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Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients Age >69 Years with Acute Myelogenous Leukemia: On Behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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A B S T R A C T

Reduced-intensity conditioning (RIC) allows for the use of allogeneic hematopoietic stem cell transplantation (HSCT) in older patients with acute myelogenous leukemia (AML). We compared outcomes between 713 patients age ≥70 years and 16,161 patients age 50 to 69 years who underwent HSCT between 2004 and 2014. A higher proportion of the older patients were male and had secondary AML, active disease, a peripheral blood stem cell graft, a matched unrelated donor, an RIC regimen, and a lower Karnofsky Performance Status (KPS) score ($P<$ .001). In multivariate analysis, the incidences of acute and chronic graft-versus-host disease and relapse were similar in the 2 age groups. Nonrelapse mortality at 2 years was 34% (95% confidence interval [CI], 31% to 38%) in patients age ≥70 years and 24% (95% CI, 25% to 32%) in those age 50 to 69 years ($P<$ .001). Survival at 2 years in the 2 groups was 38% (95% CI, 34% to 42%) and 50% (95% CI, 49% to 50%), respectively ($P<$ .001). In patients with active disease, the corresponding percentages were 35% (95% CI, 29% to 41%) in those age ≥70 years and 33% (95% CI, 31% to 34%) in those age <70 years ($P=.36$). In patients age ≥70 years, a KPS score of ≥80% was associated with improved survival (hazard ratio, 1.53; 95% CI, 1.14 to 2.06; $P=.003$). In summary, patients age ≥70 years had worse outcomes, except for those with active AML.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) may cure acute myelogenous leukemia (AML) [1-3]. The incidence of AML increases with age [4]. Age is important for survival following HSCT, and pppll younger patients generally do better, with lower nonrelapse mortality (NRM) and longer survival [5,6]. In the early era of HSCT, 40 years was considered the upper age limit [7]. With subsequent improvements in

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HSCT therapy, patients age >40 years could be offered HSCT [8-10]. The introduction of reduced-intensity conditioning (RIC) and nonmyeloablative conditioning (NMC) regimens as alternatives to myeloablative conditioning (MAC) made it possible to include patients with comorbidities and of older age [11-14]. In a prospective randomized trial in patients with myeloid leukemia demonstrated that, patients conditioned with an RIC regimen had less toxicity compared with those conditioned with an MAC regimen [14]. Whether elderly patients should be treated with HSCT has been a matter of debate [15]. There are often several challenges in elderly patients with AML, including poor cytogenetics and molecular markers, comorbidities, and compromised performancö status. Many elderly patients with AML do not receive appropriate treatment, because elderly patients are often considered intolerant of intensive therapy; for example, only 39% of patients with AML age >64 years receive treatment within 3 months from diagnosis [16]. There is a reluctance of physicians to select HSCT for elderly patients. The aim of the present study was to determine the outcomes of patients with AML age ≥70 years who had undergone HSCT in Europe. Because only 30 patients age ≥70 years received haploidentical grafts, the study was restricted to patients with matched donors. We compared this group with elderly adults treated with HSCT for AML and selected patients age 50 to 69 years. We also aimed to identify factors important for outcomes in patients in the older age group.

METHODS

Data Collection

Patients age >50 years with AML who underwent their first or second allo-HSCT between 2004 and 2014 using a matched sibling donor (MSD) or a matched unrelated donor (MUD) were included. All patients were reported to the European Society for Blood and Marrow Transplantation (EBMT), a group of >500 centers that reports consecutive HSCTs. The validation and quality control include cross-checking with the national registries and onsite visits. Each patient provided written informed consent.

Patients

This retrospective study included 713 patients age ≥70 years and 16,661 patients age 50 to 69 years with AML. The recipients and donors were matched by serologic or genomic tissue typing for HLA class I and by genomic typing for HLA class II. Among the recipients of MUD transplants, in typing for HLA-A, -B, -C, -DRβ1, and -DQβ1, 4971 were 10/10 matched and 1413 were 9/10 matched. HLA-A, -B, -DRβ1, and -DQβ1 matches were 5524 for 8/8 and 1102 for 7/8.

Definitions

Engraftment was defined as a sustained engraftment with an absolute neutrophil count $>.5 \times 10^9$/L for more than 3 consecutive days. Owing to missing data, platelet engraftment was not analyzed in 7431 patients. Acute and chronic graft-versus-host disease (GVHD) were scored according to the Seattle criteria [7,17]. Acute GVHD grade II-IV, chronic GVHD, and relapse were analyzed as GVHD and relapse-free survival (GRFS). NRM was defined as any death with no previous relapse or progression. Relapse was defined as hematologic relapse. Leukemia-free survival (LFS) was defined as survival without relapse or progression. Cytogenetic abnormalities were classified as good, intermediate, or poor, as defined previously [18]. In vivo T cell depletion (TCD) included the use of antithymocyte globulin or Campath.

Statistical Analysis

Cumulative incidence curves were used for relapse incidence and NRM in a competing-risk setting, with death and relapse competing with each other [19,20]. The probability of LFS (from the date of transplantation) were calculated using the Kaplan-Meier method. The log-rank test was used for univariate comparisons.

