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Integrative analysis of prognostic factors in Chinese core binding factor leukemia

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ABSTRACT

The characteristics of core binding factor (CBF) leukemia appear to differ between Chinese and Caucasian patients. In this study, we analyzed the biological and clinical characteristics of 76 Chinese CBF leukemia patients out of 425 newly diagnosed acute myeloid leukemia (AML) patients. The frequency of CBF AML was 17.9%. Patients harboring t(8;21) were predominant in CBF AML. The incidence of c-kit mutation in CBF AML was 28.9%. The N822K mutation appeared to be more prevalent in Chinese CBF AML patients. Multivariate analysis showed that c-kit mutation and high white blood cell count could negatively impact overall survival (OS) (HR = 2.74 and 6.24, $P = 0.007$ and 0.022, respectively) but did not affect relapse-free survival (RFS). Kaplan–Meier analysis showed a significant difference in both OS and RFS between wild-type and mutated c-kit patients. Although we had included recently reported prognostic indicators in our analysis, our results demonstrated that only c-kit mutation and high white blood cell count had prognostic impact on Chinese CBF AML patients.

1. Introduction

The chromosome translocation t(8;21) and the inversion (inv)16/t(16;16) are categorized as core binding factor (CBF) acute myeloid leukemia (AML). The alterations generate fusion proteins, AML1-ETO and CBFβ-MYH11, that disrupt the α and β subunits of the CBF complex, respectively, and result in impaired hematopoietic differentiation [1,2]. CBF AML is classified as a specific AML subtype because of not only its characteristic molecular origin but also its relatively favorable outcome compared to other non-acute promyelocytic leukemia AML subtypes [3,4]. The overall 5-year survival rate in CBF AML is over 50% when treated with high-dose cytarabine-based chemotherapy; therefore, currently, chemotherapy is the first-line treatment option for CBF AML [5,6].

Importantly, non-Caucasian populations have been regarded as one of the adverse prognostic factors in CBF AML [7]. However, until now, most reports on non-Caucasian CBF AML have been performed in the African–American population, while the prognosis of Chinese CBF AML patients remains controversial. For example, the 2-year survival of Chinese CBF AML patients in different medical centers ranges from 36.2% to 74.8% [8–10]. These studies have raised the concern of whether Chinese CBF AML has a distinct disease pattern.

Several factors are considered to have a prognostic impact on CBF AML. The most well-established risk factor is mutation of the c-kit gene [11,12]. The major forms of c-kit mutation in CBF AML are point mutations in exon 17 or small deletions/insertions in exon 8. These mutations give rise to constitutively activated receptor tyrosine kinase or hyperactivation, respectively, and are associated with the adverse prognosis of CBF AML [13–15]. In addition, aging (60 years or older) and the high expression of an alternative splice isoform, AML1-ETO9a, were documented as unfavorable prognostic indicators [10,16]. In recent years, there have been significant advances in defining genetic markers as risk stratification methods to distinguish subgroups of AML [17]. Despite the rapid advances in CBF AML therapy and risk stratification, there are limited integrative data of Chinese CBF AML available. In this study, we examined clinical features, cytogenetics, and molecular abnormalities from 2 Chinese medical centers to identify the characteristics of Chinese CBF AML patients.

2. Materials and methods

2.1. Patients and treatment

From January 2008 to December 2010, 425 patients were diagnosed with de novo AML according to the French–American–British (FAB) criteria in 2 Chinese hematological centers: Tongji Hospital in Wuhan and Jiangsu Province Hospital in Nanjing. The diagnosis of CBF AML was based on cytogenetic findings of karyotype t(8;21) and inv(16) or detection of the fusion transcripts

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AML1-ETO and CBFβ-MYH11 by reverse transcription polymerase chain reaction. Related clinical parameters were collected for data analysis. All patients received induction therapy with cytarabine (100–200 mg/m^2/d for 7 days) in combination with daunorubicin (40–60 mg/m^2/d for 3 days). The post-remission therapy consisted of 3 or more courses of the administration of cytarabine 0.5–3 g/m^2 every 12 h on days 1–3. This study was approved by the ethics board of the two hospitals.

