Original Article

The polymorphism of *JAK2* rs56118985 may be a predictive marker of the treatment responses of acute myeloid leukemia patients

Peipei Xu[1*], Miaoxin Peng[1*], Di Zhou[1], Xiaoyan Shao[1], Qiguo Zhang[1], Rongfu Zhou[1], Jiangyan Xu[1], Jian Ouyang[1], Bing Chen[2]

[1]Department of Hematology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, China; [2]Department of Hematology, Nanjing Drum Tower Hospital Clinical College of Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210008, China

Contributions: (I) Conception and design: P Xu, B Chen; (II) Administrative support: B Chen, J Ouyang; (III) Provision of study materials or patients: M Peng, X Shao, Q Zhang, R Zhou, J Xu; (IV) Collection and assembly of data: D Zhou; (V) Data analysis and interpretation: M Peng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors are considered as co-first authors.

Correspondence to: Peipei Xu, PhD. Department of Hematology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, China. Email: xu_peipei0618@163.com; Bing Chen, PhD. Department of Hematology, Nanjing Drum Tower Hospital Clinical College of Traditional Chinese and Western Medicine, Nanjing 210008, China. Email: chenb211@163.com.

Background: The Janus kinase/Signal transducer and activator of transcription (JAK/STAT) signaling pathway plays a role in ontogeny and developmental biology, hematopoietic regulation and the immune response. In this study, we aimed to investigate whether the genetic polymorphism rs56118985 (Glycine ⇒ Aspartic acid) in the *JAK2* gene is associated with the therapeutic outcomes of Ara-C-based chemotherapy regimens in acute myeloid leukemia (AML).

Methods: A total of 552 AML patients were included in our study. Genotypes were determined by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

Results: The frequency of the GG genotype was significantly higher in patients with intermediate and good therapeutic responses. In contrast, the GA genotype was found in the unfavorable response group, high ratio of blast group and was significantly associated with the poor therapeutic response group. Patients with the GA genotype were significantly more likely to die early (P<0.001).

Conclusions: In conclusion, the polymorphism of *JAK2* rs56118985 may be a predictive marker of the treatment responses of AML patients.

Keywords: *JAK2*; polymorphism; acute myelogenous leukemia (AML)

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Introduction

The Janus kinase/Signal transducer and activator of transcription (JAK/STAT) signaling pathway is activated by a variety of cytokines, hormones and growth factors. Ligand binding to cell surface receptors triggers JAK kinases, which activate JAK-mediated phosphorylation and STAT protein dimerization and translocate to the nucleus, where they regulate gene expression (*Figure 1*) (1). The JAK/STAT signaling pathway is a major signal transduction pathway in cytokine and growth factor signaling, which controls the survival, proliferation and differentiation of several cell types. Aberrant JAK/STAT signaling has been shown to be involved in tumorigenesis and the progression of several solid cancers, as well as hematopoietic malignancies.

