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MicroRNA-206 as a Novel Potential Prognostic Biomarker for Distinguishing Philadelphia Chromosome-Positive and Negative ALL Patients

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ABSTRACT

Background: MicroRNAs (miRNAs) are small non-coding RNAs that regulate protein-coding gene expression, and alterations in their expression are associated with leukemic transformation of hematopoietic cells. This study analyzed bone marrow samples from Philadelphia chromosome-positive (Ph+) and Philadelphia chromosome-negative (Ph−) acute lymphoblastic leukemia (ALL) patients to assess miR-320a and miR-206 expression and their relationship with prognosis.

Materials and Methods: miR-206 and miR-320a expression levels were assessed using real-time PCR in 50 bone marrow specimens: 10 from healthy individuals (control group), 20 from Ph+ ALL patients, and 20 from Ph− ALL patients. Data were analyzed using GraphPad Prism version 7, one-way ANOVA, and Chi-square tests.

Results: The Ph− ALL group exhibited a significant 3.8-fold reduction in miR-206 expression (P = 0.004), while the Ph+ ALL group showed a significant 5.34-fold increase (P = 0.006) compared to the control group. No statistically significant differences were observed in miR-320a expression between the Ph+ and Ph− groups relative to controls (P = 0.496 and P = 0.645, respectively). Data analysis revealed no association between age, sex, and miRNA expression.

Conclusion: MiR-206 showed differential expression, being significantly upregulated in Ph+ ALL and downregulated in Ph− ALL patients. This miRNA may serve as a potential diagnostic biomarker for distinguishing between the two ALL subgroups. However, further studies incorporating clinical outcome data are needed to confirm its prognostic value.

Keywords: Micro-RNA; Acute lymphoblastic leukemia (ALL); MiR-206; MiR-320a; Philadelphia chromosome; Biomarker

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is an invasive malignant hematological disorder that arises from the uncontrolled proliferation of lymphoid cells [1]. 80-85% of the disease is usually B-ALL type, and 20-25% appears to be T-ALL[2]. A combination of genetic changes and translocations causes a disturbance in cell proliferation and maturation pathways[2]. As a report in 2016, 6590 individuals suffered from ALL, and it was the cause of 1400 deaths in the United States of America[3]. ALL is the most prevalent malignant disorder in children, accounting for 80% of children's and 20% of adult leukemia[4]. Philadelphia chromosome (Ph), which appears as a result of a translocation between chromosomes 9 and 22, t(9;22)(q34;q11), was first recognized in chronic myeloid leukemia (CML) patients in 1960 [5]. The result of this translocation is the BCR-ABL fusion, which

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produces three protein isoforms: a 210 Kd protein that is positive in more than 90% of people with CML and 30-35% of people with ALL [6], a 190 Kd protein that is positive in 90% of children with Ph+ ALL[7,8]. These fusions are seen, and all three of these fusions increase tyrosine kinase activity, which unrestrainedly activates the JAK/STAT and RAS/MAPK/ERK cellular pathways, which increases cell proliferation signaling and resistance to apoptosis in both groups of people[9,10]. Given that treatment methods for the disease have improved in the past; however, approximately 10% of individuals with ALL do not fully recover[11]. In order to better understand the pathogenesis of ALL, it is necessary to identify the signaling and molecular pathways involved in it. To date, it has been shown that several signaling pathways are altered in patients with ALL, but the exact cause is unknown yet[12,13]. Hence, identifying appropriate biomarkers that are sufficiently sensitive and specific for the disease's prognosis is necessary.

MicroRNAs (miRNAs) are a group of small non-coding RNAs (ncRNAs) approximately 20 nucleotides in length that play a regulatory role by binding to the region of 3' untranslated region (3' UTR) in their target gene sequence, thereby inhibiting the expression or degradation of the desired mRNA [14, 15]. The earlier studies indicated the changes in the expression of microRNAs in many cancers and leukemias and their crucial role in the pathogenesis of leukemias, making them an appropriate therapeutic target in the diagnosis and follow-up process [16]. For example, miR-15a and miR-16 induce apoptosis in hematopoietic cells by affecting the anti-apoptotic gene BCL2[17]. Likewise, numerous microRNAs are mis-regulated in ALL and their expression increases or decreases, which helps to improve the prognosis and treatment of the disease[18,19].