2.2. Detection of genetic mutations

Bone marrow aspirate was collected before treatment, and mononuclear cells were isolated by Ficoll density gradient centrifugation. Genomic DNA was prepared using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Exon 8 of the c-kit gene was amplified using the primer pair F: 5′-GCT GAG GTT TTC CAG CAC TC- 3′ and R: 5′-AAT TGC AGT CCT TCC CCT CT-3′, and exon 17 was amplified using the primer pair F: 5′-TGA ACA TCA TTC AAG GCG TA-3′ and R: 5′-TCA CATG CCC CAA AAT TAC A-3′. The PCR products were subjected to direct DNA sequencing to detect mutations. Absolute quantitative PCR using a TaqMan® probe (ABI, Carlsbad, CA, USA) was employed to screen the common mutation types of NPM1, as previously reported [18]. The detection of CEBPα and WT1 mutations was performed by PCR amplification and subsequent sequencing as described previously [19,20]. FLT3-ITD was screened using 3% agarose gel electrophoresis of the PCR product spanning exons 14 and 15 [21]. Other mutations, including DNMT3A, N-RAS, K-RAS, IDH1, IDH2 and FLT3-TKD, were screened for point mutations by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). The c-kit mutations D816V and N822K were also validated by the more sensitive MALDI-TOF MS.

2.3. Statistical analysis

The analysis of categorical variables was performed using Fisher's exact test for 2×2 tables or Pearson's χ^2 test. Student's t test and the Mann–Whitney U test were applied to continuous variables. Complete remission (CR) was defined as bone marrow morphology with less than 5% blasts, a neutrophil count of 1×10^9 L^{-1} or more, a platelet count of 100×10^9 L^{-1} or more, and no evidence of extramedullary leukemia. Patients lost to follow-up were censored at the date of last contact. Multivariate models using Cox or logistic regression analysis were employed to assess the hazard ratios and odds ratios of patient characteristics on survival and CR. Differences in survival were compared using the log-rank test and estimated by the Kaplan–Meier method. All calculations were performed using SPSS Software version 16.0 (SPSS, Chicago, IL, USA). P values less than 0.05 (two-tailed) were considered to be statistically significant.

3. Results

3.1. General characteristics

Among the 425 AML patients, 76 patients (17.9%) were diagnosed with CBF AML, including 65 cases of t(8;21) and 11 cases of inv(16). As shown in Table 1, the FAB subtype was mainly M2 for t(8;21) patients and M4 for inv(16) patients ($P < 0.001$). Patients with inv(16) had considerably higher peripheral blood WBC counts ($P = 0.003$) and were more likely to have extramedullary involvement ($P < 0.001$), but no differences were found in bone marrow blast percentage, age or gender. Additional chromosomal abnormalities were observed in 41.5% of t(8;21) patients and 18.2% of inv(16) patients but showed no difference between the two groups ($P = 0.12$).

C-kit mutation was detected in 22 (28.9%) patients, including 21 cases of t(8;21) and 1 case of inv(16) ($P = 0.116$). The c-kit mutation subtypes were D816V (5/22, 22.7%), D816H (3/22, 13.6%), D816Y (3/22, 13.6%), N882K (5/22, 22.7%) and insertions/deletions at exon 8 (6/22, 27.3%). In addition, point mutations, including D816V and N822K, were further confirmed by MALDI-TOF MS. C-kit-mutated patients were younger than wild-type patients ($P = 0.042$) and had a marginally higher blast percentage in the bone marrow ($P = 0.057$). There was no significant difference in other clinical features between c-kit-mutated and wild-type patients.

3.2. Status of other mutations

The frequencies of additional gene mutations were compared between CBF AML patients and all non-CBF M2 and M4 patients in the study. Additional gene mutations were detected in 9 cases of CBF AML, including FLT3-ITD (1/76, 1.3%), CEBPα single mutation (3/76, 3.9%), DNMT3A (1/76, 1.3%), IDH1 (1/76, 1.3%), IDH2 (2/76, 2.6%) and K-RAS (1/76, 1.3%). As shown in Table 2, non-

Table 1
General characteristics of Chinese CBF AML patients.

