.7)		26.2 (18.8-33.5)		25.7 (18.8-32.5)		48.2 (40.1-56.2)	
Conditioning		.5		.5		1.0		.5
MAC	35.7 (20.3-51.1)		28.5 (13.2-43.7)		29.9 (14.3-45.6)		41.6 (26.5-56.7)	
RIC	34.8 (27.6-42.0)		29.7 (22.7-36.7)		28.5 (21.7-35.3)		41.8 (34.5-49.0)	
NMA	28.9 (10.7-47.2)		27.2 (10.0-44.4)		25.2 (12.5-37.9)		47.7 (28.2-67.0)	
Diagnosis		.2		.2		.8		.2
MDS	36.7 (29.4-44.1)		31.3 (24.2-38.3)		28.7 (22.1-35.3)		40.0 (32.8-47.3)	
sAML	27.5 (15.9-39.1)		22.8 (11.1-34.6)		27.8 (16.9-38.7)		49.3 (36.2-62.5)	
Disease status		.9		.6		.04		.4
RA/RARS/del5q/ RCMD-RS	22.9 (2.9-42.8)		23.5 (3.2-43.8)		24.2 (7.6-40.7)		52.3 (27.8-76.8)	
RAEB/RAEB-1/ RAEB-2	40.4 (27.9-52.8)		37.6 (25.5-49.8)		23.2 (12.6-33.8)		39.2 (27.4-51.0)	
RAEB-t/ transformed to AML	31.3 (14.4-48.1)		23.5 (7.4-39.6)		48.8 (29.4-68.3)		27.7 (10.7-44.5)	
sAML	29.1 (17.0-41.3)		24.1 (11.8-36.4)		27.8 (16.6-39.0)		48.1 (34.6-61.7)	

Outcome was calculated as indicated in Methods. *P* values are based either on the log-rank test (OS and RFS) or on Gray's test (RI and NRM). These tests compare the curves over the whole follow-up time.
RI indicates relapse incidence; CR, complete remission.

Table 5
Differences Between Patient Cohorts According to KPS

	KPS ≤ 80%	KPS 90-100%	*P*
Number of patients	106	168	
Median age at transplantation, yr	71.8	71.7	.627
Disease status at transplantation (n (%))			.262
RA/RARS/del5q/RCMD-RS	14 (18.7)	17 (12.8)	
RAEB/RAEB-1/RAEB-2	22 (29.3)	54 (40.6)	
RAEB-t/transformed to AL	10 (13.3)	11 (8.3)	
sAML from diagnosis onwards	29 (38.7)	51 (38.3)	
CMV status (recipient/donor match) (n (%))			.827
+/+	42 (40.8)	73 (44.0)	
+/–	21 (20.4)	35 (21.1)	
–/+	8 (7.8)	15 (9.0)	
–/–	32 (31.1)	43 (25.9)	
Conditioning (n (%))			.284
MAC	14 (13.2)	34 (20.2)	
RIC	70 (66.0)	106 (63.1)	
NMA	22 (20.8)	28 (16.7)	

To evaluate potential imbalances that could act as confounders between patients with high or low KPS that might have affected outcome after HSCT, both groups were compared regarding age, disease status, CMV status, and conditioning regimen. No significant differences could be detected.

risk groups of patients with advanced age to be superior to supportive care, erythropoiesis-stimulating agents, and hypomethylating agents, with regard to OS and quality of life, with a median OS of 36 months for RIC compared with 28 months for nontransplantation approaches.

We are well aware that the present investigation is presented with some weaknesses, due to lack of data and a retrospective approach. We could not obtain sufficient information on risk score and cytogenetic data of our patients. Nevertheless, the available cytogenetic information shows risk stratification according to IPSS-R that is very similar to the original observations [6], indicating a representative patient sample. Unfortunately, comorbidities and pretreatments were mostly unknown. The hematopoietic cell transplantation–specific comorbidity index is today considered to be an important tool for patient evaluation, and the lack of those data is another weakness of the analysis. Still, the evaluation provides valid data for a so far rarely investigated population and can give us an important insight on how this special field of treatment has developed within a short period of time. The results are encouraging, as it has been shown that quality of life of patients older than 60 years after HSCT is similar to matched nontransplanted patients and that the performance status after HSCT usually allows an independent life, compromising daily life activities only in few patients [28].