Patient-, disease-, and transplantation-related variables of the 2 groups were compared using the chi-square statistic for categorical variables and the Mann-Whitney *U*test for continuous variables. Variables considered were recipient age and sex, disease characteristics (French, American, and British [FAB] classification), cytogenetics, WBC count at the time of diagnosis, donor age and sex, cytomegalovirus serostatus of patient and donor, disease status at transplant, first complete remission (CR1), second or more complete remisison (CR2+), or more advanced disease (>5% blasts). Donor age was not included in the analysis because in MRD HSCT, donor and recipient age are closely related. In MUD transplants, donor age was missing in too many cases to allow for a meaningful analysis. Transplantation-related characteristics included year of transplantation, type of donor (MSD or MUD), stem cell source, pretransplantation conditioning regimen, previous autograft, and GVHD prophylaxis. Factors that differed between patients age ≥70 years and patients age 50 to 69 years, with a *P*value <.10 and with factors known to influence outcome, were included in the final models.

For all prognostic analyses, continuous variables were categorized, and the median was used as a cutoff point.

Associations of patient and graft characteristics with outcomes were evaluated in multivariable analyses using Cox proportional hazards regression. To test for a center effect, a random effect or frailty for each center was introduced into the model [21,22].

All tests were 2-sided. The type I error rate was fixed at .05 for determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS (IBM, Armonk, NY) and S-PLUS (MathSoft, Seattle, WA) software packages.

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. A higher proportion of the older patients were male, had secondary AML, had more advanced disease, received a peripheral blood stem cell (PBSC) graft, had an MUD, received an RIC regimen, had a poor Karnofsky Performance Status (KPS) score (<90), and underwent in vivo TCD. Follow-up was significantly longer in the younger patients compared with the older patients (median, 25 months [95% confidence interval (CI), 8 to 57 months] versus 14 months [95% CI, 4 to 34 months]; $P < .001$).

Conditioning and Immunosuppression

RIC defined as published was more common in the older patient group (Table 1) [23]. Overall conditioning differed between the younger and older patients ($P < .0001$). The most commonly used regimen in both groups was busulfan (Bu) combined with fludarabine (Flu), given to 27% of patients age ≥70 years and to 31.6% of those age <70 years [13]. Flu combined with melphalan and Flu with total body radiation (TBI) were given to 25.8% and 21.1% of the older patients and to 17.4% and 12.1% of the younger patients, respectively. Flu/cytarabine/amsacrine/antithymocyte globulin (FLAMSA) was administered to 9.5% of the older group and 8.1% of the younger group [24]. MAC with Bu combined with cyclophosphamide was given to 2 of the older patients (.3%) and 22% of the younger patients. The most common immunosuppressive regimens are shown in Table 1.

Engraftment and GVHD

The time to reach an absolute neutrophil count $>.5 \times 10^9$/L did not differ significantly between the 2 groups ($P = .6879$).

The cumulative incidence of acute GVHD grade II-IV was 23% (95% CI, 20% to 27%) in patients age ≥70 years and 25% (95% CI, 24% to 25%) in those age 50 to 69 years ($P = .3991$), and that for grade III-IV was 10% (95% CI, 8% to 12%) and 9% (95% CI, 9% to 10%), respectively ($P = .9293$).

The cumulative incidence of chronic GVHD at 2 years was 43% (95% CI, 38% to 48%) in patients age ≥70 years and 41% (95% CI, 40% to 42%) in those age 50 to 69 years ($P = .45$) (Fig. 1A). When the patients in CR1 and CR2 with advanced AML were analyzed separately, the following factors were significant for chronic GVHD in multivariate analysis: MUD as opposed to MSD (CR1), use of PBSC grafts as opposed to bone marrow grafts (all stages), female donors to male recipients (CR1), and lack of TCD in vivo (all stages) (Table 2). Advanced age was identified as a risk factor for chronic GVHD only in patients in CR2.

Table 1
Characteristics of Patients Age ≥70 Years and Patients Age 50 to 69 Years with AML

Parameter	Patients Age ≥70	Patients Age 50 to 69	*P* Value
No. of patients	713	16,161	
Age at HSCT, yr, median (range)	72 (70-79)	59 (50-69)	
Remission, n (%)			
CR1	295 (41)	9236 (57)	<.001
CR2	122 (17)	2471 (15)	
Advanced (>5% blasts in marrow)	296 (42)	4454 (28)	
FAB, n (%)			<.001
M0	39 (6)	804 (5)	
M1	72 (10)	2182 (14)	
M2	97 (14)	2679 (17)	
M3	0 (0)	110 (1)	
M4	69 (10)	1978 (12)	
M5	50 (7)	1498 (9)	
M6	10 (1)	440 (3)	
M7	3 (0)	123 (1)	
Missing	373 (52)	6347 (39)	
Cytogenetics, n (%)			
Good	11 (2)	514 (3)	
Intermediate	115 (16)	4256 (26)	
Poor	27 (4)	1405 (9)	
Missing	560 (79)	9986 (62)	
Patient sex, female, n (%)	267 (38)	7267 (45)	<.001
Donor age, yr, median (range)	43 (18-80)	44 (16-82)	.23
Donor sex, female, n (%)	203 (30)	5819 (37)	.0002
Female donor to male recipient, n (%)	101 (15)	2842 (18)	.03
CMV serostatus, n (%)			.14
CMV^+ donor, CMV^+ recipient	286 (42)	6261 (43)	
CMV mismatch donor/recipient	214 (32)	4909 (34)	
CMV^- donor, CMV^- recipient	176 (26)	3236 (23)	
Time from diagnosis to HSCT, mo, median (IQR)			
All	7.7 (4.3-16.7)	6.3 (4.3-12.7)	.0012
CR1	5.3 (3.9-8.3)	5.4 (4.1-7.3)	.8792
CR2	17.0 (12.8-25.0)	19.2 (13.5-28.7)	.0472
Advanced	9.0 (4.2-17.8)	7.3 (4.2-15.2)	.1041
Time from CR1 to HSCT			
Available, n/N	35/295	2905/9236	.2788
Median months (IQR)	3.0 (2.2-4.1)	3.4 (2.2-4.7)	
Time from CR2 to HSCT			
Available, n/N	25/122	806/2471	
Median months (IQR)	14.6 (9.7-21.3)	17.9 (12.7-27.2)	.1816
Stem cell source: PBSCs, n (%)	684 (96)	14,778 (91)	.0002
Conditioning regimen, n (%)			<.001
MAC	122 (18)	5771 (36)	
RIC	572 (82)	10,131 (64)	
Donor, n (%)	32	1383	
MSD	146 (20)	6653 (41)	<.001
UD	567 (80)	9508 (59)	
KPS score <80, n (%)	77 (11)	1080 (7)	<.001
Total body irradiation, n (%)	179 (25)	3563 (22)	.067
GVHD prophylaxis, n (%)			<.001
CYA	126 (18)	2831 (19)	
CYA + MTX	123 (18)	5331 (36)	
CYA + MMF	330 (48)	4844 (32)	
CYA + MTX + MMF	6 (1)	123 (1)	
MMF + Tac	41 (6)	586 (4)	
Tac + Sir	1 (0)	155 (1)	
MTX + Tac	12 (2)	265 (2)	