Characteristic	AML-ETO $N = 65$	CBFβ-MYH11 $N = 11$	P	Wild-type c-kit $N = 54$	Mutated c-kit $N = 22$	P
Median age, years (range)	32 (13–70)	28 (16–64)	0.86	32 (13–70)	27 (13–50)	0.042
Gender, no. of patients (%)			0.099			0.133
Male	36 (55.4)	9 (81.8)		29 (53.7)	16 (72.7)	
Female	29 (44.6)	2 (18.2)		25 (46.3)	6 (27.3)	
Median WBC count, $\times 10^9$ L^{-1} (range)	9.5 (0.96–148.2)	60.5(1.08–191)	0.003	10.98 (0.96–191)	12.95 (3–100)	0.613
Median hemoglobin, g/L (range)	67.4 (28–147)	88.3 (31–111)	0.36	64.15 (28–147)	76 (41.6–123)	0.419
Median platelet count,$\times 10^9$ L^{-1} (range)	22 (4–292)	29 (10–53)	0.51	25.5 (4–292)	21.5 (7–201)	0.671
Median BM blasts, % (range)	54.9 (0.8–94.4)	59 (22–83.6)	0.87	51.6 (0.8–85.2)	66.15 (25–94.4)	0.057
FAB subtype, no. (%)			<0.001			0.214
M2	58 (89.2)	1 (9.1)		40 (74.1)	19 (86.4)	
M4	4 (6.2)	8 (72.7)		11 (20.4)	1 (4.5)	
M5	3 (4.6)	2 (18.2)		3 (5.6)	2 (9.1)	
Additional chromosome abnormalities, no. (%)			0.12			0.857
Yes	27 (41.5)	2 (18.2)		21 (38.9)	8 (36.4)	
No	31 (47.7)	8 (72.7)		29 (53.7)	10 (45.4)	
ND	7 (10.8)	1 (9.1)		4(7.4)	4 (18.2)	
Extramedullary involvement, no. (%)			<0.001			0.209
Yes	63 (93.8)	6 (54.5)		8 (14.8)	1 (4.5)	
No	2 (6.2)	5 (45.5)		46 (85.2)	21 (95.5)	

WBC, white blood cell; BM, bone marrow.

Table 2
Distribution of other gene mutations.

Characteristic	No. of patients		*P*	No. of patients		*P*
	CBF AML	Non-CBF M2 & M4		Mutated c-kit	Wild-type c-kit	
NPM1						
Mutated	4	16	0.061	0	4	0.190
Wild type	72	101		22	50	
FLT3-ITD						
Present	1	15	0.004	0	1	0.521
Absent	75	102		22	53	
FLT3-TKD						
Mutated	0	1	0.419	0	0	NA
Wild type	76	116		22	54	
CEBPα						
Double mutation	0	13	0.004	0	0	0.862
Single mutation	3	10		1	2	
Wild type	73	94		21	52	
DNMT3A						
Mutated	1	8	0.075	0	1	0.521
Wild type	75	109		22	53	
IDH1						
Mutated	1	6	0.166	0	1	0.521
Wild type	75	111		22	53	
IDH2						
Mutated	2	7	0.281	1	1	0.506
Wild type	74	110		21	53	
N-RAS						
Mutated	0	1	0.419	0	0	NA
Wild type	76	116		22	54	
K-RAS						
Mutated	1	0	0.214	0	1	0.521
Wild type	75	117		22	53	
WT1						
Mutated	0	3	0.159	0	0	0.521
Wild type	76	114		22	54	

NA, not applicable.

CBF AML (M2 and M4) patients had a significantly higher frequency of CEBPα and FLT3-ITD mutation than the CBF AML patients. We also compared c-kit-mutated and wild-type patients. We noted that almost all additional gene mutations were clustered in CBF AML patients with wild-type c-kit. However, the frequencies of additional gene mutations were too low to have a prognostic impact on CBF AML patients.

3.3. Response to induction therapy

The response to induction chemotherapy and survival analysis was available for 61 of 76 CBF AML patients. The total CR rate of CBF AML patients to induction chemotherapy was 86.9%. The CR rate was compared according to age, WBC count, cytogenetic groups and c-kit mutation status and analyzed using logistic regression. As shown in Table 3, the CR rate was lower than 80% in the group with a WBC count over $100 \times 10^9\ L^{-1}$ (50%) and in the group with the D816V mutation (25%). In logistic regression analysis, the OR of those two groups was 10.96 ($P = 0.091$) and 35.03 ($P = 0.008$), respectively. Other factors had no significant impact on the CR rate.

3.4. Survival analysis

The Cox regression analysis of overall survival (OS) showed that c-kit mutation and WBC count could adversely influence OS. The hazard ratios of the two factors were 2.74 ($P = 0.007$) and 6.24 ($P = 0.022$), respectively (Table 4). Among the different c-kit mutation types, the D816V and N822K mutations had a significant negative impact on OS (HR = 8.42 and 4.62, $P = 0.002$ and 0.022, respectively, Table 4). For relapse-free survival (RFS) analysis, only the cytogenetic group inv(16) showed marginal protective effect compared with the t(8;21) group (HR = 0.16, $P = 0.073$). We then compared the OS and RFS of CBF AML patients according to c-kit mutation status and cytogenetic group. The median OS was 21 and 8 months and the median RFS was 16 and 6 months for wild-type and c-kit-mutated patients, respectively. The median OS was 16 months and the median RFS was 12 months for t(8;21) patients. The median OS and RFS of inv(16) patients could not be defined because most cases were censored. Notably, there was a significant difference in OS between c-kit-mutated and wild-type patients in Kaplan–Meier analysis (Fig. 1A, $P = 0.006$) and in RFS between the two groups (Fig. 1B, $P = 0.043$).