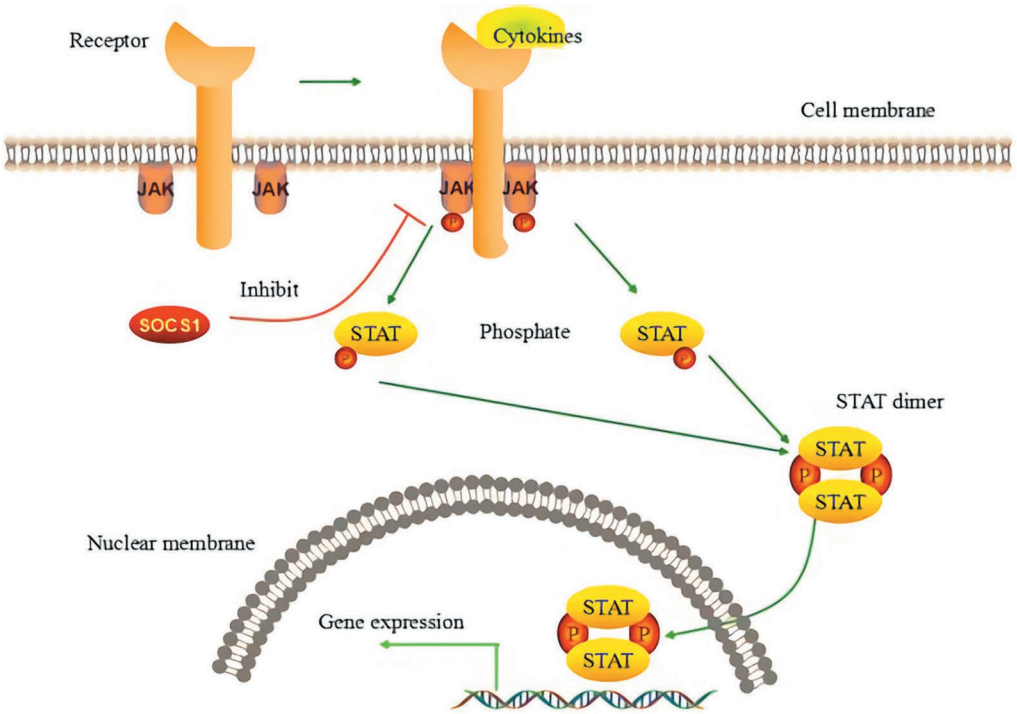

Figure 1 *JAK/STAT* activation pathway.

Recently, hematologists have turned their attention to mutations and single nucleotide polymorphisms (SNPs) of *JAK2*, an important member of the signaling pathway. An acquired somatic mutation in *JAK2* was identified in a majority of patients with myeloproliferative disorders (MPN). The V617F mutation drives the proliferation of neoplastic clones and promotes *JAK2* catalytic subunit activation and cytokine-independent signaling (2,3). In addition, in a study of V617F-negative polycythemia vera (PV) patients, Scott et al found that *JAK2* exon 12 mutations may play an important role in the progression of PV (4). Currently, association studies of SNPs of the JAK/STAT pathway and the risk of hematologic malignancies are ongoing. Animesh's group reported that three *JAK2* SNPs (rs7046736, rs10815148 and rs12342421) were significantly associated with PV and essential thrombocythemia (ET) by genotype-phenotype analysis of 179 Caucasian patients [84 with PV, 58 with primary myelofibrosis (PMF) and 37 with ET]. Pardanani *et al*. found three other *JAK2* SNPs (rs10758669, rs3808850, and rs10974947) that were also significantly associated with PV (5).

Acute myeloid leukemia (AML) is a heterogeneous group of leukemia that results from clonal transformation of hematopoietic precursors through the acquisition of chromosomal rearrangements and multiple gene mutations. Chemotherapy has been the backbone of treatment for AML. At present, more than 50% of adults with AML achieve a complete response (CR) following induction therapy with cytosine arabinoside (Ara-C)-based chemotherapy (6,7). The cause of resistance to chemotherapy has confounded hematologists. Currently, SNPs are popularly used as molecular markers to facilitate the identification of genetic factors responsible for diseases, as well as the early diagnosis and prediction of treatment outcome (8,9). Some genes have been reported to be associated with the response to chemotherapy in AML patients (10-13). Thus far, the ideal candidate gene predicting the response of AML patients to chemotherapy response has still not been identified.

In this retrospective study, we aimed to investigate whether the genetic polymorphism rs56118985 (Glycine ⇒ Aspartic acid), located at exon 5 of the *JAK2* gene, is associated with the therapeutic outcomes of Ara-C-based chemotherapy in AML patients.

