Prognosis of acute myeloid leukemia harboring monosomal karyotype in patients treated with or without allogeneic hematopoietic cell transplantation after achieving complete remission

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ABSTRACT

To evaluate the prognostic impact of monosomal karyotype on post-remission outcome in acute myeloid leukemia, we retrospectively analyzed 2,099 patients who had achieved complete remission. Monosomal karyotype was noted in 73 patients (4%). Of these, the probability of overall survival from first complete remission was 14% at four years, which was significantly lower than that reported in patients without monosomal karyotype, primarily due to a high relapse rate (86%). Monosomal karyotype remained significantly associated with worse overall survival among patients with unfavorable cytogenetics or complex karyotype, and even in patients who underwent allogeneic hematopoietic cell transplantation during first complete remission. These findings confirm that monosomal karyotype has a significantly adverse effect on post-remission outcome in patients with acute myeloid leukemia treated with and without allogeneic hematopoietic cell transplantation in first complete remission, emphasizing the need for the development of alternative therapies for this patient population.

Key words: acute myeloid leukemia, monosomal karyotype, cytogenetics, post-remission therapy, allogeneic hematopoietic cell transplantation.

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease that includes subsets with distinct biological, clinical and prognostic features. It has been well established that cytogenetic abnormalities at diagnosis are associated with the biology of the disease and have important prognostic implications.[1-3] The coexistence of multiple cytogenetic abnormalities designated as complex karyotype (CK) has been recognized as a factor that predicts an extremely unfavorable outcome in AML.[4-7] However, the prognostic significance of CK has recently been challenged by Breems *et al.* who showed that the monosomal karyotype (MK), defined as 2 or more distinct autosomal monosomies or a single autosomal monosomy in the presence of other structural abnormalities, adversely affects the prognosis, and that the overlap of MK with CK is the main contributor to the unfavorable impact of CK.[8] According to Breems *et al.* and reports published subsequently by other groups,[7-10] patients with MK$^+$ AML show low complete remission (CR) rates ranging from 18% to 48% and overall survival (OS) rates of less than 10%. On the other hand, it has been suggested that such a poor outcome may be improved by allogeneic hematopoietic cell transplantation (HCT).[11]

To further clarify the prognosis of patients with MK$^+$ AML, especially regarding outcome after allogeneic HCT during first CR (CR1), we performed a retrospective analysis by using a dataset that included more than 2,000 AML patients in CR. Since failure to achieve CR is obviously associated with a dismal prognosis regardless of the presence or absence

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of MK, the present analysis focused on patients who achieved CR with one or two courses of chemotherapy.

Design and Methods

Patients

For this study, we used a Japanese nationwide database of adult AML patients. Eligible patients were required to be between 16 and 70 years of age, to be diagnosed with AML from 1999 to 2006 according to the World Health Organization (WHO) classification,[12] and to have achieved CR with one or two courses of chemotherapy. We excluded patients with acute promyelocytic leukemia (n=386) and those without pre-treatment cytogenetic results (n=36); this left 2,099 patients available for analysis. This study was approved by the Institutional Review Board at the National Cancer Center Hospital.

Cytogenetic analysis

Cytogenetic analysis was performed on metaphases from samples of bone marrow or blood obtained prior to induction therapy by using standard banding techniques. Karyotypes were determined according to the International System for Human Cytogenetic Nomenclature.[13] An abnormality was considered to be clonal when at least 2 metaphases had the same aberration in the case of either a structural abnormality or an additional chromosome. If there was a monosomy, it had to be present in at least 3 metaphases to be considered significant. Cytogenetics was classified as favorable, intermediate, unfavorable or unknown risk according to the Southwest Oncology Group (SWOG) criteria.[5] Apart from the SWOG classification, the MK status was assessed retrospectively for this study according to the definition proposed by Breems *et al.*[8] Accordingly, patients were divided into 4 cytogenetic subgroups: core binding factor AML (CBF AML), cytogenetically normal AML (CN AML), cytogenetically abnormal non-CBF AML without MK (MK^- AML), and cytogenetically abnormal non-CBF AML with MK (MK^+ AML).

Statistical analysis

A Kaplan-Meier survival analysis was performed to estimate the probabilities of OS and relapse-free survival (RFS). OS was defined as the time from the achievement of first CR (CR1) to death or last visit, and RFS as the time from the achievement of CR1 to relapse, death or last visit. Differences in OS and RFS between groups were compared by means of the log rank test. Cumulative incidences of relapse and non-relapse mortality were calculated with relapse considered as a competing risk for non-relapse mortality, and vice versa. Cox's regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were performed with the SPSS software version 11.0.1 (SPSS, Chicago, IL, USA) and R software version 2.13.0 (The R Foundation for Statistical Computing).