In previous studies, measurements of miR-206 and miR-320a expression have shown a decrease in the expression of these two microRNAs in malignant cells compared to healthy individuals. Bioinformatics studies showed that in the PI3K/AKT/mTOR and Ras/MAPK/ERK pathways, AKT2, AKT3, PTEN, PIK3CA, and PDPK1 genes are among the targets of these two microRNAs. It has been beneficial to evaluate the expression of these two microRNAs as a diagnostic biomarker in the monitoring and treatment of several malignancies, including thyroid[20], breas[21], liver[22], and endometrium[23]. Since the affected genes seem to be major players in the pathogenesis of ALL, we aimed to measure the expression of miR-206 and miR-320a in patients with Philadelphia-positive (Ph+) and Philadelphia-negative (Ph-) ALL for the first time.

MATERIALS AND METHODS

Patients and sample collection

This case-control study has been approved by the ethics committee of Bushehr University of Medical Sciences with reference number IR.BPUMS.REC.1398.010. Regarding our inclusion criteria, Bone marrow samples derived from new case leukemic patients and during a period of one year from 20 Ph+ ALL and 20 Ph- ALL patients and transferred anonymously to the laboratory with a code. Informed consent was obtained from all patients. The diagnosis was based on French-American-British (FAB) criteria through morphology, as well as flow cytometry and cytogenetic analysis to confirm the presence of the Philadelphia chromosome. To rule out additional chromosomal abnormalities, FISH, and PCR techniques were performed for all patients. All patients demonstrated a normal chromosomal number, and the only distinguishing feature between the groups was the BCR-ABL status.

The control group consisted of 10 healthy individuals with no benign or malignant disease at the sampling time. Using this this formula: n= (Zalpha+Zbeta)2*s2/d2 and considering alpha=0.05, power=0.8 and fold change=4, we expressed the effect d as the Log fold-change. So, using d= log2(4) =2 and s= log2(5) = 2.32, the sample size in each group will be: n= (1.96+0.84)2 * $2.32^2/2^2$=42.19=10.54. So, we need at least 10-11 participants per group (cases or controls); with considered 20 individuals in each case group, we are well above determined threshold, providing strong power. When we use case-control design to compare microRNA expression level between groups, fold change serves as odds ratio (OR).

Quantitative real-time polymerase chain reaction (qRT-PCR)

RNA extraction and cDNA synthesis

RNA extraction was performed on bone marrow samples using an RNA extraction kit (Yekta Tajhiz Azma, Iran). Trizol solution was added to each microtube for cell lysis, and then, proteins were removed by adding chloroform. Qualitative analysis was performed using Nanodrop (Denovix, USA) and an electrophoresis gel containing 2% agarose. cDNA synthesis was performed with the oligo-dt method (Bon Yakhteh Technology Co., Tehran, Iran).

Quantitative Real-time PCR

To assess the expression level of miRNAs, Real-Time PCR was conducted by ABI Step-one Plus (Applied Biosystem, USA) using SYBR Green master mix (Yekta Tajhiz Azma, Iran) and specific primers for miR-206 and miR-320a as well as Snord-47 as a reference gene (Bon Yakhteh Co., Tehran, Iran) (Table 1). PCR condition was 10 min at 95°C, followed by 40 cycles for 15 sec at 95°C and then 1 minute at 60°C. The relative gene expression levels were analyzed by the $2^{-\Delta\Delta Ct}$ method, and statistical analyses were performed by GraphPad Prism software version 7.

Bioinformatics Studies

Target genes for miR-320a and miR-206 were analyzed using the DIANA TOOLS-miR Path v.3 (http://www.microrna.gr/miRPathv3) and miRWalk 2.0 databases (http://mirwalk.umm.uni-heidelberg.de). We examined both microRNAs based on the algorithms in the miRDB, miRMap, Targetscan, RNAhybrid, miRanda databases, and the target network of microRNAs focusing on the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, and regulated genes were identified.