Methods

Patients

A total of 552 patients with newly diagnosed AML according to the World Health Organization (WHO) and French-American-British (FAB) criteria in the Drum Tower Hospital and other four large hospitals in Jiangsu Province between August 2007 and January 2014 were enrolled in the study. This study was approved by the ethics committees of all participating hospitals and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment and were informed of the existence of other treatment options. Patients who were diagnosed with any other type of cancer or other hematological malignancies were excluded from the study. Patients with the M3 subtype (acute promyelocytic leukemia) and patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) or autologous HSCT were also excluded. Cytogenetic risk groups were stratified according to the Medical Research Council cytogenetic classification system (14). The presence of 5/del(5q), 7/del(7q), abn3q, complex aberrations (≥3 independent aberrations), t(9;22), and t(6;9) were identified as unfavorable karyotypes, whereas t(8;21) and inv(16) were classified as favorable karyotypes. Gene mutation risk groups were divided according to the NCCN gene mutation classification system (15). NPM1 and CEBPA were identified as favorable gene mutations, whereas FLT3/ITD and C-KIT were classified as unfavorable gene mutations. The remaining patients with normal karyotypes and patients with other karyotypic aberrations comprised the intermediate risk group. Patients were further divided into two groups according to their white blood cell (WBC) counts, hemoglobin levels and platelet counts.

Chemotherapy regimens and evaluation of the therapeutic effect

All patients enrolled were treated with standard Ara-C-based chemotherapy regimens; DA induction chemotherapy regimens, Daunorubicin (DNR) 60 mg/m^2/day for 1–3 days and Ara-C 100 mg/m^2/day for 1–7 days; HA induction chemotherapy regimens, homoharringtonine (HHT) 3–4 mg/m^2/day for 5–7 days and Ara-C 100 mg/m^2/day for 1–7 days; and MA induction chemotherapy regimens, Mitoxantrone 4 mg/m^2/day for 1–5 days and Ara-C 100 mg/m^2/day. All chemotherapeutic drugs were administered intravenously. Complete remission (CR) was defined according to the criteria of the International Working Group (15). Partial remission (PR) indicates that at least one of the standards of clinical manifestation, blood analysis and bone marrow was not met. Additionally, blast cells and promyelocytic cells should be less than 20% in the bone marrow. Non-remission (NR) indicates that clinical manifestation, blood analysis and bone marrow did not meet the standards for CR. Additionally, promyelocytic cells should be more than 20% in the bone marrow. Early death was defined as death within 8 weeks from the start of the first induction therapy course. Progression-free survival (PFS) was defined as the interval from the date of treatment to the date of confirmed relapse or death from any cause. Overall survival (OS) was defined as the length of time from the date of diagnosis to the date of death from any cause or the last follow-up.

DNA extraction and polymorphism genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the phenol-chloroform extraction method. SNP genotyping was performed by the MassARRAY system (Sequenom, USA) with matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS) according to the manufacturer's instructions.

Statistical analysis

Demographic and clinical variables of different genotypes were evaluated using the Pearson Chi-squared test or Fisher's exact test, as appropriate. The Kaplan–Meier product-limit method was used to determine OS and PFS, and the differences were assessed by the log-rank test. The prognostic impact of different variables on survival (OS and PFS) was determined by multivariate Cox proportional hazards model. All data were analyzed statistically using a commercially available statistical software package (SPSS 19.0; IBM Corp., Armonk, NY, USA). All tests were two-tailed, and a P value <0.05 was considered statistically significant. Odds ratios (ORs) with 95% confidence intervals (CIs) were also calculated.

Results

Genotyping by MALDI-TOF MS

A typical MALDI-TOF MS spectrum after mini sequencing by standard ddNTPs and a corresponding scatter plot are shown in *Figure 2*.

