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Original Article

Detection of BCR-ABL fusion gene in diagnosis and treatment of chronic myeloid leukemia

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Abstract: Objective: To investigate the effect of detection of BCR-ABL fusion gene expression in the diagnosis and treatment of chronic myeloid leukemia (CML). Methods: Fifty-seven patients with CML were enrolled into this study. BCR-ABL fusion gene expression in patients with different stages of CML and its correlation with the stages of CML were analyzed. The expression of BCR-ABL fusion gene in patients with CML was compared at different time points before and after imatinib treatment, and its predictive value for the treatment efficacy of imatinib was assessed with the Receiver Operating Characteristic (ROC) curve. Additionally, patient satisfaction and disease-free survival were compared among patients with different BCR-ABL fusion gene expression. Results: The BCR-ABL fusion gene was expressed highest in patients with acute CML and lowest in patients with chronic CML; the BCR-ABL fusion gene expression was positively correlated with the stages of CML (r=0.654, P=0.008). The expression of BCR-ABL fusion gene decreased significantly after imatinib treatment, and it had predictive value for the efficacy of imatinib treatment (P<0.05). The patients with BCR-ABL fusion gene expression at a low level had the highest satisfaction rate and the longest disease-free survival (P<0.05). Conclusion: Detection of the expression of BCR-ABL fusion gene is helpful to assess disease stages and the efficacy of imatinib treatment in patients with CML.

Keywords: Chronic myeloid leukemia imatinib, BCR-ABL fusion gene, real-time quantitative PCR

Introduction

Chronic myeloid leukemia (CML), a clinically common hematologic tumor, accounts for appropriately 15% to 20% of all cases of leukemia [1, 2]. According to a previous study, BCR-ABL fusion gene is the most important molecular feature of CML. BCR-ABL fusion protein encoded by BCR-ABL fusion gene activates tyrosine protein kinase, promotes cell proliferation in a manner of malignant cloning, prolongs cell survival, inhibits cell differentiation and maturation, and reduces cell apoptosis, ultimately leading to the presence of leukemia [3]. Results of other studies have demonstrated that abnormal cell load is correlated with BCR-ABL fusion gene expression in patients with CML [4, 5]. Imatinib is a molecule-targeted, first-line drug for the treatment of CML. Recent studies have showed that some patients are resistant to imatinib, and BCR-ABL fusion gene expression is elevated in the resistant patients [6, 7]. Therefore, effective monitoring of BCR-AB fusion gene expression is of great practical significance to the diagnosis of CML, assessment of drug efficacy and prognosis in CML patients.

Many methods, including cytogenetics, common polymerase chain reaction (PCR) and fluorescence in situ hybridization, have been applied to assess the efficacy of treatment in CML patients. However, there are still some limitations in the methods, such as, a too long period of detection, provision of only negative or positive results, low sensitivity, failure to reflect the dynamic changes or severity of CML, and inability to evaluate patients with low cellular mitotic index or poor chromosomal morphological phenotype effectively [8, 9]. With the growing development of new technology, real-time quantitative PCR has achieved a leap from qualitative to quantitative development, and it has been more frequently utilized in the assessment of the efficacy of medical treatment [10, 11]. Real-time quantitative PCR

Table 1. The primer and probe sequences of genes

Gene	Primer/Probe	Sequences 5'-3'
BCR-ABL	forward primer	TCCGCTGACCATCAATAAGGA
	downstream primer	CACTCAGACCCTGAGGCTCAA
	TaqMan probe	CCCTTCAGCGGCCAGTAGCATCTGA
ABL	forward primer	TGGAGATAACACTCTAAGCATAACTAAAGGT
	downstream primer	GATGTAGTTGCTTGGGACCCA
	TaqMan probe	CCATTTTTGGTTTGGGCTTCACACCATT

shows the advantages of convenient use, short reaction period, high specificity and sensitivity; moreover, it can quantitatively detect BCR-ABL fusion gene expression up to 10^{-6}-10^{-5} [12]. Nevertheless, it is rarely reported that real-time quantitative PCR is used in assessing disease progress in patients with CML by detecting BCR-ABL fusion gene expression, so more trials are required for further confirmation. In the current study, real-time quantitative PCR was utilized to detect BCR-ABL fusion gene expression in 57 patients with CML, and to explore the effect of BCR-ABL fusion gene expression in diagnosis and treatment of CML, in hope of providing experimental evidence for guiding clinical treatment of CML.

