Monosomal karyotype as an adverse prognostic factor in patients with acute myeloid leukemia treated with allogeneic hematopoietic stem-cell transplantation in first complete remission: a retrospective survey on behalf of the ALWP of the EBMT

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ABSTRACT

Despite the overall benefit from allogeneic hematopoietic stem cell transplantation observed in patients with poor cytogenetic risk acute myeloid leukemia in first complete remission, the precise effect of this procedure for different poor-risk subtypes has not been fully analyzed. This retrospective analysis was performed to investigate whether allogeneic hematopoietic stem cell transplantation performed in first complete remission in patients with monosomal karyotype can overcome the adverse prognosis associated with these patients. Of the 4635 patients included in the study, 189 (4%) harbored a monosomal karyotype. The presence of a monosomal karyotype was associated with a worse outcome, with an inferior leukemia-free survival and overall survival (5-year leukemia-free survival and overall survival: 24±3% and 26±3% *vs.* 53±1% and 57±1% in monosomal-karyotype and non-monosomal-karyotype, respectively; $P<0.0001$) and higher relapse risk after transplantation (cumulative incidence of relapse at 5 years: 56±4% in monosomal-karyotype *vs.* 28±1% in non-monosomal-karyotype; $P<0.0001$). The adverse negative impact of monosomal karyotype cytogenetics was confirmed in the entire cohort in a multivariate analysis [Hazard Ratio (HR): 1.88, 95% Confidence Interval (CI):1.29-2.73, $P=0.001$ for relapse incidence; HR:1.71, 95%CI:1.27-2.32, $P<0.0001$ for leukemia-free survival; HR:1.81, 95%CI:1.32-2.48, $P=0.0002$ for overall survival], and was independent of the presence of other poor-risk cytogenetic subtypes. In summary, monosomal karyotype arises as a strong negative prognostic feature in acute myeloid leukemia also in patients who undergo allogeneic hematopoietic stem cell transplantation in first complete remission, stressing the need to develop additional pre- and post-transplantation strategies aimed at improving overall results. Nonetheless, allogeneic hematopoietic stem cell transplantation in early phase is currently the best therapy for this very poor-risk acute myeloid leukemia subtype.

Introduction

Acute myeloid leukemia (AML) is a disorder of hematopoietic progenitor cells with a great biological and clinical diversity, as a result of very different genetic alterations leading to an impaired differentiation capacity and increased proliferation ability of the leukemic population.[1] It has long been recognized that several cytogenetic and molecular abnormalities are of prognostic importance, and the clinical relevance of these is reflected in the WHO 2008 classification of AML.[2] The European LeukemiaNet defines three genetic subgroups to classify AML (excluding acute promyelocytic leukemia) according to the risk of relapse: favorable, intermediate and unfavorable.[1] Between 15% and 20% of AML patients belong to the favorable group, characterized by t(8;21), inv(16) or t(16.16). The unfavorable group is a heterogeneous group of patients, with 25%-40% of AML patients with diverse cytogenetic abnormalities such as loss of long arm or monosomy of chromosomes 5 or 7, *EVI1* rearrangement associated to translocation 3q26, different types of rearrangement involving the *MLL* gene, deletion of 17p region related to TP53 loss, and other cases carrying multiple clonal cytogenetic abnormalities known as complex karyotypes (CK, ≥3 abnormalities in the karyotype). Finally, the remaining AML patients with t(9;11)(q22;q23) and cytogenetic abnormalities not otherwise classified belong to the intermediate risk group. The benefit of allogeneic hematopoietic stem cell transplantation (alloHSCT) in first complete remission has been clearly confirmed in the unfavorable risk and intermediate risk groups, presumably depending on the underlying genotypes.[3,4]

However, the precise effect of this procedure for different poor-risk subtypes has not been fully analyzed. Breems *et al*. identified a very poor prognostic cytogenetic subgroup named monosomal karyotype (MK),[5] with an overall survival (OS) of only 3% at four years. This group of MK patients was defined by the presence of one autosomal monosomy together with at least one other structural chromosomal abnormality or the presence of at least two autosomal monosomies. Cornelissen *et al*. reported that post-consolidation therapy using alloHSCT in MK AML in CR1 is associated with a significant reduction in relapse and improvement of survival with a similar relative reduction in death and relapse to other cytogenetic risk categories.[6] Similarly, Fang *et al*. and Oran *et al*. reported a negative prognostic impact on survival of MK also in patients who underwent alloHSCT.[7,8]

However, the number of transplanted patients with MK included in the studies mentioned was limited, making it difficult to accurately define the outcome of MK AML patients after alloHSCT, especially for patients in CR1. To address this issue, we performed a retrospective analysis using data from the European Group for Blood and Marrow Transplantation (EBMT) registry in patients with primary AML in first complete remission (CR1).