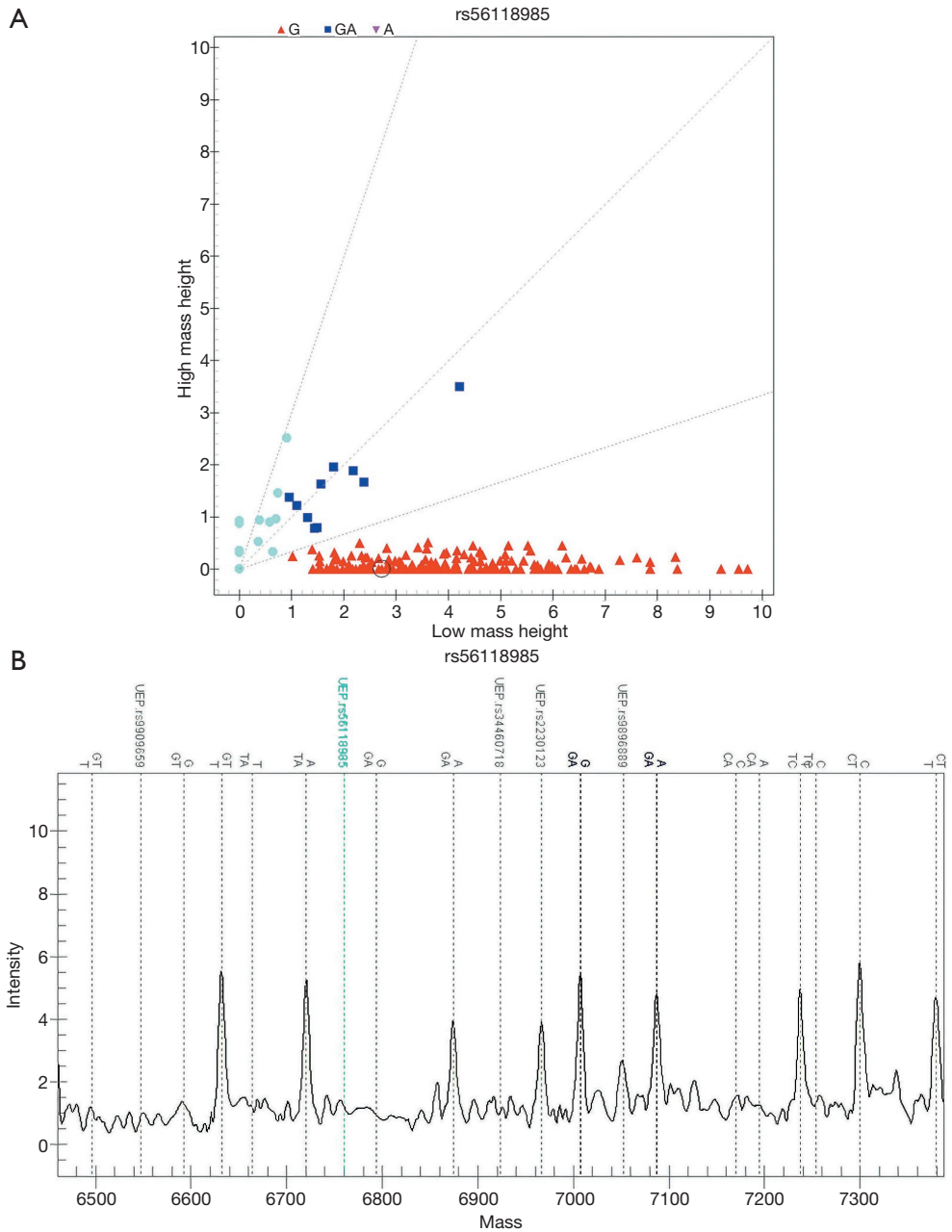

Figure 2 Results of the mass spectrometry analysis. (A) Scatter plot of MALDI-TOF MS data for rs56118985; (B) heterogeneity of the rs56118985 GA genotype.

Patient and SNP genotype characteristics

We found that genotype frequencies for the polymorphisms did not deviate from Hardy-Weinberg equilibrium, and no individuals were detected with the AA genotype in *JAK2* rs56118985 among AML patients in the Chinese population. Patient characteristics are listed in *Table 1*. The median follow-up was 24 months (range 5–54 months). The male-to-female ratio was 0.97:1 (272:280), with ages ranging from 14 to 91 years, and the median age of the AML patients at diagnosis was 47 years. No significant difference was identified with regard to age, gender and FAB classification in patients with different *JAK2* genotypes in rs56118985. The results of the analysis of cytogenetic