For future research, conventional therapies as well as cell-based therapy approaches should be investigated in the elderly patient cohort. Right now, some trials already meet this issue. The VidazaAlloStudy is comparing treatment with 5-azacytidine alone versus subsequent HCST for patients with MDS aged 55 to 70, which might open the way for future comparisons within patients above that age because it considers impact of comorbidity and quality of life measurements [32]. A US observational study starting soon is intending to gain information about the effectiveness of hypomethylating agents and lenalidomide in patients 66 years or older with AML or MDS in the United States with the aim to develop predictive models for hypomethylating agent treatment outcomes and to compare hypomethylating agent treatment with conventional chemotherapies in a large patient cohort [25]. An ongoing prospective trial is comparing outcome after RIC-based allogeneic HSCT to hypomethylating agents [33]. A very interesting approach is contributed by a new trial investigating the effect of haploidentical donor lymphocyte infusions after chemotherapy without allogeneic stem cell transplantation for patients aged ≥ 65 years with sAML, including protocol amendments even for patients older than 80 years [34]. We propose that research on infectious complications in CMV-positive older patients be extended, because the detected association with reduced OS was high ($P = .002$) and partially caused by lethal infections. As the impact of GVHD on OS was strong, strategies for GVHD prevention for the elderly need to be optimized.

In conclusion, our study confirmed that performance status, rather than age or conditioning regimen, predicts outcome. HSCT for advanced MDS patients 70 years or older is a curative treatment option with a 3-year OS rate of 34%. Good performance, determined by KPS, and recipients' sero negativity for CMV increase the estimated 3-year OS rates to 43% and 46%, respectively. The strong impact of these risk factors was confirmed in multivariate analyses. As expected, patients who received a graft from an unrelated donor

Table 6
Multivariate Analysis of Outcome

	OS		RFS		RI		NRM	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Karnofsky status*								
90-100%	1	.004	1	.03	1	.82	1	<.001
40-80%	1.62 (1.16-2.27)		1.43 (1.04-1.96)		.94 (.56-1.58)		1.88 (1.25-2.85)	
Disease status*								
RAEB-t/transf. to AL	1		1		1		1	
sAML	.95 (.50-1.87)	.84	.91 (.53-1.55)	.73	.52 (.25-1.12)	.09	1.42 (.65-3.10)	1.26 .38
RAEB/-1/-2	.82 (.46-1.47)	.51	.74 (.42-1.30)	.77 .29	.37 (.16-0.84)	.02	(.56-2.82)	1.23 .57
RA/RARS/del5q/RCMD-RS	.97 (.52-1.97)	.92	(.40-1.49)	.44	.40 (.15-1.06)	**.06**	(.49-3.10)	.65
Donor type								
Related	1	.08	1	.66	1	.06	1	.048
Unrelated	1.39 (.96-2.01)		1.08 (.77-1.52)		.62 (.37-1.03)		1.63 (1.03-2.64)	
Conditioning								
MAC	1		1		1		1	
RIC	.70 (.40-1.23)	.68	.94 (.62-1.41)	.75	1.01 (.51-1.98)	.98	.87 (.52-1.46)	.61
NMA	.63 (.34-1.19)	.21	.76 (.45-1.30)	.32	.95 (.42-2.19)	.91	.64 (.32-1.27)	.20
CMV serostatus patient								
Negative	1		1		1		1	
Positive	1.78 (1.26-2.50)	.001	1.53 (1.11-2.12)	.01	1.13 (.68-1.87)	.64	1.88 (1.23-2.88)	<.001

* Patients with missing information for this variable were kept in the analysis with variable level "missing" (HRs not shown).

had a lower incidence of relapse, which did not result in higher OS compared with those who received a graft from a related donor, due to higher NRM.

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2016.09.027.

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