

RESEARCH ARTICLE

Monosomal Karyotypes among 1147 Chinese Patients with Acute Myeloid Leukemia: Prevalence, Features and Prognostic Impact

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Abstract

A monosomal karyotype (MK), defined as ≥ 2 autosomal monosomies or a single monosomy in the presence of additional structural abnormalities, was recently identified as an independent prognostic factor conveying an extremely poor prognosis in patients with acute myeloid leukemia (AML). In the present study, after excluding patients with t(15;17), t(8;21), inv(16) and normal karyotypes, 324 AML patients with cytogenetic abnormalities were the main subject of analysis. The incidences of MK were 13% in patients aged 15 to 60 years and 18% in those between 15 and 88 years old. MK was much more prevalent among elderly patients ($p < 0.001$) and was significantly associated with the presence of -7, -5, del(5q), abn12p, abn17p, -18 or 18q-, -20 or 20q- and CK (for all $p < 0.001$ except for abn12p $p=0.009$), and +8 or +8q was less frequent in MK+ AML ($p=0.007$). No correlation was noted between monosomal karyotype and FAB subtype ($p > 0.05$); MK remained significantly associated with worse overall survival among patients with complex karyotype ($p=0.032$); A single autosomal monosomy contributed an additional negative effect in OS of patients with structural cytogenetic abnormalities ($P=0.008$). This report presents the prevalence, feature and prognostic impact of MK among a large series of Chinese AML patients from a single center for the first time.

Keywords: Acute myeloid leukemia (AML) - monosomal karyotype (MK) - Chinese - prevalence - prognosis

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Introduction

Acute myeloid leukemia (AML) is a remarkably heterogeneous group of diseases with regard to clinical presentations, morphological characteristics, immunophenotype, and cytogenetic features. Cytogenetic abnormalities are found in approximately 55% of adult patients with AML and have long been recognized as a significant independent prognostic factor in AML (Mrozek et al., 2004). Several cooperative groups have risk stratified their patients into three main groups according to cytogenetic abnormalities: favorable, intermediate and unfavorable (Slovak et al., 2000; Byrd et al., 2002; Medeiros et al., 2010). Although each cooperative group has a different risk classification scheme, there is general consensus that the presence of t(15;17)(q22;q12), t(8;21)(q22;q22) or inv(16)(p13.1q22)/t(16,16)(p13.1;q22) predicts a relatively favorable outcome and, conversely, that cases of AML where cytogenetic analysis shows inv(3)(q21q26.2)/t(3,3)(q21;q26.2), del(5q), -5, -7 or a complex karyotype with 3 or more abnormalities generally have a very poor prognosis (Medeiros et al., 2010).

Recently, a new prognostic factor of cytogenetic

abnormalities, referred to as monosomal karyotype (MK), has been identified as an independent unfavorable risk factor in AML (Breems et al., 2008). MK-AML, defined as 2 or more autosomal monosomies or a single autosomal monosomy in the presence of additional structural abnormalities, were suggested as a more homogeneous distinguishable subset of AML representative with an extremely poor outcome (Breems et al., 2008). The better predictability of very unfavorable risk AML by the monosomal karyotype in comparison to "complex karyotypes" holds up regardless whether complexity is defined by ≥ 3 or ≥ 5 clonal cytogenetic abnormalities (Breems et al., 2008). Several subsequent investigations confirmed the prognostic value of MK in AML and even other myeloid malignancies including myelodysplastic syndrome (MDS) and primary myelofibrosis (PMF) (Medeiros et al., 2010; Oran et al., 2011; Patnaik et al., 2011; Vaidya et al., 2011). However, most of these observations were from western populations and few systematical research based on large sample sizes from Asian populations was available. The presence of geographic heterogeneity of cytogenetic abnormalities in hematological malignancies has been described

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(Johansson et al., 1991; Nakase et al., 2000; Chen et al., 2005), so the aim of the present study was to investigate the prevalence, feature, and specific prognostic relevance of MK in Chinese AML patients from a single center in China.