Results and Discussion

The entire cohort consisted of 2,099 AML patients who had achieved CR with one or two courses of chemotherapy, among whom CBF AML, CN AML, MK^- AML and MK^+ AML accounted for 21%, 49%, 27% and 4%, respectively. Table 1 shows the patients' characteristics according to these cytogenetic subgroups. Among the 73 patients with MK^+ AML, 68 (93%) had a cytogenetically unfavorable risk, while the remaining 5 had an unknown risk. In patients younger than 60 years, intensive therapy defined as "3+7" or its equivalent, was given to more than 95% in all of the cytogenetic subgroups. In patients aged 60 years or older, the proportion of those given intensive therapy seemed slightly lower in MK^+ AML but, nevertheless, 75% of them received intensive therapy.

Allogeneic HCT was performed in 32 patients with MK^+ AML, including 15 during CR1, 4 during second CR (CR2) and 13 during other disease phases. The details of patients who underwent allogeneic HCT in CR1 are summarized in the *Online Supplementary Table S1*. The median time from CR1 to transplantation was 93 days (range 14-540 days) for the 15 patients with MK^+ AML, which was significantly shorter than those in the other groups (P=0.011).

Figure 1A compares survival curves from the time of CR1 according to the cytogenetic subgroups. With a median follow up of 4.1 years for surviving patients, the 4-year probabilities of OS were 68% in CBF AML, 58% in CN AML, 46% in MK^- AML and 14% in MK^+ AML, respectively (P<0.001). This significantly inferior OS in MK^+ AML patients can mainly be explained by a high risk of relapse, since the relapse rate was 86% at four years, which was significantly higher than those in the remaining groups (P<0.001). No patient with MK^+ AML survived four years without allogeneic HCT, and the difference in OS was more pronounced when patients undergoing allogeneic HCT were analyzed as censored cases (83%, 66%, 54% and 0% at four years in CBF AML, CN AML, MK^- AML and MK^+ AML, respectively; P<0.001).

Next, we examined whether MK identified a very poor prognostic subset within 2 cytogenetically distinct subpopulations representing poor prognosis, i.e. unfavorable cyto-

Table 1. Patient's characteristics according to cytogenetic subgroup.

	CBF n=437	CN n=1,027	MK- n=562	MK+ n=73
Age, years				
Median	45	51	48	53
Range	16-70	16-70	16-70	20-70
Sex				
Male	279 (64%)	576 (56%)	311 (55%)	47 (64%)
Female	158 (36%)	451 (44%)	251 (45%)	26 (36%)
Cytogenetic risk by SWOG				
Favorable	411 (94%)	-	-	-
Intermediate	-	1,027 (100%)	64 (11%)	-
Unfavorable	26 (6%)	-	300 (53%)	68 (93%)
Unknown	-	-	198 (35%)	5 (7%)
WBC count, $\times 10^9$/L				
Median	11.2	13.0	8.5	4.4
Range	0.7-281.2	0.4-40.2	0.3-22.3	0.8-408.0
Dysplasia				
Yes	35 (8%)	220 (20%)	136 (24%)	33 (45%)
No	402 (92%)	807 (80%)	426 (76%)	40 (55%)
N. induction courses				
1 course	378 (86%)	825 (80%)	419 (75%)	56 (77%)
2 courses	59 (14%)	202 (20%)	143 (25%)	17 (23%)
Allogeneic HCT				
CR1	32 (7%)	256 (25%)	183 (33%)	15 (21%)
CR2	78 (18%)	106 (10%)	57 (10%)	4 (5%)
Other disease phase	66 (15%)	125 (12%)	87 (15%)	13 (18%)
Not performed	261 (60%)	540 (53%)	235 (42%)	41 (56%)

CBF: core binding factor AML; CN: cytogenetically normal AML; MK-: cytogenetically abnormal non-CBF AML without monosomal karyotype; MK+: cytogenetically abnormal non-CBF AML with monosomal karyotype; SWOG: Southwest Oncology Group; WBC: white blood cell count; HCT: hematopoietic cell transplantation; CR1: first complete remission; CR2: second complete remission.