Statistical analysis

The results were analyzed by GraphPad Prism software version 7. Also, Chi-square and one-way ANOVA tests were used to evaluate the gene expression differences between the studied groups, and the receiver-operating characteristic (ROC) curve and the area under the ROC curve (AUC) were used to assess the feasibility of using the miRNA expression levels as diagnostic markers for detecting and monitoring ALL. A value of $P < 0.05$ was considered a significant level in all statistical analyses, and the results are represented as mean ± SD.

RESULTS

Demographic and laboratory parameters

This study included 20 individuals with Ph+ ALL consisting of 14 males (70%) and 6 females (30%), 20 Ph- ALL patients involving 13 males (65%), and 7 females (35%), and 10 normal subjects. The mean age distribution of patients in the Ph+ ALL group was 21.18 ± 35.05, in the Ph- ALL group was 23.34 ± 25.5, and in the control, group was 22.77 ± 36.9. Demographic and laboratory data are presented in Table 2. A comparison of the studied groups and ALL types did not show a significant difference. There was no significant difference between both sexes and the ALL subcategories.

MiR-206 is a biomarker for Ph- and Ph+ ALL patients

Based on a one-way ANOVA test, there was a significant difference between the three groups in miR-206 expression ($P = 0.0001$). The Ph- ALL group showed a 3.8-fold decrease in expression compared to normal individuals, and the Ph+ ALL group showed a 5.34-fold increase in expression compared to normal individuals ($P = 0.004$ and $P = 0.006$, respectively). The Ph+ ALL group had a 20.5-fold increase in expression compared to the Ph- ALL group, which was statistically significant ($P = 0.0001$) (Figure 1).

MiR-320a in studied patients

According to the results of the miR-320a expression, based on a one-way ANOVA test, there was no statistically significant difference between the three groups ($P = 0.791$). The Ph- ALL group showed a 1.48-fold increase in expression compared to normal individuals, and the Ph+ ALL group showed a 1.8-fold increase in expression. Also, the Ph+ ALL group showed a 1.21-fold increase in expression compared to the Ph- ALL group which was not significant ($P = 0.645$, $P = 0.496$, and $P = 0.786$, respectively) (Figure 2).

The diagnostic value of miR-206 in ALL groups

MiR-206 in the Ph- ALL group showed an AUC of 0.795 (95% confidence interval [CI] = 0.627-0.962), a sensitivity of 75% and a specificity of 100%, and a *P* value of 0.009. Thereupon, this microRNA seems to have good diagnostic power in the Ph- ALL group, according to the *P* value. Besides, miR-206 in the Ph+ ALL group has an AUC of 0.720 (95% CI = 0.532-0.907) and has a sensitivity of 75% and specificity of 80% (*P* = 0.052) which according to the AUC value, miR-206 has also good diagnostic power in the Ph+ ALL group (Figure 3).

Table 1: The sequence of primers

Gene	Direction	Primer Sequence (5'→3')
MicroRNA-320a	F	AAGGTGGGTTGAG
MicroRNA-206	F	GTAGCAGTGATAGGCATT
Snord47	F	ATCACTGTAAAACCGTT
Universal reverse	R	GTAGCAGTGATAGGCATT

F: forward; R: reverse

Table 2: Demographic and laboratory data analysis

Variable	Control (n=10)	Ph+ ALL (n=20)	Ph- ALL (n=20)	*P* value
	N (%)	N (%)	N (%)	
Gender				
Female	6 (60)	6 (30)	7 (35)	0.262
Male	4 (40)	14 (70)	13 (65)	
ALL-Type				
Early Pre-B ALL		5 (25)	5 (25)	
Pre-B ALL		5 (25)	7 (35)	
Pro-B ALL		2 (10)	3 (15)	0.867
B-ALL		2 (10)	1 (5)	
T-ALL		6 (30)	4 (20)	
Age (SD)	22.77 (36.9)	21.18 (35.05)	23.34 (25.5)	0.292