(*continued*)

Table 1 (*Continued*)

Parameter	Patients Age ≥70	Patients Age 50 to 69	*P* Value
PTCy	9 (1)	166 (1)	
Other	36 (5)	582 (4)	
TCD in vitro, n (%)	6 (1)	358 (2)	.0181
Campath, n (%)	116 (16)	1981 (12)	.0018
ATG/ALG, n (%)	356 (50)	7429 (46)	.0415
TCD in vivo, n (%)	465 (65)	9336 (58)	<.001
Previous autograft, n (%)	5 (1)	483 (3)	<.001
Follow-up, mo, median (range)	14 (4-34)	25 (9-58)	<.001

FAB indicates French, American, and British; CYA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; Tac, tacrolimus; Sir, sirolimus; ATG, antithymocyte globulin; ALG, antilymphocyte globulin.

NRM

NRM at 2 years was 34% (95% CI, 31% to 38%) in patients age ≥70 years and 24% (25 to 32%) in those <70 years of age (p < .001, Fig. 1B). In multivariate analysis, patients age ≥70 years in CR1 or CR2 had increased NRM, but those with advanced AML did not (Table 2). Other factors significant for NRM in the multivariate analysis included secondary AML as opposed to de novo AML (CR1), female donor to male recipient (CR1), CMV seronegative donor-recipient pair (CR1), KPS score <80 (all stages), MAC as opposed to RIC (all stages), MUD graft as opposed to MSD graft (all stages), and in vivo TCD (CR1) (Table 2).

Relapse

The overall probability of relapse at 2 years was 33% (95% CI, 29% to 36%) in patients age ≥70 years and 32% (95% CI, 31% to 33%) in those age 50 to 69 years. There were no significant differences in relapse between the 2 age groups in the multivariate analysis (Table 2). Factors of importance for relapse in the multivariate analysis were secondary AML versus de novo AML (CR1), KPS score ≥80 (advanced disease), RIC versus MAC (CR1 and CR2), MSD versus MUD (CR1 and advanced disease), in vivo TCD (CR1 and CR2), and time from diagnosis to HSCT <6 months (CR1 and CR2) ($P = 1 \times 10^{-4}$).