Methods

Study population

We searched the registry of the EBMT with the following criteria: patients aged 18 years or over, initial diagnosis of AML, in CR1, transplanted with allogeneic donors (related and unrelated; syngeneic excluded), transplant source of bone marrow and/or peripheral blood stem cells (cord blood excluded), transplanted

Table 1. Main characteristics of patients with and without monosomal karyotype.

	Non-MK AML	MK AML	*P*
N. of patients (%)	4446 (96)	189 (4)	
Sex (female:male), n (%)	2213:2230 (50:50)	97:92 (51:49)	0.76
Age (years), median (range)	45 (18-76)	48.5 (18-68)	0.007
AML subtype (FAB), n (%)			
M1 to M6	3691 (86)	125 (68)	
M0	296 (7)	23 (15)	<0.0001
M7 & other	298 (7)	36 (19)	<0.0001
Cytogenetics at diagnosis, n (%)			
MK	0	189 (100)	<0.0001
CK	182 (4)	130 (69)	<0.0001
OP	706 (16)	151 (82)	<0.0001
Any 7 abnormality	222 (5)	119 (66)	<0.0001
Monosomy 5 or del5q	91 (2)	70 (37)	<0.0001
17p abnormality	16 (0.4)	28 (15)	<0.0001
WBC at diagnosis (10^9/L), median (range)	12.9 (0.2-879)	4.6 (0.45-290)	<0.0001
Patients requiring >1 induction course to achieve CR1, n (%)	1072 (31)	61 (41)	0.01
Interval diagnosis to CR1, days median (range)	46 (15-110)	53 (10-174)	0.008
Donor type (MRD/MUD), n (%)	3174 (71)/1272(29)	110 (58)/79 (42)	<0.0001
Stem cell source (BM/PB), n (%)	1514 (34)/2932(66)	60 (32)/129(68)	0.51
Intensity of conditioning regimen (MAC/RIC), n (%)	3023 (69)/1375(31)	117 (64)/67(36)	0.14

AML: acute myeloid leukemia; MK: monosomal karyotype; CK: complex karyotype; OP: other poor risk cytogenetics; any 7 abnormality: any abnormality involving chromosome 7; WBC: white blood cell count; MRD: matched related donor; MUD: matched unrelated donor; BM: bone marrow; PB: peripheral blood stem cells; MAC: myeloablative conditioning; RIC: reduced intensity conditioning.

Table 2. Multivariable analysis among the entire cohort (n=4635).

Prognostic factors	Relapse incidence HR (95% CI)	P	Non-relapse mortality HR (95% CI)	P	Leukemia-free survival HR (95% CI)	P	Survival HR (95% CI)	P
Age > 45 years	0.97 (0.82-1.14)	0.69	1.70 (1.41-2.05)	<0.0001	1.26 (1.12-1.42)	0.0002	1.30 (1.15-1.47)	<0.0001
WBC at diagnosis (>12.3x10^9/L)	1.47 (1.26-1.71)	<0.0001	0.98 (0.83-1.17)	0.83	1.19 (1.07-1.33)	0.001	1.20 (1.07-1.34)	0.001
Time to achieve CR (>45 days)	1.56 (1.34-1.81)	<0.0001	1.26 (1.07-1.50)	0.007	1.40 (1.26-1.56)	<0.0001	1.45 (1.29-1.62)	<0.0001
Unrelated donor	1.02 (0.87-1.20)	0.81	1.31 (1.09-1.57)	0.005	1.16 (1.04-1.31)	0.01	1.19 (1.06-1.35)	0.004
Conditioning intensity (RIC *vs.* MAC)	1.28 (1.07-1.53)	0.006	0.70 (0.57-0.86)	0.001	1.08 (0.95-1.22)	0,26	1.04 (0.91-1.19)	0.53
Acute GvHD (grade 2-4 *vs.* 0-1)	0.75 (0.62-0.90)	0.002	2.74 (2.30-3.26)	<0.0001	1.39 (1.24-1.56)	<0.0001	1.55 (1.37-1.74)	<0.0001
Chronic GvHD (present *vs.* absent)	0.77 (0.64-0.93)	0.007	2.50 (2.00-3.11)	<0.0001	1.20 (1.06-1.37)	0.005	0.96 (0.85-1.10)	0.58
Monosomal karyotype (present *vs.* absent)	1.88 (1.29-2.73)	0.001	1.30 (0.72-2.34)	0.39	1.71 (1.27-2.32)	<0.0001	1.81 (1.32-2.48)	0.0002
Complex karyotype (present *vs.* absent)	1.59 (1.20-2.11)	0.001	0.90 (0.59-1.37)	0.62	1.26 (1.01-1.58)	0.04	1.28 (1.01-1.61)	0.04
Other poor cytogenetics								
No (reference)	1		1		1		1	
Monosomy 7	1.85 (1.28-2.67)	0.001	1.13 (0.65-1.97)	0.67	1.43 (1.07-1.92)	0.02	1.32 (0.97-1.79)	0.08
Other	1.41 (1.17-1.70)	0.0003	0.87 (0.68-1.12)	0.28	1.17 (1.02-1.35)	0.03	1.08 (0.93-1.26)	0.30
AML subtype (FAB) (M0-M7 *vs.* other)	1.08 (0.88-1.32)	0.46	1.04 (0.82-1.32)	0.76	1.16 (1.01-1.34)	0.05	1.15 (0.99-1.34)	0.07