Table 1 Demographic data and characteristics of patients

Demographic data and characteristics	Overall (n=552)	Genotype			Allele		
		GG	GA	P value	G (%)	A (%)	P value
Gender							
Female	272	232	40	0.434	92.6	7.4	0.602
Male	280	232	48		91.4	8.6	
Age (years)							
≤40	276	230	46	0.300	91.7	8.3	0.489
40–60	170	140	30		91.2	8.8	
≥60	106	94	12		94.3	5.7	
FAB classification							
M0	40	40	0	0.031[a]	100.0	0.0	0.433
M1	54	54	0		100.0	0.0	
M2	210	140	70		83.3	16.7	
M4	68	68	0		100.0	0.0	
M5	101	83	18		91.1	8.9	
M6	44	44	0		100.0	0.0	
M7	35	35	0		100.0	0.0	
Cytogenetic risk group							
Favorable	129	126	13	0.000[b]	95.0	5.0	0.000[c]
Intermediate	283	278	15		97.3	2.7	
Unfavorable	120	60	60		78.6	21.4	
Gene mutation							
Favorable	400	353	47	0.000[d]	94.1	5.9	0.015[e]
Unfavorable	152	111	41		86.5	14.5	
Blast (%)							
>50	383	302	81	0.007[f]	89.4	10.6	0.000[g]
<50	169	162	7		97.9	2.1	
Lab at diagnosis							
WBC ($\times 10^9$/L)							
≤50	472	383	69	0.356	92.7	7.3	0.228
>50	80	81	19		88.1	11.9	
Hemoglobin (g/L)							
≤100	282	232	50	0.241	91.1	8.9	0.602
>100	270	232	38		93.0	7.0	
Platelets ($\times 10^9$/L)							
≤60	280	234	46	0.751	91.8	8.2	1.000
>60	272	230	42		92.3	7.7	

Note: [a], P<0.05, odd ratio (95% CI) =0.845 (0.725–0.985); [b], P<0.05, odd ratio (95% CI) =0.185 (0.121–0.281); [c], P<0.05, odd ratio (95% CI) =0.340 (0.190–0.608); [d], P<0.01, odd ratio (95% CI) =0.327 (0.169–0.634); [e], P<0.05, odd ratio (95% CI) =0.378 (0.157–0.911); [f], P<0.01, odd ratio (95% CI)= 0.161 (0.073–0.357); [g], P<0.01, odd ratio (95% CI)= 0.201 (0.071–0.571). FAB, French-American-British criteria; WBC, white blood cells; M0: minimally differentiated AML; M1, AML without maturation; M2, AML with maturation; M4, acute myelomonocytic leukemia; M5, acute monocytic leukemia; M6, erythroleukemia; M7, acute megakaryoblastic leukemia.

Table 2 Outcomes of treatment according to *JAK2* rs56118985 polymorphism genotypes

Outcomes	JAK2 rs56118985		P value
	GG (n=464)	GA (n=88)	
CR after 1st course, n (%)	252 (54.3)	16 (18.2)	0.000[a]
CR after 2nd course, n (%)	85 (18.3)	2 (2.2)	0.000[b]
PR, n (%)	80 (17.2)	16 (18.2)	0.831
NR, n (%)	37 (8.0)	16 (18.2)	0.003[c]
Early death, n (%)	10 (2.2)	38 (43.2)	0.000[d]
Good response (CR + PR), n (%)	417 (89.9)	34 (38.6)	0.000[e]
Bad response (NR+ early death), n (%)	47 (10.1)	54 (61.4)	

[a], P<0.05, odd ratio (95% CI) =0.189 (0.106–0.331); [b], P<0.05, odd ratio (95% CI) =0.104 (0.025–0.430); [c], P<0.05, odd ratio (95% CI) =0.390 (0.206–0.738); [d], P<0.05, odd ratio (95% CI) =0.029 (0.014–0.062); [e], P<0.05, odd ratio (95% CI) =0.071 (0.042–0.120). CR, complete remission; PR, partial remission; NR, non-remission.

risk showed that the frequency of the GG genotype was significantly higher in the intermediate group than in the other two groups, whereas the GA genotype was observed more in the unfavorable group (P<0.01). Moreover, patients with M5, unfavorable gene mutation factor, and high ratio of blast were associated with the GA genotype. (P=0.031, P=0.000, P=0.000, and P=0.007, respectively). Meanwhile, the A allele in rs56118985 was more frequently associated with the unfavorable group, the unfavorable gene mutation factor group, and high ratio of blast group (P<0.01, P=0.015, and P=0.000, respectively). We then stratified the patients into two groups according to their WBC counts, hemoglobin levels and platelet counts, the results were similar in patients with different *JAK2* rs56118985 genotypes (P>0.05).