Materials and methods

Study subjects

A total of 57 patients with CML admitted to The People's Hospital of Yuyao from January 2015 to May 2017 were selected into this study. All patients were diagnosed with CML by bone marrow smear or biopsy. Patients were eligible to enter the study if they met the diagnostic criteria for CML, had no previous targeted drug treatment nor contraindications in chemotherapy, had expected survival of more than 1 year, an age of more than 18 years, complete clinical data, and actively cooperated in this study [13]. CML patients were excluded from this study if they had major organ dysfunction, were lactating or pregnant women, had other malignant tumors, brain or bone metastasis, were allergic to imatinib (a targeted drug) or had a mental disorder. In terms of the criteria for different stages of CML, patients were classified into: chronic, accelerated or acute CML; according to BCR-ABL fusion gene expression (less than 10%, 10-50%, and more than 50%), patients were assigned to a low level group, medium level group or high level group [14]. This study obtained written informed consent from patients and their families, and it was approved by the ethics committee of The People's Hospital of Yuyao.

Detection of BCR-ABL fusion gene expression in leukocytes

In the morning, fasting venous blood (3-5 mL) was drawn from each patient and placed in an EDTA anticoagulation tube for use. After mixing, leukocytes were conventionally extracted with the use of human lymphocyte separation medium (Sigma, USA), and total RNA was extracted using the Trizol reagent (Invitrogen, USA). Subsequently, total RNA was synthesized into cDNA under the action of reverse transcriptase. The internal reference gene was ABL gene [14]. The primer and probe sequences of BCR-ABL and ABL genes are shown in **Table 1**. PCR was performed in accordance with the instructions on the real-time fluorescent quantitative PCR kit (Thermo Fisher Scientific, USA). The reaction system was set as 20 uL, including 10 uL of Premix Ex Taq™ (2×), 2 uL of cDNA, 0.8 uL of fluorescent probe solution, 0.3 uL of forward primer and 0.3 uL of backward primer, and 6.6 uL of dH2O. PCR amplifications were performed on a 7500 quantitative PCR system (Applied Biosystems). The reaction conditions were set as follows: pre-denaturation at 95°C for 30 s, followed by 50 cycles of denaturation at 95°C for 5 s, renaturation at 58°C for 20 s, and extension at 60°C for 20 s. The relative expression of BCR-ABL fusion gene was counted based on the standard curve and Ct value.

Outcome measures

Primary outcome measures: Primary outcome measures included the correlation between BCR-ABL fusion gene expression and disease progress, and the predictive value of BCR-ABL fusion gene expression for the efficacy of imatinib.

All patients received targeted therapy with imatinib. Before treatment, BCR-ABL fusion gene expression and its correlations with disease progress were statistically analyzed and compared in patients with chronic, acute or accelerated CML. BCR-ABL fusion gene expression in such patients was measured before treatment,

Table 2. Basic information of patients

Indicators	Value
Total number of cases	57
Gender	34
Male	23
Female	42.70±3.67
Average age (years)	35
Disease process	10
Chronic stage	12
Acute stage	2.57±1.31
Accelerated stage	21.72±1.28
Disease course (years)	57
Body mass index (kg/m^2)	34

at 3, 6, 9 and 12 months after treatment, respectively. The predictive value of BCR-ABL fusion gene expression for the efficacy of imatinib was assessed in patients with CML.

Secondary outcome measures: Secondary outcome measures were patient satisfaction with imatinib and disease-free survival in patients with BCR-ABL fusion gene at different levels.

One year after treatment, patient satisfaction was compared among patients with BCR-ABL fusion gene at different levels. The criteria for judging patient satisfaction are as follows: patients achieve partial remission at cytogenetical and hematological examination if they complete 3 months of treatment; they achieve complete remission at cytogenetical examination if they complete 6 months of treatment; they achieve complete remission at molecular examination if they complete 12 months of treatment [15].

All patients were followed once every 3 months in the forms of clinic appointments or telephone calls. Relapse and death of patients were recorded. Disease-free survival was statically analyzed and compared among patients with BCR-ABL fusion gene at different levels.