*HR: hazard ratio; CI: confidence interval; WBC: white blood cell count; CR: complete remission; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; GvHD: graft-*versus*-host disease; FAB: French-American-British Classification.*

between 1995 and 2010, and known cytogenetics. A total of 11,001 patients were identified. Data were provided and approved for this study by the Institutional Review Board of the Acute Leukemia Working Party (ALWP) of the EBMT group registry. This a voluntary working group of more than 500 transplant centers that are required to report all consecutive stem cell transplantations and follow-up visits once a year. Audits are routinely performed to determine the accuracy of the data. Since 1990, patients have been providing informed consent authorizing the use of their personal information for research purposes. The participating centers are listed on the *Online Supplementary Appendix*.

Cytogenetic categories

Cytogenetics was based on local reports. All cytogenetic data were reviewed by 2 of the authors (AVMBN, JE) according to the European LeukemiaNet.[1] Patients with two or more autosomal chromosome monosomies or a single autosomal monosomy in the presence of at least one other structural chromosomal abnormality, excluding those patients with unidentified marker chromosomes, were assigned to the MK group (as defined by Breems *et al.*[5]) while the remainder of patients were assigned to the non-MK group. Two additional cytogenetics categories were distinguished within the unfavorable risk group, namely AML with a complex karyotype (CK) and other poor-risk cytogenetic entities (OP). CK was defined as the presence of three or more structural chromosomal abnormalities in the absence of a recurrent cytogenetic abnormality.[1,2] OP comprised the following cytogenetic abnormalities: t(3;3)(q21;q26) or inv(3q)/EVI1 rearrangement, t(6;9)(p23;q34)/*DEK-NUP*214, del5q/-5, del7q/-7, t(1;22)(p13;q13), MLL rearrangement and t(9;22)/BCR-ABL.[1,9] Those cases with insufficient information to be cytogenetically assigned were excluded from the analysis and those not fulfilling criteria for MK, OP or CK were defined to have intermediate risk (IR). Overall, 4635 patients met the inclusion criteria and were included in the study.

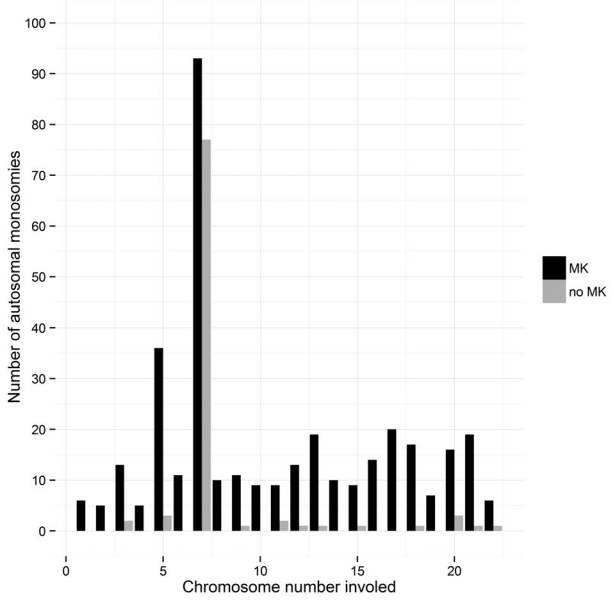

Figure 1. Distribution of autosomal monosomies within the study group.