Treatment outcomes in relation to genetic polymorphism

All 552 patients were administered Ara-C-based standard induction chemotherapy regimens [DA (daunorubicin and cytosine arabinoside), MA (mitoxantrone and cytosine arabinoside), HA (homoharingtonine and cytosine arabinoside)]. Patient responses to treatment were evaluated after every cycle of chemotherapy, which was subdivided into four groups, namely CR, PR, NR, and early death. Differences in responsiveness to chemotherapy on the basis of the *JAK2* rs56118985 genotypes are shown in *Table 2*. There were 260 cases that achieved CR after the first course of treatment and 87 cases that achieved CR after the second course. We found statistically significant association between the GA and GG genotypes in the CR and NR patients. No differences were identified between the two genotypes (GA and GG) in PR. A statistically significant association was found between the GA and GG genotypes with respect to the percentage of early death. The patients with the GA genotype suffered from a higher early death rate (P<0.01). As reflected in the statistical analyses, more AML patients with the GG genotype in rs56118985 achieved a good response than patients with the GA genotype (P<0.01).

The Kaplan-Meier method and log-rank test show that patients with the GG genotype in rs56118985 had significantly better OS than those with the GA genotype (P=0.028, with a 24-month OS of 62.5% versus 40.0%) (*Figure 3A*). The 24-month PFS rates of patients with the GG and GA genotype were 42.5% and 40.0%, respectively. Patients with GA genotype did not have significantly poorer PFS than those with the GG genotype (P=0.170) (*Figure 3B*).

The survival analyses by Cox regression model are shown in *Table 3*. On univariate analysis, FAB classification (P=0.020, P=0.036), CR after 1st Course (P=0.018, P=0.034), cytogenetic risk (P=0.027, P=0.003), gene mutation (P=0.001, P=0.001), and rs56118985GA/GG genotype (P=0.013, P=0.021) were significantly associated with EFS and PFS. However, on multivariate Cox regression analysis, only cytogenetic risk (P=0.048, P=0.046, respectively) and r rs56118985GA/GG genotype (P=0.015, P=0.039, respectively) remained as an independent significant predictor for EFS and PFS.

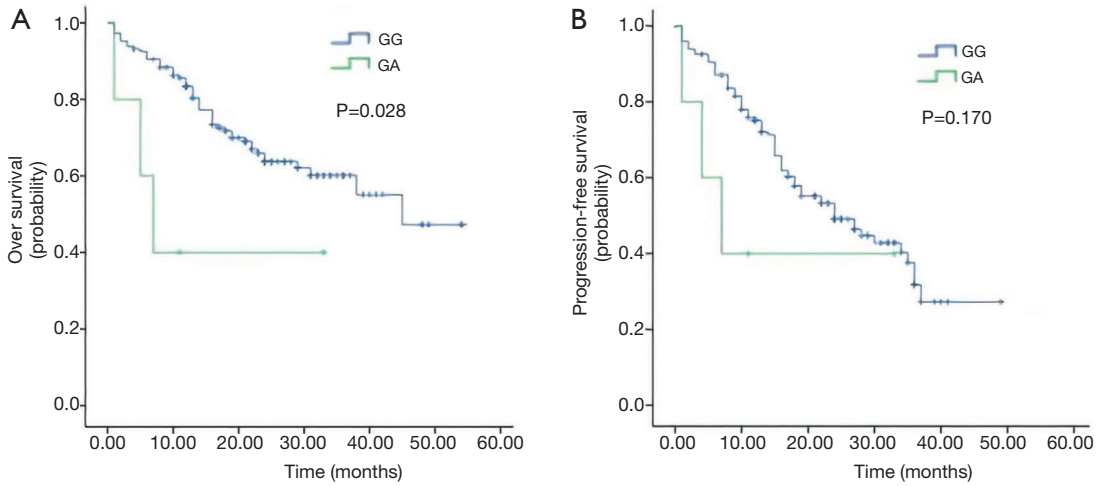

Figure 3 Kaplan-Meier curve for overall survival and progression-free survival of AML patients according to the *JAK2* rs56118985 genotype polymorphism. (A) Overall survival according to the *JAK2* rs56118985 genotype polymorphism (Log-rank test, P=0.028); (B) progression-free survival according to the *JAK2* rs56118985genotype polymorphism (Log-rank test, P=0.170).