Statistical analysis

Experimental data were analyzed with the use of SPSS statistical software, version 22.0. Measurement data were expressed as mean ± standard deviation and the t-test of independent samples was used for comparison between the two groups. One-way ANOVA and post hoc Bonferroni test were used to compare the three groups. Count data were described as percentage; comparisons between two groups were conducted by chi-square tests, while comparisons among three groups were performed by partitions of chi-square. Pearson's correlation analysis was used to test the correlation between BCR-ABL fusion gene expression and disease progress. Receiver Operating Characteristic (ROC) curve was established, and the predictive value of BCR-AB fusion gene expression for the efficacy of imatinib was evaluated based on the area under the ROC curve. A p-value of less than 0.05 was used to show statistical significance.

Results

Basic information of patients

In this study, 57 CML patients were enrolled. Among them, 35 were in a chronic stage, 10 in an acute stage, and 12 in an accelerated stage; 34 patients were male, and 23 females; they had a mean age of 42.70±3.67 years, body mass index of 21.72±1.28 kg/m^2 and a disease course of 2.57±1.31 years (**Table 2**).

Comparison of BCR-ABL fusion gene expression among patients with different stages of CML

BCR-ABL fusion gene expression was markedly higher in patients with acute (95.87±2.58%) or accelerated CML (81.69±3.42%), compared to ones with chronic CML (32.19±5.37%), and the difference was statistically significant ($P<0.001$). BCR-ABL fusion gene expression in patients with acute CML was markedly higher than that in patients with accelerated CML, and the difference showed clear significance ($P<0.001$; **Table 3**). Results from Pearson's correlation analysis indicate that BCR-ABL fusion gene expression was positively correlated with disease progress of patients with CML ($r=0.654$, $P=0.008$; **Table 4** and **Figure 1**).

BCR-ABL fusion gene expression in patients with CML before and after imatinib treatment

The expression of BCR-ABL fusion gene was 55.743±4.622% before treatment, and the corresponding levels were 10.631±3.412%, 2.520±1.262%, 1.024±0.831% and 0.039±0.002% at 3, 6, 9 and 12 months after imatinib treatment, respectively. BCR-ABL fusion gene

Table 3. Comparison of BCR-ABL fusion gene expression among patients with different stages of CML

Stages	Number of cases	BCR-ABL fusion gene expression level (%)	F	P
Chronic stage	35	32.19±5.37	10.02	<0.001
Acute stage	12	81.69±3.42***		
Accelerated stage	10	95.87±2.58***,###		

Note: Compared to chronic patients, ***P<0.001; compared to accelerated patients, ###P<0.001.

Table 4. Correlation analysis of BCR-ABL fusion gene expression level and disease course

Indicator	R	P
BCR-ABL fusion gene expression level	0.654	0.008

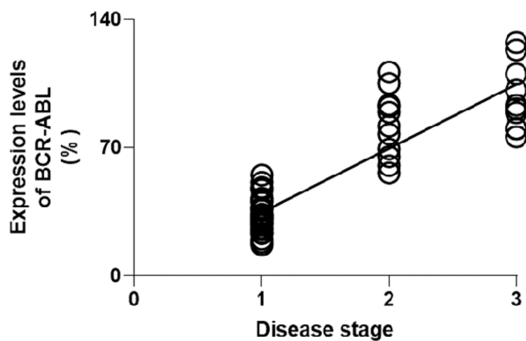

Figure 1. Scatter plot of BCR-ABL fusion gene level and stage of chronic myeloid leukemia. Different disease stages are assigned in order of severity of the disease. The chronic phase is assigned to 1, the accelerated phase to 2, and the abrupt phase to 3.

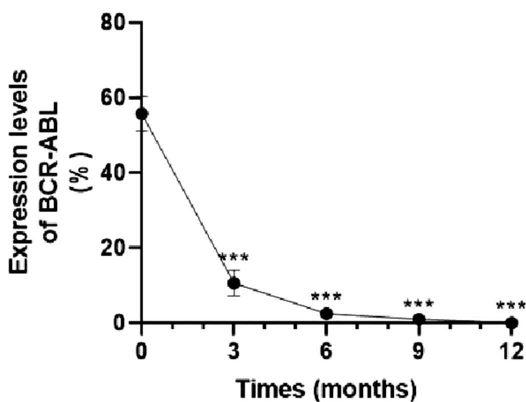

Figure 2. Changes in the expression level of BCR-ABL fusion gene in patients with chronic myeloid leukemia before and after imatinib treatment. Compared to before treatment, ***P<0.001.

expression decreased with the extension in imatinib treatment. The levels of BCR-ABL fusion gene in CML patients at different time points after treatment were considerably lower than that before treatment (P<0.001; **Figure 2**).