Statistical analysis

The probabilities of overall survival (OS), leukemia-free survival (LFS), relapse incidence (RI), and non-relapse mortality (NRM) were the primary study end points. LFS was defined as time interval from alloHSCT until either relapse or death in months, and was calculated using the Kaplan-Meier estimate. NRM was defined as death in the absence of relapse. RI and NRM were calculated using cumulative incidence curves in a competing risks setting, death in remission being treated as a competing event to relapse and relapse in the NRM estimation setting, respectively.[10] Univariate analyses were performed using log rank test for OS and LFS while Gray's test was applied for RI and NRM. Patient-, disease-, and transplant-related variables of both groups were compared, using the χ^2 test for categorical and the Mann-Whitney test for continuous variables. Variables considered were: recipient age, sex, disease characteristics [FAB classification, white blood count

Table 3. Multivariate analysis among patients with a monosomal karyotype acute myeloid leukemia (n=189).

	P	HR	95% CI		% at 5 years
LFS					
Poor-risk cytogenetics					
No (reference)		1.00			34.3 (18.3-51.4)
Monosomy 7	0.04	1.85	1.02	3.38	18.2 (7.7-28.8)
Other poor-risk	0.07	1.69	0.95	2.98	20.1 (11.6-28.6)
Age					
<35 (years)					46.2 [29.5-62.8]
[35-60] *vs.* <35 (years)	0.005	2.16	1.26	3.69	19.8 [12.2-27.3]
≥60 (years) *vs.* [35-60]	0.12	1.55	0.89	2.67	10.3 [0-21.4]
Interval diagnosis-CR1>median (53d)	0.71	1.07	0.74	1.55	18.3 (9.6-27)
Donor (UD *vs.* HLA-id sibling)	0.55	1.10	0.77	1.62	23.3 (13.7-32.8) *vs.* 24.1 (15.7-32.5)
Conditioning intensity (RIC *vs.* MAC)	0.13	0.71	0.45	1.1	16.6 (6.9-26.2) *vs.* 27.9 (19.5-36.4)
RI					
Poor-risk cytogenetics					
No (reference)		1.00			46.6 (28.4-62.8)
Monosomy 7	0.06	2.11	0.98	4.54	62.2 (47.4-73.9)
Other poor-risk	0.07	1.97	0.95	4.09	59 (47.8-68.6)
Age					
<35 (years)					45.5 [28.2-61.3]
[35-60] *vs.* <35 (years)	0.05	1.89	1.0	3.58	57.6 [47.8-66.3]
≥60 (years) *vs.* [35-60]	0.33	1.4	0.71	2.79	65.5 [44.2-80.3]
Interval diagnosis-CR1>median (53d)	0.62	0.95	0.61	1.49	54 (42.3-64.3)
Donor (UD *vs.* HLA-id sibling)	0.64	1.11	0.71	1.75	52 (40.1-62.6) *vs.* 59.2 (48.9-68.1)
Conditioning intensity (RIC *vs.* MAC)	0.36	0.78	0.45	1.34	66.8 (52.9-77.4) *vs.* 51.1 (41.3-60)
NRM					
Poor-risk cytogenetics					
No (reference)		1.00			18.6 [9.5-30]
Monosomy 7	0.89	1.08	0.36	3.25	19.6 [10.2-31.1]
Other poor-risk	0.98	1.01	0.36	2.84	20.9 [11.2-32.6]
Age					
<35 (years)					8.3 [0.8-27.6]
[35-60] *vs.* <35 (years)	0.02	5.4	1.24	23.4	22.6% [5.6-46.3]
≥60 (years) *vs.* [35-60]	0.57	1.39	0.45	4.31	24.1 [6.4-47.9]
Interval diagnosis-CR1>median (53d)	0.15	1.73	0.82	3.64	27.7 [18.4-37.7]
Donor (UD *vs.* HLA-id sibling)	0.20	1.60	0.78	3.29	24.7 [17-33.2] *vs.* 16.7 [10.4-24.4]
Conditioning intensity (RIC *vs.* MAC)	0.16	0.52	0.21	1.29	16.7 [10.5-24.1] *vs.* 21 [14-28.9]
OS					
Poor-risk cytogenetics					
No (reference)		1.00			34.3 (17.8-50.9)
Monosomy 7	0.10	1.65	0.9	3.03	22 (10.9-33.1)
Other poor-risk	0.33	1.33	0.75	2.37	22.1 (13.2-31.1)
Age					
<35 (years)					48.7 [32-65.4]
[35-60] *vs.* < 35 (years)	0.007	2.1	1.23	3.6	22.7 [14.9-30.6]
≥60 (years) *vs.* [35-60]	0.53	1.74	0.99	3.05	10.3 [0-21.4]
Interval diagnosis-CR1>median (53 d)	0.34	1.2	0.83	1.74	20.3 (11.3-29.3)
Donor (UD *vs.* HLA-id sibling)	0.35	1.19	0.82	1.73	23.9 (14.2-33.6) *vs.* 27.6 (18.9-36.3)
Conditioning intensity (RIC *vs.* MAC)	0.05	0.63	0.39	0.99	22.5 (12.4-32.7) *vs.* 28.2 (19.5-36.8)