Table 3 Univariate and multivariate analysis for OS and PFS outcomes

Covariates	OS			PFS		
	HR	95% CI	P value	HR	95% CI	P value
Univariate analysis						
Age (>60 y)	0.78	0.39–1.39	0.243	0.82	0.43–1.18	0.192
Gender	0.84	0.41–1.75	0.735	1.08	0.67–1.78	0.935
FAB classification	2.13	1.13–4.01	0.020	1.75	1.04–2.95	0.036
Blast >50 (%)	1.59	0.23–2.62	0.127	1.35	0.81–2.64	0.053
CR after 1st course	0.20	0.05–0.75	0.018	0.31	0.10–0.91	0.034
Cytogenetic risk	1.19	1.03–1.62	0.027	1.35	1.11–1.64	0.003
Gene mutation	1.31	1.04–1.83	0.001	1.43	1.19–1.71	0.001
rs56118985GA/GG genotype	1.44	1.13–1.83	0.013	1.44	1.18–1.76	0.021
Multivariate analysis						
Gene mutation	1.02	1.04–2.95	0.048	1.16	1.39–3.46	0.046
rs56118985GA/GG genotype	2.20	1.19–6.26	0.015	1.65	1.02–2.93	0.039

AB, French-American-British criteria; OS, overall survival; PFS, progression-free survival.

Discussion

In the present study, we found that the polymorphisms of *JAK2* rs56118985 were significantly associated with risk status and prognosis of AML patients. Patients with GA genotype tended to have higher risk status, lower response rate to Ara-C based chemo-regimen, higher early death rate and shorter OS. With multivariate Cox regression analysis, we revealed that *JAK2* rs56118985 GA/GG genotype was an independent predictor for EFS and PFS in AML. In this retrospective study in which Ara-C-based standard chemotherapeutic regimens were used to treat AML patients, the predictive role of *JAK2* rs56118985 was shown to be clinically important. It suggested that

JAK2 rs56118985 genotype could be used as an important predictive marker for the prognosis of AML patients. Considering that patients who receive allo or auto-hematopoietic stem cell transplantation have quite different prognosis from those who only receive chemotherapy, we excluded the AML patients who underwent stem cell transplantation in our study. Since the number of patients who received stem cell transplantation was small compared with the study population, we do not think that this selection would cause significant bias to our results.

The prevalence of patients with AML is the highest in leukemia patients, with 3.8 cases per 100,000 adults rising to 17.9 cases per 100,000 adults aged 65 years and older (16). It is a great challenge for hematologists to control the occurrence and development of AML. A majority of studies regarding the association of SNPs with AML have examined disease susceptibility (17). SNPs can also contribute to the diversity of drug tolerances and differences in responses to environmental factors. In the present study, we investigated the association between chemotherapy outcomes, as well as survival outcomes, and *JAK2* rs56118985 in the AML patients for the first time. Like *JAK2* V617F, many of the *JAK2* mutations affect amino acids located within the pseudokinase domain JH2, which result in over-activation of the JAK-STAT pathway (18-22). It may also be the mechanism behind the association between *JAK2* rs56118985 polymorphism and AML patient prognosis, but further studies are required to testify the hypothesis.

In summary, we found that the rs56118985 polymorphism of *JAK2* was associated with the response of Chinese AML patients to Ara-C-based standard induction chemotherapy regimens. However, well-designed, larger studies will be necessary to further define the role and value of this polymorphism in the conventional treatment setting for patients with AML. We also look forward to the development of potential novel target therapies with the clinical application of SNPs.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.06.40). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committees of all participating hospitals and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment and were informed of the existence of other treatment options.

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