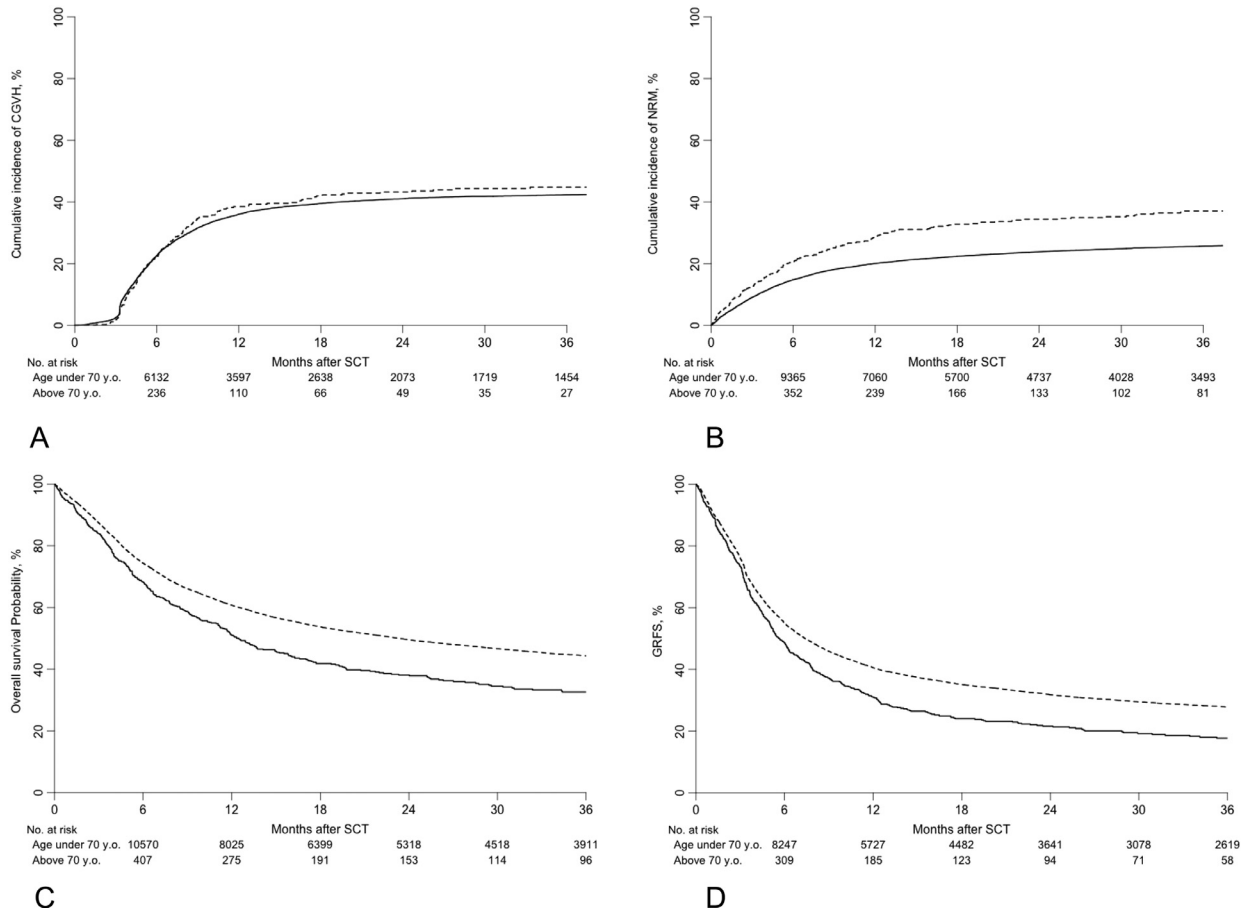

Figure 1. (A) Cumulative incidence of chronic GVHD in patients age ≥70 years (solid line) and patients age 50 to 69 years (dashed line) ($P = .40$) at different time intervals. (B) Cumulative incidence of NMR in patients age >70 years (solid line) and patients age 50 to 69 years (dashed line) patients age ≥70 years (dashed line) and patients age 50 to 69 years (solid line) ($P < .001$ at different time intervals. (C) Estimated overall survival in patients age ≥70 years (solid line) and patients age 50 to 69 years (dashed line) (P < .001) at different time intervals. (D) Estimated rate of GVHD and leukemia-free survival in patients age ≥70 years (solid line) and those age 50 to 69 years (dashed line) ($P < .001$) at different time intervals.

Table 2
Multivariable Analysis of HSCT Recipients with AML Age ≥70 Years and Age 50 to 69 Years

Parameter	CR1			CR2			Advanced Disease		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Chronic GVHD, age ≥70 vs 50-69	.98	.77-1.25	.89	1.48	1.08-2.02	.01	.97	.76-1.24	.82
Female donor to male recipient	1.31	1.19-1.44	.0000	1.12	.92-1.37	.24	1.10	.93-1.30	.24
UD vs MSD	1.17	1.07-1.27	.0004	1.12	.94-1.34	.20	1.02	.88-1.18	.79
TCD in vivo	.62	.57-.68	.0000	.56	.48-.66	.0000	.70	.61-.81	<.001
PBSCs vs bone marrow	1.18	1.03-1.35	.02	1.65	1.26-2.16	.0003	1.99	1.45-2.74	<.001
NRM, age ≥70 vs 59-69	1.59	1.25-2.03	.0002	2.10	1.54-2.86	2e-06	1.07	.85-1.35	.57
Secondary AML vs de novo AML	1.20	1.09-1.34	.0016	1.24	.97-1.59	.09	1.09	.97-1.24	.12
Female donor to male recipient	1.21	1.07-1.37	.003	1.23	.98-1.57	.07	1.15	.99-1.34	.07
CMV status, seronegative donor to seronegative recipient vs other	.69	.60-.78	.0000	.91	.74-1.12	.36	.95	.82-1.09	.46
KPS <80 vs ≥80	2.02	1.66-2.47	.0000	1.63	1.18-2.26	.003	1.70	1.46-1.99	<.001
RIC vs MAC	.86	.77-.95	.0003	.79	.65-.95	.01	.84	.74-.96	.007
UD vs MSD	1.73	1.54-1.94	.0000	1.29	1.04-1.61	.02	1.24	1.07-1.44	.004
Relapse at age ≥70 yr vs 50-69 yr	1.18	.92-1.51	.19	1.00	.69-1.46	.99	.97	.76-1.24	.82
Secondary AML vs de novo AML	1.34	1.22-1.48	.0000	1.21	.96-1.51	.11	.93	.84-1.03	.15
KPS <80 vs ≥80	1.09	.87-1.36	.44	1.32	.96-1.84	.09	1.36	1.18-1.56	<.001
RIC vs MAC	1.11	1.01-1.22	.02	1.21	1.01-1.45	.04	1.00	.89-1.21	.98
UD vs MSD	.84	.77-.92	.0003	.97	.80-1.17	.72	.72	.64-.81	<.001
TCD in vivo	.87	.74-.99	.03	1.29	1.07-1.55	.0008	1.01	.90-1.14	.81
Time from diagnosis to HSCT >6 mo vs ≤6 mo	.84	.77-.91	8e-05	.47	.36-.63	.0000	.98	.88-1.09	.69