RI: relapse incidence; NRM: non-relapse related mortality; LFS: leukemia-free survival; OS: overall survival; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; CK: complex karyotype; OP: other poor-risk cytogenetics; ID sibling: HLA identical sibling; UD: unrelated donor.

(WBC) at time of diagnosis, interval from diagnosis to CR1 in days], donor characteristics (age, sex) and transplant characteristics (including type of donor, conditioning, and source of stem cells). Factors differing in distribution between the two groups with $P<0.15$ were included in the final models. We also performed a separate analysis of MK patients to determine prognostic factors associated to patient, donor and transplant characteristics in this subgroup.

For all prognostic analyses, continuous variables were first categorized into five categories according to the quintiles. If there was no substantial difference in relative event rates between two or more adjacent categories, these categories were grouped. Otherwise, the median was used as a cut-off point.

Associations of MK with outcomes were evaluated in multivariate analyses, using Cox proportional hazards model including time-dependant variables.

All tests were two-sided. The type I error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analyses were performed with SPSS 19 (SPSS Inc., Chicago, USA) and R (R Development Core Team, Vienna, Austria) software packages.

Results

Patients' characteristics

From a total of 4635 patients 189 (4%) harbored a MK. Basic characteristics of this group are listed in Tables 1 and 2, compared to the remaining 4446 patients. Patients with MK were older (median age 45 years for non-MK *vs.* 48.5 years for MK; $P=0.007$), presented with a lower white blood cell count (WBC) at diagnosis ($12.9x10^9$/L for non-MK *vs.* $4.6x10^9$/L for MK; $P<0.0001$), presented with a higher proportion of FAB AML subtype M0 (7% for non-MK (n=296) *vs.* 15% for MK (n=23); $P<0.0001$) and required a longer interval to achieve CR1 (46 days for non-MK *vs.* 53 days for MK; $P=0.008$), indicative of a higher proportion of patients with an MK AML who required more than one induction course to achieve CR1 (41% among MK *vs.* 31% among non-MK; $P=0.01$).

Cytogenetic features

Two-thirds of patients with an MK also harbored a CK, and 82% of MK had a karyotype fulfilling criteria for OP