Table 3
Comparison and multivariate analysis of CR rate using a logistic regression model.

Characteristic	CR, no. of patients (%)	*P*	OR	95% CI
Total	53/61 (86.9)			
Age (years)		0.999	<0.001	NA
<60	46/54 (85.2)			
⩾60	7/7 (100.0)			
WBC ($\times 10^9\ L^{-1}$)		0.091	10.96	0.69, 175.39
<100	51/57 (89.5)			
⩾100	2/4 (50.0)			
Cytogenetic group		0.985	1.025	0.08, 17.08
t(8;21)	44/50 (88.0)			
inv(16)	9/11 (81.8)			
C-kit mutation				
Mutated	15/19 (78.9)	0.283	2.47	0.47, 12.88
D816V	1/4 (25.0)	0.008	35.03	2.55, 481.09
Other D816	5/5 (100.0)	0.999	<0.001	NA
N822K	4/4 (100.0)	0.999	<0.001	NA
Exon 8	5/6 (83.3)	0.895	1.20	0.08, 17.07
Wild type	38/42 (90.6)			

WBC, white blood cell; BM, bone marrow; CR, complete remission; OR, odds ratio; CI, confidence interval; NA, not applicable.

Table 4
Multivariate analysis of OS and RFS using the Cox regression model.

	P	HR	95% CI
OS			
WBC			
$<100 \times 10^9\ L^{-1}$ *vs.* $\geqslant 100 \times 10^9\ L^{-1}$	0.022	6.24	1.30, 29.97
C-kit mutation			
Mutated *vs.* wild type	0.007	2.74	1.32, 5.66
D816V *vs.* wild type	0.002	8.42	2.18, 32.548
N822K *vs.* wild type	0.022	4.62	1.24, 17.17
RFS			
t(8;21) *vs.* inv(16)	0.073	0.16	0.02, 1.19

OS, overall survival; WBC, white blood cell; RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval.

4. Discussion

There have been several reports on the clinical outcome of AML patients with t(8;21) in China, and the results have varied among different centers [8–10]. These studies questioned whether CBF AML was different in Chinese patients compared with Caucasian patients. To address this question, we performed an integrative analysis of 76 cases of CBF AML regarding clinical features, cytogenetics, and molecular abnormalities. The results of this study allowed us to reach several conclusions.

On the basis of our screening results, the frequency of CBF AML was 17.9%, indicating the clinical significance of Chinese CBF AML. This incidence was higher than previous reports in both Chinese and Caucasian populations [3,4,9]. One possible reason is that from January 2008 to March 2009, only cryopreserved samples were enrolled. Bias may occur, as not all patients diagnosed in that period had cryopreserved cell samples. However, because we did not intentionally selected patients for sample cryopreservation, the incidence of CBF AML in our study could reflect the characteristics of the Chinese population to some extent. Moreover, there were much more patients with the t(8;21) mutation than the inv(16) mutation in our study. The incidence of inv(16) was in accordance with a large-scale cytogenetic study in China but much lower than for Caucasian populations reported in the literature, in which the incidence of inv(16) was almost the same as t(8;21) [16,22,23].

In our study, the total incidence of c-kit gene mutations (28.9%) was within the range (14.9–46.2%) that has been reported in Caucasians [11,12,23,24]. However, the mutation subtypes were markedly different. The N822K mutation appeared to be more prevalent in Chinese CBF AML patients than Caucasian patients, while the incidence of the D816V mutation was only 22.7%. There was no predominant mutation type in our study. Shimada et al. previously reported that N822K was frequently detected in pediatric AML patients with t(8;21) in Japan, implying that N822K might be another typical mutation subtype in addition to D816V in Asian CBF AML patients [25].