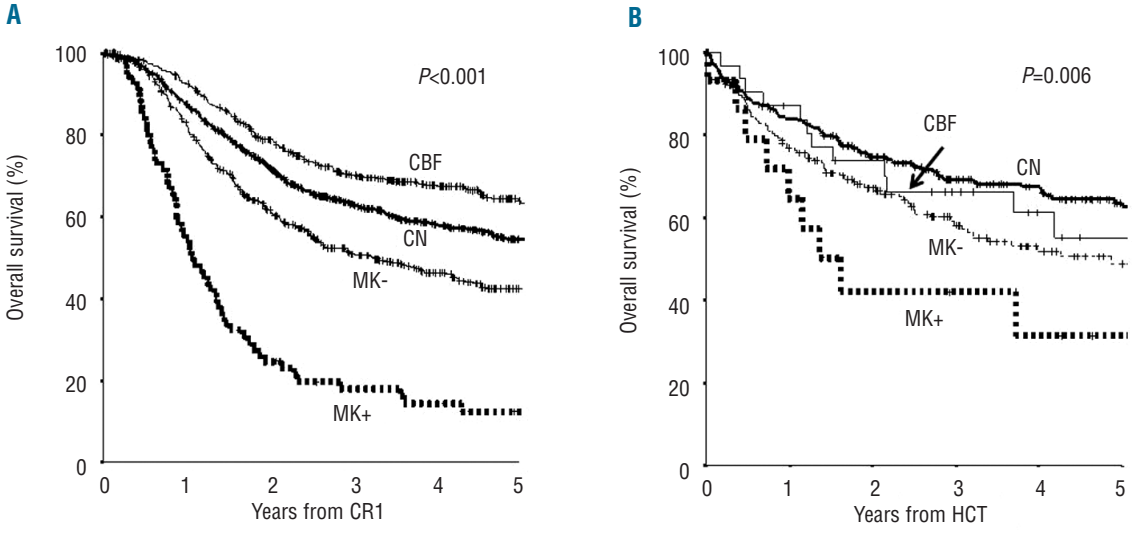

Figure 1. Kaplan-Meier curves for (A) OS after achieving CR1 for the entire cohort, and for (B) OS after allogeneic HCT for patients who underwent allogeneic HCT in CR1, according to the cytogenetic subgroups. CBF represents core binding factor AML; CN: cytogenetically normal AML; MK$^-$, cytogenetically abnormal non-CBF AML without monosomal karyotype; MK$^+$, cytogenetically abnormal non-CBF AML with monosomal karyotype. *P* values are presented for comparisons among the 4 groups.

genetics and CK. MK accounted for 17% of those with unfavorable cytogenetics (68 of 394), and 41% of those with CK (39 of 96). Among patients with unfavorable cytogenetics, there was a statistically significant difference in OS between those with and without MK (16% *vs.* 46% at four years, *P*<0.001; *Online Supplementary Figure S1A*). Similar findings were seen in patients with CK, with 4-year OS rates of 11% and 34% in those with and without MK (*P*<0.001; *Online Supplementary Figure S1B*).

Allogeneic HCT was performed during CR1 in 32 of 437 CBF AML patients (7%), 256 of 1,027 CN AML patients (25%), 183 of 562 MK$^-$ AML patients (33%), and 15 of 73 MK$^+$ AML patients (21%). Figure 1B shows Kaplan-Meier curves for OS after HCT in patients who were transplanted during CR1. These subgroups showed significantly different OS, with 4-year OS rates of 61%, 67%, 52% and 31% in CBF AML, CN AML, MK$^-$ AML, and MK$^+$ AML, respectively (*P*=0.006). A statistically significant difference was observed in terms of post-transplant relapse (*P*=0.025) (*Online Supplementary Table S2*). Non-relapse mortality in patients with MK$^+$ AML appeared to be higher than those in the other groups, but these differences were not statistically significant (*P*=0.595). Table 2 shows results of univariate and multivariate analyses on factors associated with post-transplant OS in patients undergoing allogeneic HCT in CR1. After adjusting for other covariates, MK remained significantly associated with inferior post-transplant OS (HR 3.12; 95% CI, 1.58-6.15; *P*=0.001, with reference to CN AML).

MK is a recently proposed subgroup of cytogenetic abnormalities that confers a very unfavorable prognosis in AML.[8] Reported CR rates have been quite low, ranging between 18 and 48%,[8-10] and this represents a major cause of the poor prognosis. Since patients who fail to achieve CR generally have a very unfavorable prognosis regardless of the presence or absence of MK, we decided to restrict our analysis to patients who had achieved CR. In our patient population, MK was observed in 4%; this was lower than the values reported previously (6-13%).[7-9] The most probable explanation for this could be the fact that our cohort included only patients who had achieved CR, while the other studies included newly diagnosed patients.