Survival and LFS

The 2-year survival was 38% (95% CI, 34% to 42%) in patients age ≥70 years and 50% (95% CI, 49% to 50%) in patients age 50 to 69 years ($P < .001$) (Fig. 1C). LFS in the 2 groups was 33% (95% CI, 29% to 37%) and 44% (95% CI, 43% to 45%), respectively ($P = .001$). In patients in CR1, 2-year survival was 43% (95% CI, 37% to 51%) in the older group and 57% (95% CI, 56% to 58%) in the younger group ($P < .001$) (Fig. 2A). In patients who underwent HSCT in CR2+, 2-year survival in the 2 groups was 36% (95% CI, 27% to 27%) and 52% (95% CI, 50% to 54%), respectively ($P = .002$) (Fig. 2B). However, in patients with advanced AML, 2-year survival in the 2 groups was 35% (95% CI, 29% to 41%) and 33% (95% CI, 31% to 34%), respectively ($P = .36$) (Fig. 2C).

In multivariate analysis, patients age ≥70 years had worse survival than the younger patients in CR1 and CR2 (Table 3). Other factors associated with poorer survival included secondary AML as opposed to de novo AML (CR1 and CR2), KPS score <80 (all stages), RIC as opposed to MAC (advanced stage), MUD as opposed to MSD (CR1), and time from diagnosis to HSCT <6 months (CR1 and CR2).

In multivariate analysis for LFS, age was also different in patients in CR1 and CR2, but not in patients with advanced AML (Table 3). Other significant factors included secondary AML as opposed to de novo AML (CR1 and CR2), CMV-seronegative donor to seronegative recipient (CR1), KPS score ≥80 (all stages), and MSD as opposed to MUD (CR1 and advanced disease) (Table 3).

GRFS

In multivariate analysis, GRFS was significantly poorer for patients age ≥70 years in CR1 and CR2 than for patients aged 50 to 69 years (Table 3, Fig. 1D). GRFS did not differ significantly according to age in patients with advanced AML. Other factors that were significant for GRFS were secondary AML as opposed to de novo AML (CR1 and CR2), female donor to male recipient (CR1 and advanced disease), CMV-seronegative donor to seronegative recipient (CR1), KPS score <80 (all stages), no in vivo TCD (CR1 and advanced disease), RIC as opposed to MAC (advanced disease), and time from diagnosis to HSCT <6 months (CR1 and CR2) (Table 3).

Prognostic Factors for Outcome in Patients Age ≥70 Years

MUD HSCT recipients age ≥70 years had a higher risk of acute and chronic GVHD in the multivariable analysis (Table 4). NRM was also increased in MUD HSCT recipients in patients in CR2 as opposed to those in CR1 and patients with secondary AML (Table 4). There was no significant difference in NRM between patients in CR1 and those with advanced disease, but the probability of relapse was significantly higher in the latter group.

In patients age ≥70 years, a KPS score ≥80% was associated with improved NRM, survival, and LFS (Fig. 2D, Table 4). Survival was also better in CMV-seronegative patients with a seronegative donor compared with all other patients.

No Major Role for Year of Transplantation

We compared patients who underwent HSCT between 2004 and 2009 and those who did so between 2010 and 2014. We first performed this comparison for the entire sample, which comprised 6715 patients in the first group (2004 to 2009) and 10,159 patients in the second group (2010 to 2014). Owing to the large sample size, small differences in value showed statistical significance (Fig. 3A). In the more recent time period, there was an increase in median age at HSCT (58.1 versus 59.9 years), a decrease in the median interval from diagnosis to HSCT (6.4 months versus 6.2 months), an increase in patients undergoing transplantation in CR1 (53.1% versus 58.7%), an increase in the use of PBSC grafts (90.5% versus 92.3%), an increase in the use of unrelated donors (51.2% versus 65.3%), a decrease in the rate of poor performance at HSCT (8.7% versus 6.4%), a decrease in the use of TBI (28.9% versus 18%), and an increase in the use of in vivo TCD (46.4% versus 65.8%).