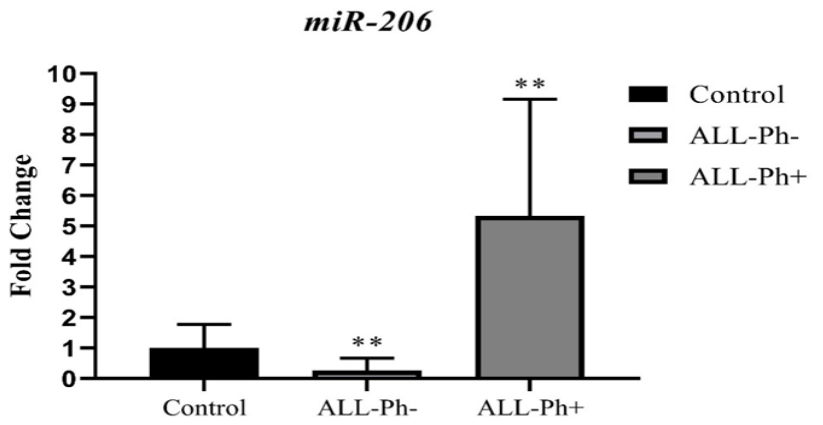

Figure 1. Expression of miR-206 in Ph- and Ph+ ALL groups compared to the control group, *P < 0.05

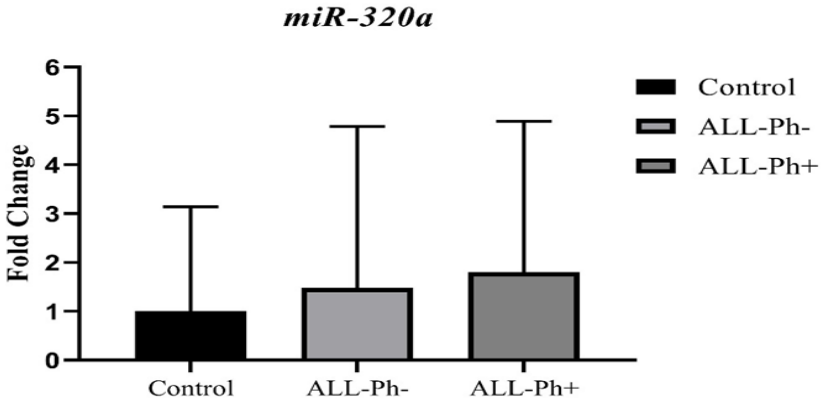

Figure 2**.** MiR-320a expression in the Ph+ and Ph- ALL group compared with the control group