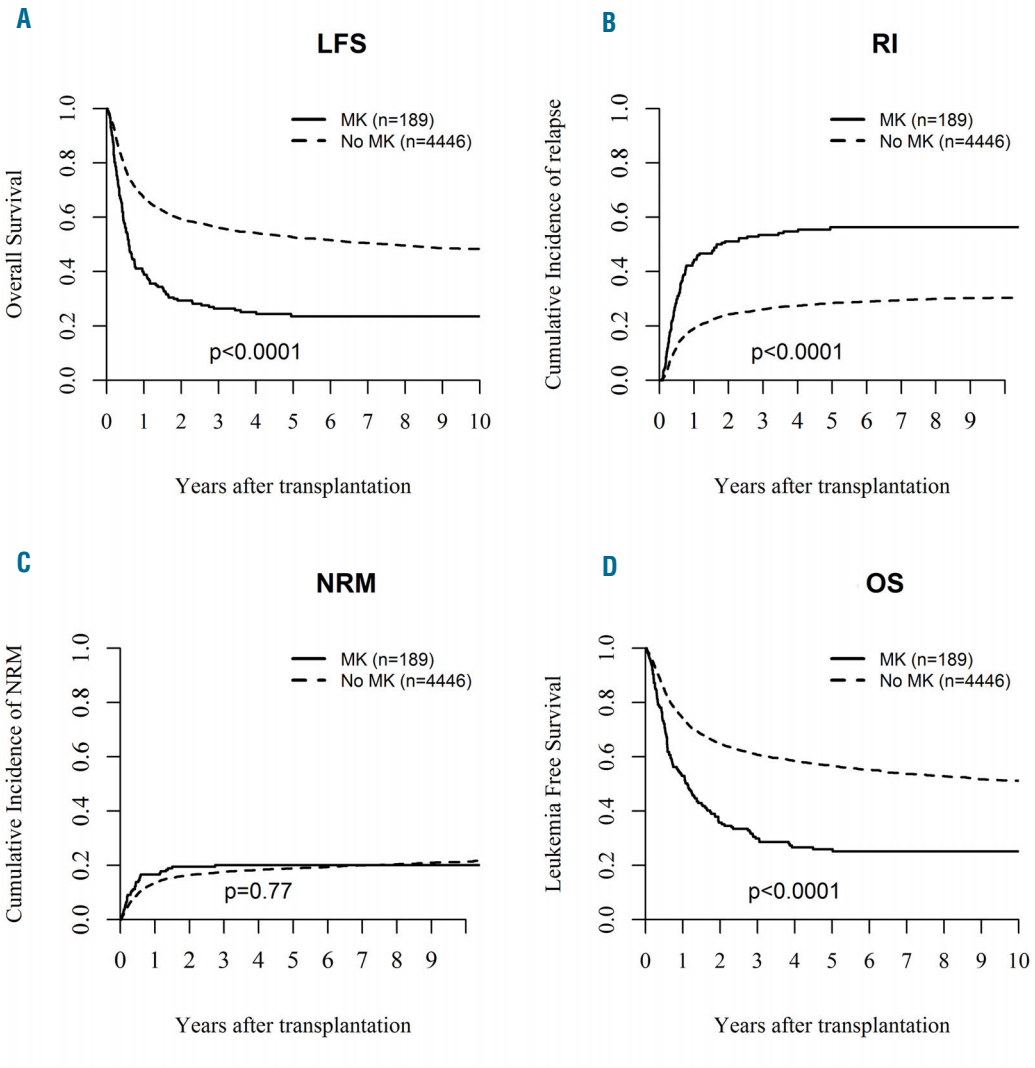

Figure 2. Outcome after alloHSCT in patients harboring a monosomal karyotype compared to other cytogenetic abnormalities. (A) Leukemia-free survival (LFS). (B) Relapse incidence (RI) after alloHSCT. (C) Non-relapse mortality (NRM). (D) Overall survival (OS) after alloHSCT.

as described in the Methods section. On the contrary, 58% of the CK AML patients did not correspond to MK and MK only represented a minority (15%) of OP. The distribution of autosomal monosomies present in both MK and non-MK patients is shown in Figure 1. In MK patients, monosomy 7 was the most frequent (93 patients, 24.3%), followed by monosomy 5 (39 patients, 10.2%), 17 (24 patients, 6.3%), 13 (22 patients, 5.7%), and monosomies of chromosomes 18 and 20 (both 18 patients, 4.7%). In non-MK patients, monosomy 7 was also the most frequent (80 patients, 68.4%), followed by monosomy 5 (5 patients, 4.3%), monosomy 11 and 20 (both 4 patients, 3.4%), and monosomy 21 (3 patients, 2.6%).

Outcome after alloHSCT

Median follow up of patients was 75 months (range 1.2-235) and median year of transplant was 2005. Five-year probability of LFS in MK and non-MK patients was 24±3% and 53±1%, respectively (P<0.0001) (Figure 2A). Cumulative incidence of relapse at five years was markedly increased in MK, with 56±4% *versus* 28±1% in non-MK (P<0.0001) (Figure 2B), whereas there was no difference in NRM between the two groups (5-year NRM: 20±3% for MK and 19±1% for non-MK; P=0.77) (Figure 2C). MK patients also experienced a shorter survival after alloHSCT, with OS at five years of 26±3% for MK *versus* 57±1% for non-MK (P<0.0001) (Figure 2D). In the subgroup of patients with CK, 5-year OS was significantly decreased in MK (n=130), with 27.1% *versus* 51.8% in patients without MK (n=182, 51.8%; P<0.0001). Similarly, in this subgroup of patients, LFS was significantly decreased in patients with MK, with 24.1% compared to 45% in patients without MK (P<0.0001).