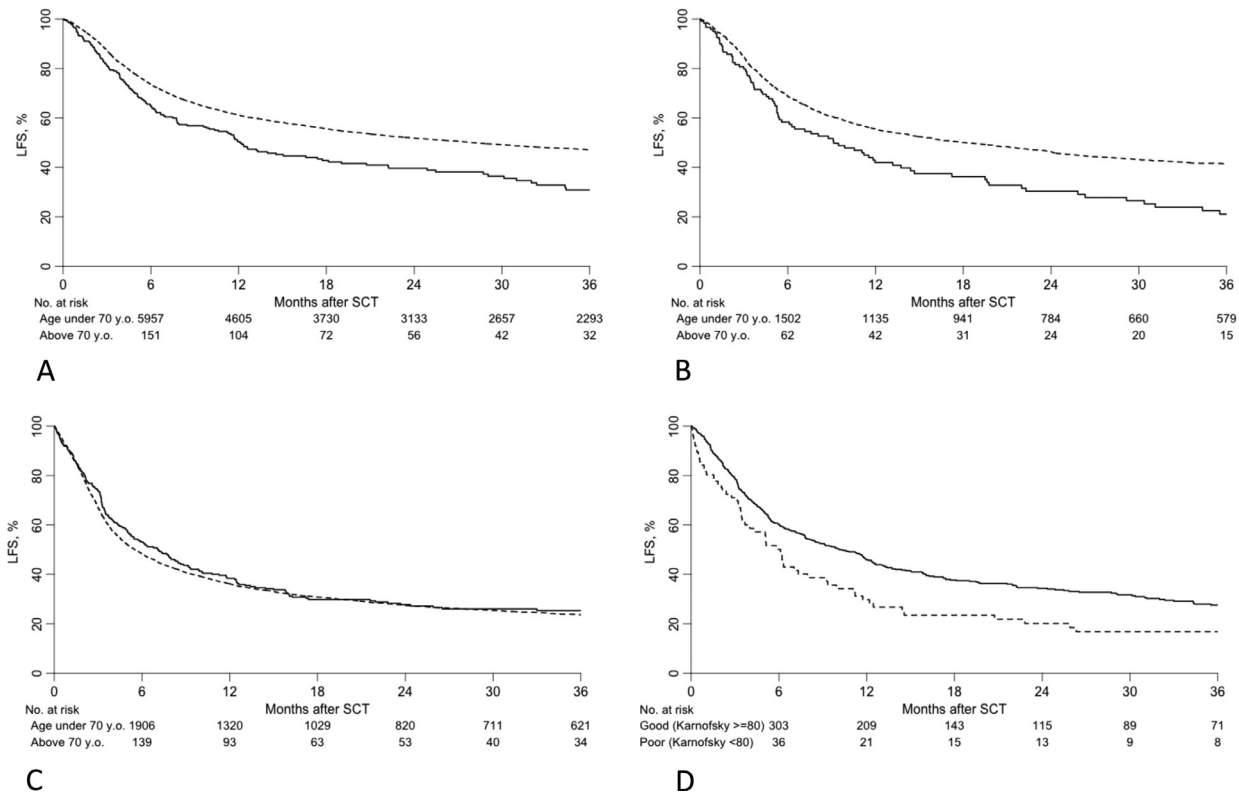

Figure 2. (A) Estimated LFS in patients age ≥70 years (solid line) and patients age 50 to 69 years (dashed line) in CR1. Adjusted multivariable analysis: HR, 1.37; 95% CI, 1.16 to 1.63 ($P = .0003$). (B) Estimated LFS in patients age ≥ 70 years (solid line) and patients age 50 to 69 years (dashed line) in second CR2. Adjusted multivariable analysis: HR, 1.48; 95% CI, 1.16 to 1.87 ($P = .0013$). (C) Estimated LFS in patients age ≥70 years (solid line) and patients age 50 to 69 years (dashed line) in advanced-stage disease (HR, 1.01; 95% CI, .87 to 1.18; $P = .85$). (D) Estimated LFS in patients age ≥70 years with a KPS score of ≥80 (solid line) or <80 (dashed line). Adjusted multivariable analysis: HR, 1.84; 95% CI, 1.16 to 2.04 ($P = .003$).

The 2-year overall and progression-free survival were better in the more recent time period (58.1% versus 59.9%) (Fig. 3a)

We then performed this comparison only in patients age ≥70 (170 patients in 2004 to 2009 versus 543 patients in 2010 to 2014). In the more recent time period, patients more often underwent HSCT in CR1 (33% versus 44%), and there was a decrease in the use of TBI (35.2% versus 22%), and an increase in use of in vivo TCD (57.6% versus 67.6%).

Two-year overall survival was similar in the 2 periods (Fig. 3B)

To test the sensitivity of our model, we added the period of transplantation to the multivariate analysis. Similarly, in all groups (CR1, CR2, and advanced disease), this variable is not significant, and results were similar (data not shown).

Causes of Death

Number of deaths was 415/713 in patients above and 8303/16161 in patients 50 to 69 years of age. The most common causes of death in patients age ≥70 years and those age 50 to 69 years) were original disease (41.7% versus 48.2%), infection (23.9% versus 18.5%), GVHD (12.8% versus 15.8%), nonspecified transplantation-related (4.1% versus 3.0%), secondary malignancy (1.2% versus 1.5%), interstitial pneumonia (1.7% versus 1.4%), cardiac toxicity (1.2% versus .7%), hemorrhage (.5% versus .8%), rejection (.7% versus .4%), sinusoidal obstructive syndrome (.5% versus .6%), and other or unknown (11.8% versus 9.1%).

DISCUSSION

In the last decade, approximately 700 patients age ≥70 years have undergone HSCT for AML in Europe. HSCT recipients age ≥70 years have worse NRM and survival compared with those age 50 to 69 years. Notably, in our series, a higher proportion of older patients had secondary AML and a poorer KPS score, factors associated with worse outcome. There is a selection of patients who are fit for HSCT. With increasing age, the risk of comorbidities increases, which was probably the reason for the lower KPS scores in the older patients. There is of course a problem of selection. There are clear differences between the groups, which may have introduced selection bias. At the various centers, we do not have a denominator to understand why the decision to perform HSCT was made in the patients age ≥70 years.

A higher proportion of patients age ≥70 years had an MUD compared with the younger group. Several studies have shown similar results after HSCT using MUDs and MSDs [25-27]. MUD HSCT recipients age ≥70 years generally had more GVHD than MSD HSCT recipients. Whether a young MUD is preferable to an old MSD remains a subject of debate [28-30]. The present study showed similar LFS using MUDs or MSDs in patients age ≥70 years.