Materials and Methods

Patients and treatment protocols

A total of 1381 newly diagnosed AML patients were identified retrospectively from the database of AML between January 2005 and December 2010 at our center. We excluded 234 patients whose cytogenetic analyses were unsuccessful. As one of the largest center of hematology in China, patients from 12 provinces were covered in this study. The study was approved by the Medical Ethical Committee of the First Affiliated Hospital, Soochow University.

All young adult AML patients who were conducted survival analysis received at least two cycles of standard induction therapy consisting of daunorubicin (45mg/m²/day for 3 days) or idarubicin (10mg/m²/day for 3 days) or mitoxantrone (10mg/m²/day for 3 days) and cytarabine (100mg/m²/day for 7 days). In case of complete remission, patients were consolidated with high-dose cytarabine (1-2g/m²/day for 3 days) based combination chemotherapy or stem cell transplantation (SCT). Among 25 MK+CK+ and MK-CK+ AML patients younger than 60 years old, 3 of 13 MK-CK+ cases and 2 of 12 MK+CK+ cases received allogeneic SCT respectively. 7 of 36 young adult AML patients with structural cytogenetic abnormalities and 1 of 6 patients with structural cytogenetic abnormalities plus a single autosomal monosomy were also treated with SCT.

Cytogenetic analysis

Chromosome preparations were performed on bone marrow samples using the standard procedures of conventional R-banding technique. Final karyotypic results were described according to the International System for Human Cytogenetic Nomenclature 2009. An abnormality was considered clone when at least two metaphases had the aberration in case of a structural abnormality or an extra chromosome. For classification as a monosomy, the monosomy had to be present in at least three metaphases. At least 20 bone marrow metaphase cells were analyzed in patients designated as having a normal karyotype. The karyotype analysis was based on 20 or more metaphase cells for more than 85% of patients included in this analysis. Cytogenetic abnormalities were grouped according to published criteria adopted by the Southwest Oncology Group (SWOG) as favorable, intermediate, unfavorable, and unknown (Slovak et al., 2000). Due to the high cost of the procedure, fluorescence in situ hybridization was not performed as a routine analysis.

Statistical analysis

Statistical analyses were carried out using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Pearson Chi-square analysis and Fisher exact test were carried out to compare the difference of categorical variables between

patients groups. Overall survival (OS) was analyzed according to the Kaplan-Meier method and Logrank tests were employed to compare survival curves between groups. For all analyses, the p values were two-tailed and a p value of less than 0.05 was considered statistically significant.

Results

Incidence of cytogenetic abnormalities in Chinese patients with AML

Initially, the frequency of distinct cytogenetic abnormalities in all 1147 newly diagnosed AML patients (between 15 and 88 years of age) was investigated. A normal karyotype was found in 525 patients (45%), while 622 (55%) patients had an abnormal karyotype. 132 patients presented with a core binding factor (CBF) AML, including 118 patients with t(8;21) and 14 patients with inv(16). There were 166 patients presenting with t(15;17). The 324 remaining patients presenting with a variety of cytogenetic abnormalities were the main subject of analysis of the current study. Of these, 197 patients were classified into unfavorable group, 40 patients into intermediate group and 87 patients into unknown risk group according to SWOG criteria (Slovak et al., 2000). A complex karyotype (CK), defined as 3 or more chromosomal abnormalities, was noted in 93 patients (93/324; 28%) and 44 patients had a CK as defined by

Table 1. Distribution of Autosomal Chromosomal Monosomies among 324 AML Patients with Aberrant Karyotype