Comparison of disease-free survival and satisfaction in patients with BCR-ABL fusion gene at different levels after imatinib treatment

After imatinib treatment, the rates of patient satisfaction in the low-level group, the medium level group and the high level group were 61.11% (11/18), 42.15% (12/26) and 15.38% (2/13), respectively. There were statistically significant differences in patient satisfaction among the three groups (χ^2=6.512, P=0.039; **Figure 3A**). Mean disease-free survival was 20.3±7.4 months in the low-level group, 13.9±6.2 months in the medium level group, and 4.8±2.7 months in the high-level group. Disease-free survival differed significantly among the three groups (F=24.74, P<0.001; **Figure 3B**). Findings of the ROC curve show that BCR-ABL fusion gene expression was useful in predicting the curative effect of imatinib in CML patients (AUC=0.702, 95% CI, 0.543-0.862), the cutoff value was 67.392%, the sensitivity was 0.792, the specificity was 0.446, and there were statistical differences (P=0.013; **Figure 4**).

Discussion

An epidemiological survey reveals that the incidence of CML rises significantly with the increase in age; however, there is a trend of younger patients, and the disease seriously threatens the life and health of patients [16]. BCR-ABL fusion protein is expressed in more than 99% of CML patients, and it persistently activates tyrosine protein kinase and interferes with normal signaling pathway of cells, resulting in abnormal proliferation of cells [17]. Therefore, BCR-ABL fusion gene seriously affects progress of CML, and plays an active role in the development of the disease.

Currently, the accuracy for detecting BCR-ABL fusion gene expression by real-time quantitative PCR has been widely recognized. In the present study, BCR-ABL fusion gene expression in 57 patients with CML was measured using real-time quantitative PCR. The results indicate

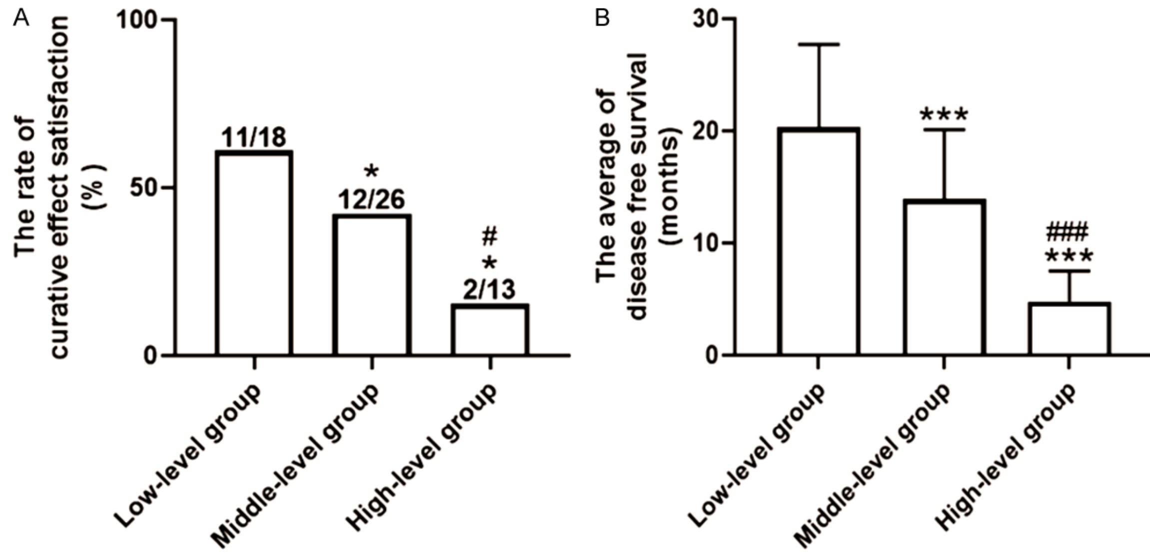

Figure 3. (A) is the comparison of the satisfaction rate of efficacy among patients with different BCR-ABL fusion gene expression levels. (B) is a comparison of disease-free survival among patients with different BCR-ABL fusion gene expression levels. Compared with the low-level group, $^{*}P<0.05$, $^{***}P<0.001$; compared with the intermediate group, $^{\#}P<0.05$, $^{\#\#\#}P<0.001$.