The incidences of acute and chronic GVHD were similar in the patients age ≥70 years and the younger cohort. The Center for International Blood and Marrow Transplant Research (CIBMTR) also found a similar risk of acute GVHD in patients age >60 years and <60 years who received an RIC regimen [28]. In contrast to our data, several studies have shown that older age is associated with an increased risk of chronic GVHD [31,32]. This was not seen for patients in CR1 and with advanced AML, who composed 85% of the patients. Overall, there appears to be conflicting data regarding whether or not chronic GVHD is further increased in patients age >65 years [29,33,34].

Table 3
Multivariable Analysis of HSCT Recipients with AML Age ≥70 Years and Age 50 to 69 Years

Parameter	CR1			CR2			Advanced Disease		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Overall survival, age ≥ 70 vs 50–69	1.41	1.18-1.70	.0002	1.51	1.18-1.95	.001	1.02	.87-1.20	.78
Secondary AML vs de novo AML	1.24	1.15-1.34	.0000	1.28	1.07-1.52	.007	.98	.90-1.06	.64
CMV serostatus, negative donor to negative recipient vs all others	.81	.75-.89	3e-06	.89	.77-1.07	.12	.93	.85-1.03	.21
KPS score <80 vs ≥80	1.60	1.38-l.87	.0000	1.55	1.22-1.97	.0003	1.62	1.46-1.81	< .001
RIC vs MAC	.96	.89-1.03	.28	.98	.86-1.12	.79	.87	.80-.95	.002
UD vs MSD	1.22	1.13-1.32	.0000	1.13	.97-1.32	.11	.98	.89-1.07	.62
Time from diagnosis to HSCT >6 mo vs ≤6 mo	.92	.86-.99	.018	.59	.48-.75	1.6e-05	1.01	.93-1.10	.84
Leukemia-free survival, age ≥ 70 vs 50–69	1.37	1.16-1.63	.0003	1.48	1.16-1.87	.0013	1.01	.87-1.18	.85
Secondary AML vs de novo AML	1.28	1.19-1.38	.0000	1.22	1.04-1.45	.02	.99	.92-1.08	.97
CMV serostatus, negative donor to negative recipient vs all others	.86	.79-.92	.0001	.93	.81-1.07	.32	.97	.88-1.07	.54
KPS score <80 vs ≥80	1.47	1.27-1.70	.0000	1.46	1.16-1.83	.0001	1.50	1.35-1.66	.0000
RIC vs MAC	1.00	.93-1.07	.99	.99	.87-1.12	.90	.92	.86-1.01	.08
UD vs MSD	1.13	1.05-1.21	.0011	1.10	.95-1.27	.20	.90	.82-.99	.03
Time from diagnosis to HSCT >6 mo vs ≤6 mo	.91	.85-.97	.006	.57	.46-.72	1e-06	1.00	.92-1.08	.97
GRFS, age ≥70 yr vs 50-69 yr	1.33	1.13-1.57	.0005	1.47	1.16-1.87	.003	.97	.84-1.13	.73
Secondary AML vs de novo AML	1.18	1.11-1.27	1e-06	1.22	1.04-1.45	.02	.99	.92-1.07	.86
Female donor to male recipient vs all others	1.15	1.07-1.24	.0002	1.08	.92-1.27	.34	1.11	1.01-1.22	.03
CMV serostatus, negative donor to negative recipient vs all others	.86	.80-.93	67e-05	.93	.81-1.07	.32	.98	.90-1.07	.67
KPS score <80 vs ≥80	1.36	1.18-1.56	2e-05	1.46	1.16-1.83	.001	1.42	1.28-1.57	< .001
RIC vs MAC	.97	.92-1.04	.43	.97	.86-1.09	.61	.91	.84-.98	.016
UD vs MSD	1.15	.07-1.22	5.4e-05	1.10	.95-1.27	.20	.95	.87-1.04	.28
TCD in vivo	.78	.73-.84	.0000	1.05	.92-1.21	.45	.87	.80-.95	.0013
Time from diagnosis to HSCT >6 mo vs ≤6 mo	.91	.85-.96	.0014	.57	.46-.72	1e-06	.95	.88-1.07	.21

Table 4
Multivariable Analysis of AML Patients Age ≥70 Years Who Underwent HSCT

Parameter	HR	95% CI	*P* Value
Acute GVHD II-IV, UD vs MSD	1.79	1.09-2.93	.022
Acute GVHD III-IV, UD vs MSD	1.94	1.16-3.24	.011
Chronic GVHD, UD vs MSD	1.99	1.20-3.32	.008
NRM, UD vs MSD	1.59	1.08-2.34	.018
CR2 vs CR1	1.54	1.06-2.24	.023
Advanced vs CR1	1.04	.75-1.45	.81
Secondary AML vs de novo AML	1.37	1.01-1.85	.041
KPS score <80 vs ≥80	1.74	1.17-2.58	.006
Relapse, advanced vs CR1	1.64	1.20-2.23	.002
Survival, CMV seronegative donor to seronegative recipient vs other	.77	.60-.98	.034
KPS score <80 vs ≥80	1.53	1.14-2.06	.005
LFS, secondary vs de novo	1.24	1.01-1.52	.039
KPS score <80 vs ≥80	1.54	1.16-2.04	.003
Time from diagnosis to HSCT >6 mo	1.23	1.00-1.52	.049
GRFS, advanced vs CR1	1.26	1.02-1.56	.032