Our data clearly demonstrated that MK confers a significantly worse prognosis in patients who have achieved CR. Notably, MK identified patients with a worse prognosis

Table 2. Factors associated with post-transplant OS in patients who underwent allogeneic HCT in CR1.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Cytogenetic subgroup				
CBF	1.14 (0.62-2.09)	0.671	1.17 (0.63-2.15)	0.622
CN	1.00	-	1.00	-
MK$^-$	1.43 (1.05-1.96)	0.023	1.45 (1.06-1.98)	0.021
MK$^+$	2.74 (1.42-5.28)	0.003	3.12 (1.58-6.15)	0.001
Age				
As a numerical variable (1 year older)	1.01 (1.00-1.02)	0.294	1.01 (0.99-1.02)	0.377
Sex				
Male	1.00	-	1.00	-
Female	1.08 (0.81-1.45)	0.597	1.16 (0.86-1.57)	0.327
WBC count				
As a numerical variable (10×10^9/L lower)	1.02 (1.00-1.03)	0.037	1.02 (1.01-1.04)	0.007
Donor				
Related*	1.00	-	1.00	-
Other	1.39 (1.04-1.87)	0.026	1.47 (1.09-1.98)	0.011
Conditioning				
Myeloablative	1.00	-	1.00	-
Reduced-intensity	1.13 (0.81-1.58)	0.465	1.04 (0.70-1.56)	0.846

*HR: hazard ratio; CI: confidence interval; CBF: core binding factor AML; CN: cytogenetically normal AML; MK$^-$: cytogenetically abnormal non-CBF AML without monosomal karyotype; MK$^+$: cytogenetically abnormal non-CBF AML with monosomal karyotype; WBC: white blood cell count. *"Related" indicates a matched or 1 antigen-mismatched family donor.*

even among those with unfavorable cytogenetics or those with CK. The detrimental prognostic impact of MK was primarily due to high relapse rates and, importantly, similar results were seen in patients who received allogeneic HCT in CR1. Post-transplant relapse occurred more than 20% more frequently in MK+ AML patients than in those in each of the remaining cytogenetic subgroups. This finding is consistent with published studies.[11,14] Investigators at the University of Minnesota analyzed 134 AML patients, including 17 patients with MK who were allografted in CR1, and showed that the MK classification could significantly predict the risk of post-transplant relapse.[14] A report from the Fred Hutchinson Cancer Research Center described the outcome of 35 patients with MK and 193 patients without MK who underwent allogeneic HCT in CR1, in which the 4-year OS rates were 30 and 65% in those with and without MK.[11] Those results taken together with our present results suggest that allogeneic HCT may be able to improve but not completely override the poor prognosis with MK+ AML. It is widely recognized that allogeneic HCT in CR1 is the treatment of choice for patients with AML at cytogenetically unfavorable risk,[15-17] if they have a suitable donor and are fit enough to undergo the procedure. In this study, allogeneic HCT was given to only 21% of patients with MK+ AML during CR1. This low transplantation rate could partly be due to a short CR1 duration, which likely decreased the chance of receiving allogeneic HCT in CR1. A significantly shorter time to transplantation in our MK+ AML patients might reflect the short duration of their CR1 that precluded an implementation of allogeneic HCT after a relatively long interval after achieving CR. Despite a considerable risk of relapse even after transplantation, it is still conceivable that these cytogenetically very unfavorable patients would benefit from allogeneic HCT. We observed that no patient survived long-term without allogeneic HCT, which is in line with reports from the SWOG study.[9]

Our study has several limitations and the results must, therefore, be interpreted with caution. These limitations include the retrospective nature of the study, and the relatively small number of patients with MK+ AML, especially of those who underwent allogeneic HCT in CR1, leaving room for selection bias or chance effect. However, given that MK+ AML accounted for only 4% of our AML patients in CR, it would be quite impractical to conduct a prospective comparison to assess the role of allogeneic HCT in CR1. Under such conditions, the findings from a large-scale retrospective study could have important implications.

In summary, our data confirm that MK exerts a significantly adverse effect on post-remission outcome in AML patients treated with and without allogeneic HCT in CR1. Although our results suggest that allogeneic HCT is already an available treatment of choice, the development of alternative therapies is warranted for this patient population.

Authorship and Disclosures

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