Type of monosomy	A	B	C	D
-1	2	0	1	1
-2	2	0	1	1
-3	2	0	0	2
-4	2	0	0	2
-5	13	0	4	9
-6	5	1	1	3
-7	34	8	13	13
-8	2	1	1	0
-9	2	0	1	1
-10	1	0	0	1
-11	1	0	0	1
-12	7	0	1	6
-13	6	0	0	6
-14	4	0	1	3
-15	7	0	0	7
-16	6	0	0	6
-17	12	1	3	8
-18	8	0	0	8
-19	2	0	0	2
-20	3	0	0	3
-21	7	1	1	5
-22	1	0	0	1
Total no. (%) of patients	72(22)	12(4)	28(8)	32(10)

A, No. of patients with autosomal chromosomal monosomy; B, No. of patients with 1 monosomy and without other structural abnormality; C, No. of patients with 1 monosomy and at least 1 additional structural abnormality; D, No. of patients with 2 or more autosomal monosomies; All monosomies (isolated or associated) are taken into account, explaining that the total number of monosomies exceeds the total number of patients

Table 2. Baseline Characteristics of the Subset of Cytogenetically Abnormal Patients According to the MK Status (n=324)

	MK-		MK+		p-value
	NO.	%	NO.	%	
Patients with aberrant karyotype ^a	264		60		
Age groups					
30y or younger	64	24	8	13	0.06
31-60y	143	54	23	38	0.02
Older than 60y	57	21	29	48	<0.001
Sex					0.22
Male	159	60	31	51	
Female	105	40	29	49	
Cytogenetic risk					<0.001
intermediate	41	15	0	0	
unfavorable	136	52	60	100	
unknown	87	33	0	0	
Cytogenetic abnormalities					
inv(3)/t(3;3)	4	1	2	3	0.68
-5	0	0	13	21	<0.001
-7	7	2	26	43	<0.001
del(5q)	5	2	13	21	<0.001
del(7q)	13	5	5	8	0.46
t(6;9)	2	1	0	0	1
t(9;22)	20	7	1	1	0.16
+8 or +8q	64	24	5	8	0.007
+11 or +11q	11	4	1	1	0.58
abn11q23	19	7	1	1	0.19
abn12p	7	2	6	10	0.009
+13 or +13q	8	3	2	3	1
abn17p	1	0.4	5	8	<0.001
-18 or 18q-	1	0.4	8	13	<0.001
-20 or 20q-	3	1	7	11	<0.001
+21 or +21q	18	6	1	1	0.22
+22 or +22q	11	4	2	3	1
CK(at least 3 clonal abn.)	45	17	48	80	<0.001
CK(at least 5 clonal abn.)	19	7	25	41	<0.001

^aAML patients with t(15;17) and core binding factor abnormalities were excluded

5 or more chromosomal abnormalities (44/324; 13%). At least 1 autosomal monosomy was observed in 72 patients (72/324; 22%). Monosomal abnormalities involved all 22 autosomes (Table 1). However, the most frequent autosomal monosomies were -7 (n=34) and -5 (n=13) followed by -17 (n=12), -18 (n=8), -12 (n=7) and -15 (n=7). In total, 60 patients (60/324; 18.5%) fulfilled criteria for a MK; Of these, 32 patients had 2 or more autosomal monosomies in the presence or absence of other structural abnormalities and the remaining 28 patients had a single autosomal monosomy plus at least 1 other structural abnormality. Among MK+ patients, monosomies of 7 and 5 were also the most common, with monosomy 7 present in 26 cases of MK and monosomy 5 in 13 respectively.

Patients characteristics according to the MK status

Patient characteristics of both MK negative (MK-) and MK positive (MK+) groups were summarized in Table 2. The proportion of patients with MK+ AML increased with age. Whereas only 11% (8/72) of patients younger than age 30 had a MK, the fraction increased to 33.7% (29/86) for those over age 60. No sex distribution differences

Table 3. Correlation Between FAB Subtypes and Monosomal Karyotype (n=324)