In the CR patients age ≥70 years had higher NRM, lower survival, and lower LFS compared with younger patients. A similar outcome has been reported for patients with AML age 60 to 64 years compared with those age ≥65 years [34]. In patients who received an NMC regimen for acute leukemia, outcomes were similar in different age-stratified groups between 60 and 75 years [35]. Chevallier et al [33] also reported that age was not an adverse factor for outcome in patients age ≥60 years with AML. We included many more patients and patients of older age. NRM, survival, and LFS are similar to those in a recent report from the CIBMTR in patients age >70 years [36]. Interestingly, in patients with active disease, survival and LFS were the same in patients age ≥70 years and those age 50 to 69 years.

GRFS was lower in the older patient cohort compared with the younger patient cohort, owing to the higher NRM in the older patients. When the patients age ≥70 years were analyzed separately for prognostic factors, those with a KPS score of ≥80 had significantly better overall survival, LFS, and GRFS than those with a KPS score <80. These findings underscore the importance of patient selection. A KPS score <80 has previously been associated with poor survival in older patients with AML [28]. A high comorbidity score was also found to be associated with poor survival in patients age >60 years with acute leukemia treated with NMC HSCT [35].

The multivariate analysis identified several risk factors, many of which are well known, including female donor to male recipient, secondary AML, time from diagnosis to HSCT, in vivo TCD, and CMV seropositivity in recipient and/or donor [1-3,11-13,18,27,29,30,37]. In vivo TCD had no effect on survival and LFS, in contrast to other studies [38,39], but was associated with improved GRFS. The discrepant findings between this study and others may be due to the fact that the current study included patients of older age, whereas the other studies included mostly adults age <50 years.

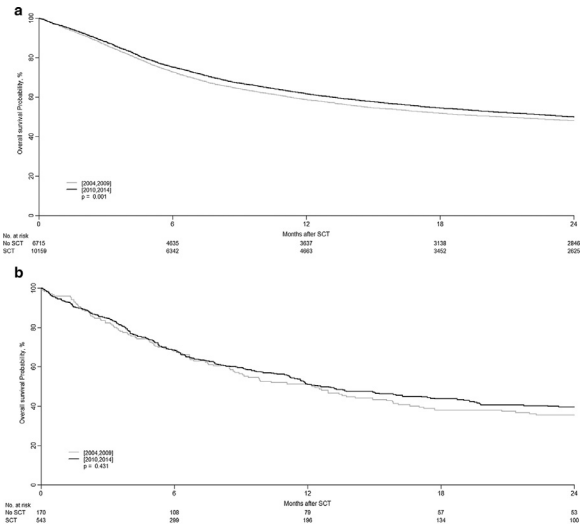

Figure 3. (A) Estimated progression-free survival in all patients undergoing HSCT in 2004 to 2009 (gray line) and in 2010 to 2014 (black line) ($P < .001$). (B) Estimated overall survival in patients age ≥70 years treated with HSCT in 2004 to 2009 (gray line) and in 2010 to 2014 (black line) ($P = .431$).

Recipients of HSCT from an MUD experienced less relapse than recipients of MSD HSCT, in contrast to a report from the CIBMTR indicating a similar probability of relapse regardless of donor type [40]. The Acute Leukemia Working Party and others have reported less relapse in recipients of MUD HSCT than in recipients of MSD HSCT—for example, in patients undergoing transplantation at relapse—but this is debatable [41].

There is a center effect in Europe. Patients with acute leukemia undergoing HSCT in countries with a high Human Developmental Index (HDI), a scale of socioeconomic achievement, have better LFS than patients from countries with a low HDI [42]. In the multivariable analysis, a random effect on frailty for each center was introduced to correct for this [21].

Several studies have shown improving outcomes after HSCT in recent years [43-45]. In the present study, improved survival was seen in univariate analysis but not in multivariate analysis. Factors that changed over time were more important, such as decreased interval from diagnosis to HSCT, more patients in CR1, fewer patients with a poor KPS score, and increased use of TCD in vivo. In patients age ≥70 years, year of HSCT had no impact on survival. These findings may be related to our large sample size and also to the smaller number of patients age ≥70 years.

Some limitations of this present study should be acknowledged. This was a retrospective multicenter registry study, with various protocols used. Although several important variables were controlled for, there still may have been some differences that could not be accounted for. Thus, our data should be interpreted with caution. A further limitation is missing data regarding cytogenetic abnormalities and comorbidity score. Strengths of the study included the large number of patients and the restriction to patients with AML.

In a propensity score-based analysis, patients age <70 years with AML treated with HSCT had better survival than those treated with chemotherapy [46]. This also may be the case for patients >70 years of age with AML. Therefore, we recommend that patients age >70 years with AML in good health (eg, KPS score ≥80%) be considered for HSCT regardless of disease stage. Analyzing and reporting outcomes is important to expand the use of HSCT in elderly patients.

In conclusion, the probabilities of acute and chronic GVHD and relapse were the same in patients age ≥70 years and those age 50 to 69 years. In patients in CR, survival and LFS were inferior in the older patients compared with the younger patients. Patients age ≥70 years with active disease should be offered the opportunity to undergo HSCT. A KPS score ≥80% was associated with improved outcome of HSCT in these patients.

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