In order to analyze the impact of MK on outcome, a multivariate analysis was performed including the following covariates: age, FAB subtype, WBC at diagnosis, interval from diagnosis to CR, donor type, conditioning intensity, diagnosis, GvHD (acute and chronic) and cytogenetic categories (including separately MK, CK and other cytogenetics, which was categorized into 3 classes: non-OP, monosomy of chromosome 7, and OP subtypes). MK was an independent adverse prognostic factor in multivariate

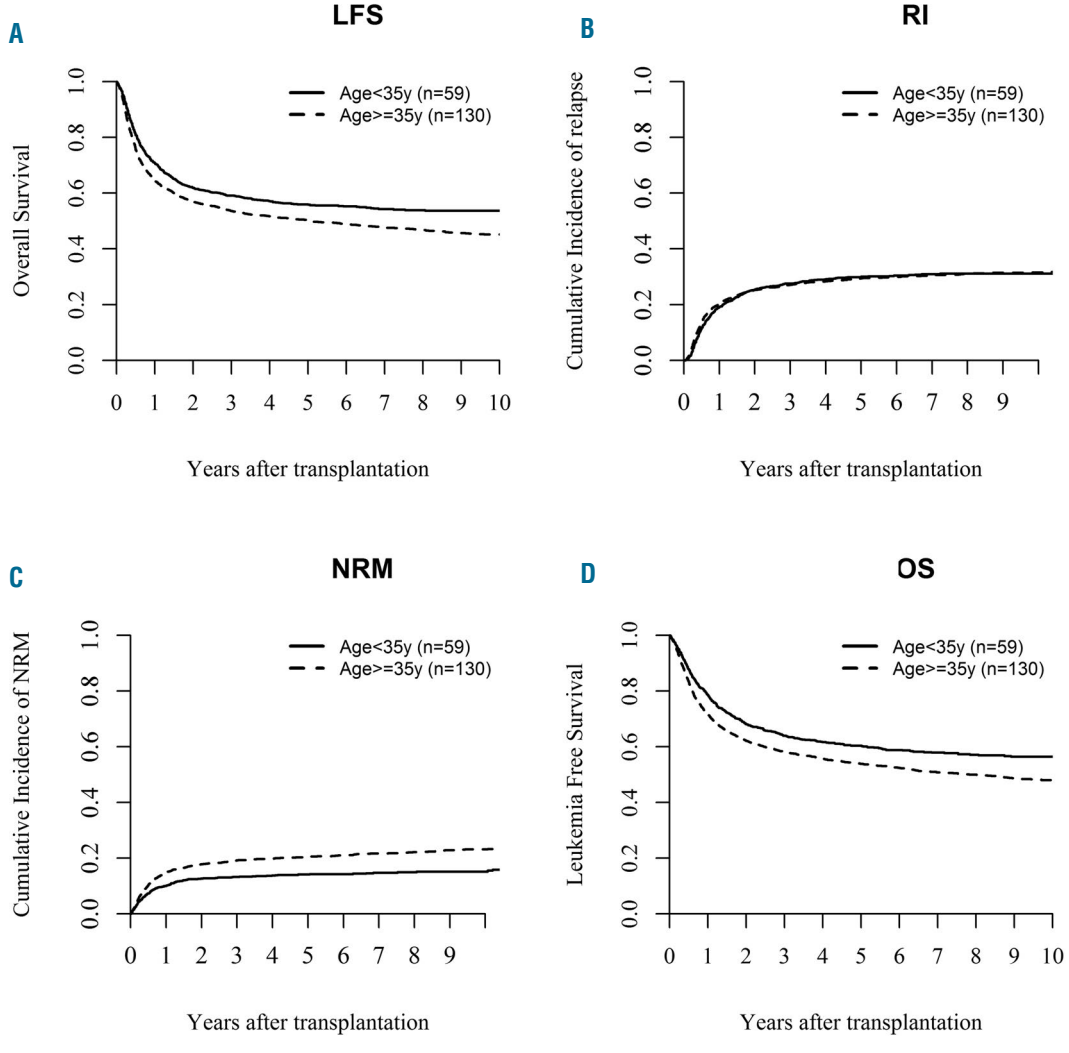

Figure 3. Outcome after alloHSCT among patients with MK-AML according to age. (A) Leukemia-free survival (LFS). (B) Relapse incidence (RI) after alloHSCT. (C) Non-relapse mortality (NRM). (D) Overall survival (OS) after alloHSCT.

analysis for LFS (HR: 1.71, 95%CI: 1.27-2.32; *P*<0.0001), RI (HR 1.88, 95%CI: 1.29-2.73; *P*=0.001) and OS (HR: 1.81, 95%CI: 1.32-2.48; *P*=0.0002). Remarkably, the adverse impact of MK was independent of the presence of a CK and OP. Details of other prognostic factors in multivariate analysis are shown in Table 2.