FAB classification	MK-		MK+		p-value
	NO.	%	NO.	%	
Patients with aberrant karyotype ^a	264		60		
M0	2	1	1	1	0.46
M1	33	12	5	8	0.36
M2	52	19	9	16	0.4
M3	5	2	1	1	1
M4	43	16	11	18	0.7
M5	71	26	21	35	0.2
M6	12	4	6	10	0.17
M7	0	0	0	0	
NOS ^b	46	17	6	10	0.15

^aAML patients with t(15;17) and core binding factor abnormalities were excluded; ^bFAB subtype not otherwise specified in record

were noted between MK+ and MK- AML patients. The majority of MK+ patients (80%; 48/60) also had a CK. However, there were discrepancies between presence of MK and CK in 57 patients. Of those patients, 12 MK+ AML patients had no CK and a number of AML patients with CK lacked MK (ie, 45 patients with 3 or more chromosome abnormalities and 19 patients with 5 or more abnormalities). Of other cytogenetically abnormalities, the most frequent abnormalities among MK+ cases were (in order of decreasing frequency): -7(26/60; 43%), -5(13/60; 22%), del(5q)(13/60; 22%), -18 or 18q-(8/60; 13%), -20 or 20q-(7/60; 11%), abn12p(6/60; 10%), abn17p(5/60; 8%), and del(7q)(5/60; 8%). MK+ AML were significantly associated with -7, -5, del(5q), abn12p, abn17p, -18 or 18q-, -20 or 20q- and CK (for all p < 0.001 except for abn12p p=0.009), and they less frequently exhibited +8 or +8q (p=0.007).

Correlation between FAB subtypes and monosomal karyotype

The patients were categorized into FAB subtypes based on morphological diagnoses and the correlation between FAB subtypes and MK status was shown in Table 3. Among MK+ AML patients, the most common FAB subtypes were as follows: M5(21/60; 35%), M4(11/60; 18%), M2(9/60; 16%), M6(6/60; 10%), and M1(5/60; 8%). There was no difference in the distribution of FAB subtypes between MK+ and MK- AML patients (p>0.05).

Prognostic value of MK in relation to complex karyotype

We next determined the prognostic value of MK in CK+ AML patients, since 80% MK+ AML patients also had a CK. In the present study, there were 55 patients younger than 60 years old among 93 CK+ AML patients. 25 MK+CK+ and MK-CK+ young adult AML patients who were treated in our hospital and had follow-up information were considered for survival analysis. The OS of MK+CK+ young adult AML patients was significantly shorter than MK-CK+ cases (p<0.05, Figure 1). The median survival time was 5 months (95% confidence interval 1-8 months, MK+CK+ patients) and 18 months (95% confidence interval 7-28 months, MK-CK+ patients), respectively. With respect to response

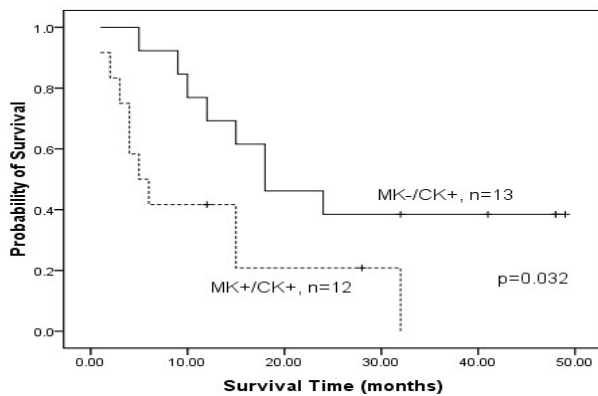


Figure 1. Impact of Monosomal Karyotype in Patients Exhibiting a Complex Karyotype on Survival