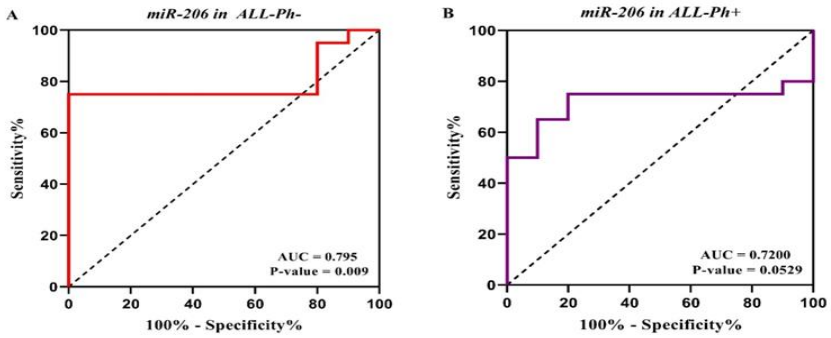

Figure 3. ROC curve in the Ph- ALL group and Ph+ ALL group for miR-206

DISCUSSION

Past studies have shown that the expression of microRNAs in cancers and leukemias could be up- or down-regulated and might be involved in the disease process [24]. MicroRNAs by binding to the 3'UTR region of their target mRNA can reduce or increase the expression of many genes involved in cellular signaling pathways, thereby can be divided into oncogenes and tumor suppressors [25]. These studies also suggested that measuring the expression of microRNAs in serum and tissue samples can indicate the process of treatment and diagnosis of the disease and be considered as a suitable biomarker[26]. In this study, we sought new microRNAs in patients with Ph+ and Ph- ALL patients, and their role as biomarkers for diagnosis and monitoring of the disease. Previous studies have revealed that the expression level of miR-206 was notably downregulated in leukemia and cancer, and this downregulation may contribute to the development of disease and poor prognosis and can play a tumor-suppressive role by affecting the cell proliferation process. But, in this study we found that miR-206 has a different expression pattern in patients compared to healthy individuals. The results of this study illustrated that the expression level of miR-206 was remarkably upregulated in patients with Ph+ ALL compared with Ph- ALL and healthy controls. Likewise, analysis of miR-206 revealed that the expression level of miR-206 was considerably downregulated in patients with Ph- ALL in comparison to Ph+ ALL and healthy controls. These findings were consistent with a study of Liu H et al. that reported miR-206 is downregulated in the serum of AML patients and be the cause of poor prognosis[27]. Other studies on solid tumors confirmed the results of this study. For instance, Wang N et al. in a study on lung cancer has asserted that the upregulation of miR-206 is accompanied by the suppression of tumor growth and cancer progression[28]. In addition, Zheng Y et al. found that in patient with endometrial cancer, miR-206 was downregulated and upregulation of this microRNA could inhibit tumor progression through the PTEN/AKT/mTOR pathway[29]. However, studies on other cancers, such as lung cancer [30], liver carcinoma[31], and breast [32], have also shown reduced expression of this microRNA and invasion of the disease. In our study, we also evaluated the expression level of miR-320a. We found no significant differences between patients with Ph- ALL and Ph+ ALL with healthy controls. So far, reduced expression of miR-320a in cancers such as breast[33], liver[34], lung[35], colon[36], prostate[37], have been reported, and only one case of increased expression of this microRNA reported in neuroblastoma compared to normal retinal tissues [38]. Another study found that miR-320a, which inhibits survivin expression and induces apoptosis, was downregulated in TEL/AML1-positive ALL cases[39]. Another study conducted in 2015 on patients with chronic myelocytic leukemia found that overexpressing miR-320a could reduce proliferation and invasion, increase apoptosis in these patients, as well as inhibiting NFKB/PIK3/AKT phosphorylation by binding to the 3'UTR and 5'UTR region of BCR-ABL mRNA[40]. Bioinformatics studies and the KEGG pathway analysis demonstrated that miR-206 and miR-320a target key genes in PI3K/PTEN/AKT, and RAS/MAPK signaling pathways, which are related to the development and progression of ALL. This result was consistent with a study by Q Chen et al. Which demonstrated that increased expression of miR-206 could inhibit tumor invasion in lung cancer by affecting genes in the PI3K/AKT pathway. Other studies have suggested that increased expression of miR-320a may control survivin expression, an inhibitory factor in apoptosis, and improve prognosis in patients with ALL. Also, based on the present study, according to ROC curve analysis, the expression of miR-206 in patients has a favorable sensitivity and specificity, and it seems that it could be used as a diagnostic biomarker in this malignancy. Analysis of miRNA expression data showed that miR-206 has upregulated in Ph+ ALL patients and downregulated in Ph- ALL patients. This result may be attributed to the high progression of the disease through the cellular signaling pathway and could be a biomarker for distinguishing between these groups of patients.

CONCLUSION

Our results suggest that inducing increased expression of miR-206 in people with Ph- ALL could be a proper therapeutic goal in future studies. Moreover, preparing an anti-miR against miR-206 can neutralize the oncogenic effect of miR-206 in Ph+ ALL and inhibit their disease development. Experiments on more samples, RNA extracted from serum and peripheral blood, and the expression of these microRNAs in newly diagnosed patients and after treatment is one of the subsequent suggestions of this study.

Abbreviations

ALL: Acute lymphoblastic leukemia
AML: Acute myeloid leukemia
CML-N: neutrophilic-chronic myeloid leukemia
JAK/STAT: Janus kinase/signal transducer and activator of transcription
MiRNA: micro ribonucleic acid
ncRNAs: non-coding RNAs
PDPK1: 3-Phosphoinositide Dependent Protein Kinase 1
PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PTEN: Phosphatase and tensin homolog
Real-Time PCR: real-time polymerase chain reaction
ROC, receiver operating characteristics curve
UTR: untranslated region

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

Compliance with Ethical Standards

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request and with permission from the Bushehr University of Medical Sciences (Iran).

Research involving human participants and/or animals

The present study included human participants in two groups of ALL patients and healthy individuals as control.

Informed consent

Informed consent was obtained from all patients.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Bushehr University of Medical Sciences.

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