The total CR rate after induction chemotherapy was high and similar to that reported in Caucasians [11,12,23]. Of all factors, only the D816V mutation showed a poor response to induction chemotherapy. However, the 95% CI of the OR for the D816V mutation was wide, which reflected the relatively small sample size of enrolled patients. Thus, more cases are needed to further confirm the negative impact of the D816V mutation on the CR rate of CBF AML patients. In the Cox regression analysis of OS and RFS, the 95% CI of the HR for D816V was reasonable, suggesting that the D816V mutation was a highly adverse indicator for survival. Other aggravating factors included a WBC count over $100 \times 10^9\ L^{-1}$ and

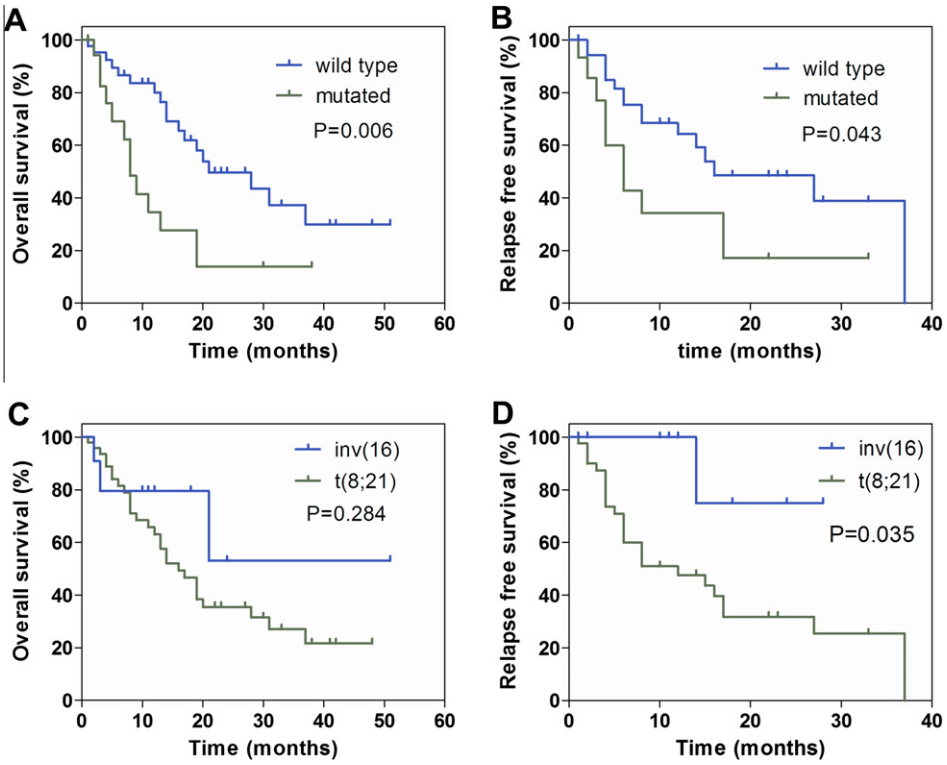

Fig. 1. Comparison of OS and RFS in CBF AML patients according to their c-kit mutation and cytogenetic status. The OS and RFS were compared using the log-rank test and estimated by Kaplan–Meier analysis. (A) The median OS was 21 months for c-kit-mutated patients and 8 months for wild-type patients, with a significant difference between the two groups ($P = 0.006$). (B) The median RFS was 16 months for c-kit-mutated patients and 6 months for wild-type patients, with a significant difference between the two groups ($P = 0.043$). (C) The median OS was 16 months for t(8;21) patients but not applicable for inv(16) patients, and there was no difference between the two groups ($P = 0.284$). (D) The median RFS was 12 months for t(8;21) patients but not applicable for inv(16) patients, and there was a significant difference between the two groups ($P = 0.035$).

the N822K mutation. Interestingly, although the c-kit mutation presented as an aggravating factor only for OS and not RFS in Cox regression analysis, survival analysis using Kaplan–Meier analysis showed that the c-kit mutation could significantly affect both OS and RFS. Similarly, inv(16) patients had a significantly longer RFS than t(8;21) patients, but Cox regression analysis showed only a marginal protective effect of inv(16). This statistical discrepancy may also be due to the relatively small number of sample size. Based on these findings, we concluded that c-kit mutation and high WBC count had negative impact on the outcome of Chinese CBF AML patients. Meanwhile other factors, including the molecular markers recently reported as prognostic indicators, did not have significant impact on outcome. However, as the sample size of the present study was relatively small, a large-scale clinical trial with standardized therapy is warranted in the future to further prove our observations.

Conflict of interest

The authors have no conflicts of interest.

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