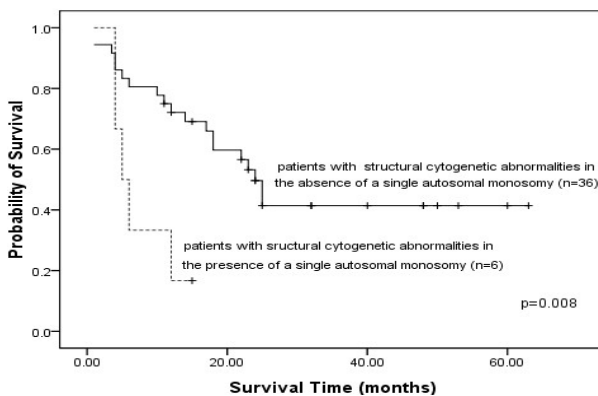


Figure 2. Overall Survival of Young Adult AML Patients with Structural Cytogenetic Abnormalities in the Presence or Absence of a Single Autosomal Monosomy

to induction therapy, 9 of 12 MK+CK+ young adult AML patients couldn't achieve complete remission (CR) whereas the CR rate of MK-CK+ patients was 54% (7/13) (25% VS 54%). Although MK+CK+ patients had an in trend inferior CR rate compared to MK-CK+ patients, the difference was not statistically significant ($p=0.28$).

Prognostic effect of a single autosomal monosomy in presence of structural cytogenetic abnormalities

A single autosomal monosomy plus additional structural abnormalities was regarded as MK with extremely poor outcome. Subsequently, we investigated if the impact of structural chromosomal abnormalities on prognosis also depended on a single autosomal monosomy in Chinese AML population. In our study the OS of 6 young adult AML patients with a single autosomal monosomy plus at least one other structural abnormality (median survival time 5 months, 95% confidence interval 2.6-7.4 months) was also significantly shorter than that of 36 patients with structural cytogenetic abnormalities in the absence of autosomal monosomy (median survival time 24 months, 95% confidence interval 20.6-27.4 months) ($p=0.008$, Figure 2).

Discussion

Cytogenetic risk is one of the most important prognostic factors in AML, predicting the probability of OS and relapse-free survival (RFS). Monosomal

karyotype was initially reported as a new independent unfavorable cytogenetic risk factor in AML patients younger than 60 years old in the Dutch-Belgian Hemato-oncology Cooperative Group/Swiss Group in association with only 4% four-year OS (Breems et al., 2008). This poor prognostic impact on survival of AML patients was validated in another large group of patients, who were treated according to the SWOG protocol (Medeiros et al., 2010). Several reports published subsequently by other groups confirmed patients with MK+ AML show low CR rates ranging from 18% to 48% and OS rates less than 10% (Grimwade et al., 2010; Perrot et al., 2011). It has also been suggested that such a poor outcome may be improved by allogeneic hematopoietic cell transplantation (HCT) (Fang et al., 2011). However, few studies on MK were from Asian populations. Here we contribute MK related data among newly diagnosed AML from a large series of Chinese patients.

Cytogenetic analysis of a total of 1381 newly diagnosed AML patients were performed at our center. A successful analysis rate of 83% and a normal karyotype frequency of 45% were comparable to most published series (Sanderson et al., 2006; Cheng et al., 2009), reflecting the high quality of data in the present study. Initially, we determined the frequency and baseline character of MK in Chinese AML patients. In our study, the incidences of monosomy karyotype were 13% in patients age 15 to 60 years and 18% in patients between 15 and 88 years old, which were obviously lower than those reported by Breems et al. (25.1% in patients age 15 to 60 years) (Breems et al., 2008), SWOG (28.5% in patients between 16 and 88 years old) (Medeiros et al., 2010), Kayser et al. (2012) (30% in patients age 16 to 85 years), and other investigators (Grimwade et al., 2010; Haferlach et al., 2012). This discrepancy might be attributed to two main factors: (1) Compared with many currently published studies on MK, most of which were from large multicenter clinical trials, the present study was from large single-center. Although patient sample sizes were generally large in those cooperative trials, differences in inclusion and exclusion criteria, variation in expertise in karyotypic analysis and culturing techniques existed among different centers. Such heterogeneity could affect data accuracy. However, our large single center study was based on fairly homogeneous populations. (2) Uneven geographic distribution of nonrandom chromosome aberrations in malignant disorders and ethnic differences could be another possible explanation. Recently, Masamitsu Y et al. reported MK was noted in 4% patients of Japanese AML patients who had achieved complete remission (Yanada et al., 2012). Given MK+ AML patients had a lower CR rate than MK- patients, the incidence of MK among newly diagnosed Japanese AML patients might be similar with that in our study. Consistent with previous reports, MK was seen in all age groups and the proportion of MK+ patients increased with age: 11% in patients younger than 30 years, 14% in patients between 30 and 60 years of age, and 34% in patients older than 60 years. There were no differences in sex distribution between MK+ and MK- AML patients. All of MK cases were seen in patients with unfavorable cytogenetics, and MK accounted for