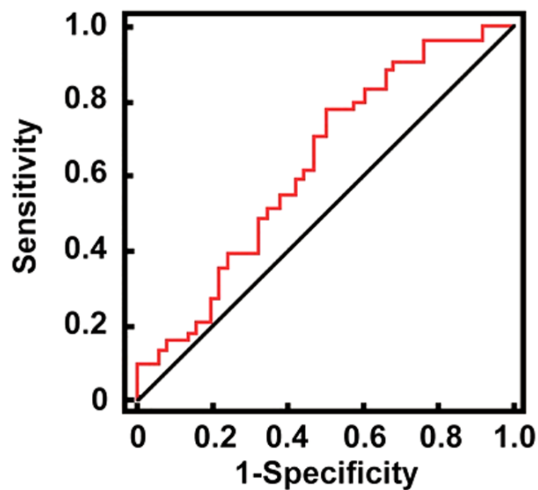

Figure 4. The ROC curve of BCR-ABL fusion gene expression level predicted the efficacy of imatinib in the treatment of chronic myeloid leukemia.

that BCR-ABL fusion gene expression was strikingly higher in patients with acute and accelerated CML than in patients with chronic CML, and BCR-ABL fusion gene expression in patients with acute CML was significantly higher than that in patients with accelerated CML. Findings of correlation analysis demonstrate that BCR-ABL fusion gene expression was clearly correlated with the stages of CML. With the levels of BCR-ABL fusion gene, the disease stages in CML patients can be accurately assessed, which is basically consistent with the findings reported by Yan et al and Dominy et al [18, 19]. A clinical trial in which BCR-ABL fusion gene expression was detected by real-time quantitative PCR reveals that dynamic monitoring of BCR-ABL fusion gene expression is helpful to screen patients with relapsed leukemia, which in turn contributes to early intervention as well as survival improvement in the patients [20]. According to another study, the positive rates of BCR-ABL fusion gene in patients with CML were profoundly higher those of patients in the control group, and the differences were statistically significant, suggesting that monitoring BCR-ABL fusion gene is helpful for diagnosis of patients and important in clinical practice.

Additionally, BCR-ABL fusion gene also plays a key role in monitoring the efficacy of allogeneic hematopoietic stem cell transplantation (Allo-HSCT) and minimal residual disease [22, 23]. A previous study reported CML patients with hematopoietic stem cell transplantation (HSCT) received post-transplant intervention based on their BCR-ABL fusion gene expression, and found that patients with immunomodulation had the highest negative conversion rate of BCR-ABL fusion gene [24]. Moreover, a cytogenetic test revealed 5-10% of CML patients had negative Ph chromosome, but approximately

30-50% of them showed positive Ph chromosome by a BCR-ABL gene test, indicating that detection of BCR-ABL fusion gene is favorable for evaluation of minimal residual disease [25]. In the present study, we assessed the effect of dynamic detection of BCR-ABL fusion gene expression by real-time quantitative PCR in monitoring the efficacy of targeted therapy with imatinib. The results show that within one year after targeted therapy with imatinib, BCR-ABL fusion gene expression decreased with the extension of treatment time, and the greatest decline occurred at 3 months after treatment, which is consistent with the finding of Khokar et al [26]. The results of the current study also demonstrate that patients with BCR-ABL fusion gene at a low level had the highest satisfaction rate and the longest disease-free survival, which were statistically different from those in patients with BCR-ABL fusion gene at a medium or high level. The area under the ROC curve reveals that detection of BCR-ABL fusion gene expression was helpful to assess the efficacy of targeted therapy with imatinib. Hence, dynamic monitoring of BCR-ABL fusion gene helps to detect patients with poor response or ones resistant to imatinib at an earlier time. This helps us to adopt more appropriate regimens for treatment early, thereby realizing accurate treatment in patients with different stages of CML and survival improvement in such patients.

In conclusion, detection of BCR-ABL fusion gene by real-time quantitative PCR is helpful to judge the stages of CML. Dynamic monitoring of BCR-ABL fusion gene is useful to assess the efficacy of imatinib and provides evidence for early detection of changes in the disease and timely adjustment of the regimens of chemotherapy, thereby improving prognosis of patients.

There are still some limitations in the present study, such as being a single center study, small sample size, unclear fluctuation of BCR-ABL fusion gene expression in different patients at the same stage of CML, and no supply of the cut-off values for BCR-ABL fusion gene expression of CML patients at relapse by the molecular and biological examination. More samples are needed in future studies, and more prospective, controlled, multi-center studies with longer follow-up are also required for further validation.

Disclosure of conflict of interest

None.

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