Prognostic factors among MK patients

After confirming the negative prognostic impact of MK in the entire cohort, we performed a separate analysis of MK patients to determine the prognostic effect of additional variables. A total of 189 MK patients were identified in this cohort. The results of the multivariate analysis are summarized in Table 4. After adjustment, the only factor significantly associated with OS, NRM, RI and LFS was age, with a more favorable outcome among the subgroup of 37 patients under 35 years of age (Table 3 and Figure 3). A comparison of the main characteristics of MK patients under and over 35 years of age is indicated in *Online Supplementary File 2.*

Discussion

This analysis confirms the negative prognostic impact on survival of the well-recognized high-risk cytogenetic subcategory of MK also in patients who undergo alloHSCT in CR[1,7] mainly due to a high relapse incidence observed after transplant (over 50% at 5 years). The detrimental effect of MK on outcome was independent of other variables, including the presence of other known adverse cytogenetics features such as monosomy 7 and CK, supporting the recognition of this entity as a challenging subgroup of patients with distinct biological and clinical features. Therefore, the prognosis of patients with a CK was significantly worse in the subgroup of patients with both CK and MK compared to patients with CK alone. Nonetheless, alloHSCT in early phase still represents the best available option for this very high-risk group of patients, providing a long-term response for a significant subgroup, not observed with other approaches.[6]

Despite the overall unfavorable results associated with MK, the outcome of this cohort of patients transplanted in CR1 seems to be improved compared to those transplanted in a more advanced phase or who do not receive an alloHSCT, with a long-term LFS plateau of 24% possibly indicative of the curative potential of an alloHSCT in a fraction of these patients.[11] Moreover, this observation emphasizes the importance of increasing the proportion of MK patients who achieve CR1 and who could benefit from an alloHSCT in this early phase. In this regard, a subanalysis of the results from the HOVON/SAKK trial addressing the effect of higher doses of cytarabine in induction and consolidation (200 mg/m^2 for 6 days in induction and 1000 mg/m^2 for 5 days in first consolidation *vs.* high-dose cytarabine, 1000 mg/m^2 for 6 days in induction and 2000 mg/m^2 for 4 days in first consolidation) showed a better outcome in the subgroup of younger MK-AML patients who received higher cytarabine dose, with an increase in event-free survival and OS at five years from 0% to 13% and 0% to 16%, respectively.[12] In contrast, a similar study from the same group comparing escalated dose of daunorubicin (90 mg/m^2 for 3 days *vs.* 45 mg/m^2 for 3 days in induction) in patients over 60 years of age, was not associated with a statistically improved outcome in the MK subgroup.[13]

These findings support the design of specific studies aimed to identify that combination of induction chemotherapy associated with the highest initial CR rate for this subgroup of patients with MK that could increase the proportion of the patients who could benefit from an alloHSCT. Our analysis here, however, is based on a highly selected patient population of patients who have reached CR1 and who were suitable for an alloHSCT in the setting of a matched donor being available. Therefore, the incidence of MK identified in this large population of allografted patients (4%) is lower than that previously reported in unselected AML populations (16%-37% depending on age).[4] Given the high relapse incidence in MK patients, and the higher number of induction courses necessary for reaching CR1 compared to other cytogenetic groups (41% of MK patients required more than one induction course to achieve CR), the majority of MK patients are obviously not able to reach alloHSCT or are transplanted in a more advanced phase. The outcome of alloHSCT for MK patients in more advanced phase was analyzed in a study by the AML Study Group which showed a very poor prognosis, with only 5 out of 46 patients undergoing alloHSCT not in CR being alive at two years after the procedure. These results emphasize the importance of improving the efficacy of pre-transplant therapy in this AML subtype to increase the proportion of patients who can ultimately benefit from an alloHSCT.[14]

Other measures that can be implemented to reduce the relapse risk are optimization of the conditioning regimen and development of post-transplant strategies aimed at preventing relapse. Myeloablative regimes are associated with a lower relapse risk, although this beneficial effect, coupled with a higher NRM among more intensive regimens, does not translate into a neat clinical benefit in more heterogeneous high-risk groups. Therefore, implementation of novel regimes maintaining the anti-leukemic effect of more intensive conditioning schemes but with reduced toxicity are warranted. Potential post-transplant intervention that could result in a reduced relapse incidence are the administration of prophylactic or pre-emptive donor lymphocyte infusion (DLI), or the use of azacitidine maintenance.[15]

In conclusion, the presence of a monosomal karyotype is associated with a worse outcome compared to other cytogenetic abnormalities in patients undergoing alloHSCT in CR1, with a high relapse risk after transplantation and a durable response only in approximately one-quarter of patients. Improvement of induction regimens, conditioning regimens and post-transplant treatment for prevention of relapse is warranted in this high-risk group of patients, in order to improve the number of patients that can benefit from alloHSCT and therefore improving outcome.

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