30% (60/197) of patients with unfavorable cytogenetics. MK was significantly associated with the presence of -7, -5, del(5q), abn12p, abn17p, -18 or 18q-, -20 or 20q- and CK, and +8 or +8q was less frequent in MK+, which were concordant with other reports (Medeiros et al., 2010; Kayser et al., 2012). Of all monosomies, -7 was the most frequent. The preponderance of monosomy 7 implicated a pathogenetic role for haploinsufficiency of genes associated with chromosome 7.

Previous studies didn't investigate the correlation between monosomal karyotype and FAB subtype. In our study, we observed M5, M4, M2, M6 were prevalent in MK+ AML patients and there was no difference in the distribution of FAB subtypes between MK+ and MK- AML. Breems et al demonstrated that MK was a better predictor of very poor prognosis than CK and CK lost its prognostic significance when MK was taken into account (Breems et al., 2008). In our study, 25 MK+CK+ and MK-CK+ AML patients younger than 60 years old were considered for survival analysis since age was the independent prognostic factor in AML. We also found that OS in MK+CK+ young adult AML patients was significantly shorter than MK-CK+ group, confirming the prognostic value of MK in CK+ AML patients. Failure to achieve CR is obviously associated with a poor prognosis. We speculated that the dismal outcome of MK+CK+ patients in our study might be partly due to their lower CR rate than MK-CK+ group, although the difference was not statistically significant. In addition, inferior OS of MK+ AML patients can also be explained by a high risk of relapse of AML (Yanada et al., 2012). To further determine the implication of MK in response to induction therapy and RFS, a larger series of cases need to be studied. Consistent with Breems et al (Breems et al., 2008), a single autosomal monosomy contributed an additional negative effect on OS of patients with structural cytogenetic abnormalities in our study. However, to further confirm this result in Chinese AML population, more patients with a single autosomal monosomy plus at least one other structural abnormality need to be investigated.

Besides Breems et al (Breems et al., 2008) and SWOG (Medeiros et al., 2010), a few groups have investigated the prognostic impact of MK status in several clinical conditions. Two recent studies have shown the use of high-dose cytarabine-based regimens may improve the outcome of patients with MK+ AML (Lowenberg et al., 2011; Medelros et al., 2011). Allogeneic SCT was also shown to result in a limited or significant improvement of OS in this subgroup of patients with MK+ in other studies (Fang et al., 2011; Kayser et al., 2012; Cornelissen et al., 2012). On the other hand, there was little insight into the mechanism of MK contributing to dismal prognosis. Some studies implicated that MK in AML associated with high functional multidrug resistance activity or TP53 alterations (Ahn et al., 2012; Rucker et al., 2012). However, these observations need to be further investigated.

In conclusion, our study presents the prevalence, feature and prognostic value of MK in a large cohort of Chinese AML patients for the first time. We confirm that MK-AML represents a new distinct aggregate of cytogenetically abnormal AML, although its frequency

is obviously lower in Chinese patients than in western populations. MK remains significantly associated with worse overall survival among patients with CK, emphasizing the need for new approaches for such patients.

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