How is Aurora Kinase A Expression Altered in Chronic Lymphocytic Leukemia?

Kronik Lenfositik Lösemide Aurora Kinaz A Ekspresyonu Değişikliği

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Abstract

Aurora kinase A is an enzyme which regulates the maturation and separation of centrosomes and the assembly and stability of mitotic spindles during mitosis. The dysregulation of Aurora kinase A is related with aneuploidy and a pronounced increase in cancer risk. This study aims to determine how the expression of Aurora kinase A is altered in chronic lymphocytic leukemia (CLL). This prospective case-control study reviewed 41 patients who were newly diagnosed with CLL and 18 patients with benign hematological diseases. Bone marrow aspiration and biopsy were performed in all patients. Aurora kinase A expression in bone marrow cells was assessed by quantitative reverse transcriptase-polymerase chain reaction. Bone marrow specimens were immunohistochemically stained for Aurora-A antibody. Chromosomal abnormalities including 13q deletion, 17p deletion and trisomy 12 were investigated by fluorescence in situ hybridization in bone marrow aspirates of CLL patients. The CLL patients and the patients with benign hematological diseases were statistically similar in aspect of Aurora kinase A mRNA expression through β-actin and GAPDH housekeeping genes (respectively p=0.742 and p=0.229). Positive immunohistochemical staining for Aurora kinase A was significantly more frequent in CLL patients (p<0.001). Immunohistochemical staining for Aurora kinase A in bone marrow biopsies of CLL patients did not change significantly with respect to cytogenetic abnormalities such as 13q deletion, 17p deletion or trisomy 12 (p>0.05 for all). Aurora kinase A may play a role in the pathogenesis of CLL but this role may not be as evident as it has previously been specified.

Keywords: Aurora Kinase A, Bone Marrow, Chronic Lymphocytic Leukemia

Öz

Aurora kinaz A, sentrozomların olgunlaşması ve ayrılmasını, mitoz sırasında iğ ipliklerinin oluşumu ve stabilitesini düzenleyen bir enzimdir. Aurora kinaz A'nın düzensizliği anöploidi ve kanser riskinde belirgin artış ile ilişkilidir. Bu çalışma, Aurora kinaz A ekspresyonunun kronik lenfositik lösemide (KLL) nasıl değiştiğini belirlemeyi amaçlamaktadır. Bu prospektif olgu-kontrol çalışmasında yeni tanı konmuş 41 KLL hastası ve benign hematolojik hastalıklara sahip 18 hasta değerlendirildi. Tüm hastalara kemik iliği aspirasyon ve biyopsisi uygulandı. Kemik iliği hücrelerinde Aurora kinaz A ekspresyonu, kantitatif ters transkriptaz-polimeraz zincir reaksiyonu ile belirlendi. Kemik iliği kesitleri immunhistokimyasal olarak Aurora-A antikoru için boyandı. KLL hastalarının kemik iliği aspiratlarında floresans insitu hibridizasyon yöntemiyle 13q delesyonu, 17p delesyonu ve trizomi 12 kromozom anomalileri araştırıldı. KLL hastaları ve benign hematolojik hastalığı olan hastalar, Aurora kinaz A mRNA ekspresyonu açısından istatistiksel olarak benzerdi (β-actin ve GAPDH housekeeping genleri için sırasıyla p=0.742 ve p=0.229). Aurora kinaz A için pozitif immunhistokimyasal boyanma KLL hastalarında anlamlı olarak daha sıktı (p<0.001). KLL hastalarının kemik iliği biyopsilerinde Aurora kinaz A immunhistokimyasal boyanması açısından, 13q delesyonu, 17p delesyonu veya trizomi 12 gibi sitogenetik anormaliklerle ilgili anlamlı farklılık gözlenmedi (p>0.05 her biri için). Aurora kinaz A, KLL patogenezinde rol oynayabilir ancak bu rol daha önce belirtildiği kadar belirgin olmayabilir.

Anahtar Kelimeler: Aurora Kinaz A, Kemik Iliği, Kronik Lenfositik Lösemi

Introduction

Chronic lymphocytic leukemia (CLL) is the most frequently encountered type of leukemia in adults living throughout Europe. This disease has been characterized with the accumulation of CD5+ B-lymphocytes in blood, bone marrow and lymph nodes. Since CLL cells in peripheral circulation are at the G0 phase of cell cycle and have a relatively long life, it has been hypothesized that CLL is a stabile clinical entity. However, considerably high proliferation rate of leukemic cells acts as a contradiction for this hypothesis (1-3).

Aurora kinases are a group of mitotic serine/threonine kinases which participate in the regulation of the maturation and separation of centrosomes, formation of mitotic spindles, segregation of sister chromatids and division of cytoplasmic volume. Aurora kinases are categorized into three types which are named as Aurora kinase A, Aurora kinase B and Aurora kinase C which have high sequence homology. The three Aurora mitotic kinases are situated within the centrosome during different phases of mitosis (4-6).

Aurora kinase A is an enzyme encoded by the AURKA gene which has a chromosomal

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localization of 20q13.2. Aurora kinase A is associated with centrosome maturation and separation and thereby regulates the assembly and stability of mitotic spindles during mitosis. As Aurora kinase A is required for the completion of cytokinesis, its dysregulation leads to aneuploidy and, thus a pronounced increase in cancer risk. Normally, the expression of Aurora kinase A is kept under the control of tumor suppressor protein p53 (7-10).

It has been shown that Aurora kinase A undergoes overexpression in solid tumors, multiple myeloma, acute leukemia, and lymphomas (11-16). Moreover, mutations that involve the chromosomal localization of AURKA gene are generally considered as a poor prognostic factor (17-19). However, there are few studies showing that the expression of Aurora kinase increases in chronic lymphocytic leukemia and there are conflicting results regarding the relationship with cytogenetic abnormalities. This study aims to determine how expression of Aurora kinase A changes in CLL patients and whether there is any relationship between cytogenetic abnormalities and Aurora kinase expression.

Material and Method

This prospective case-control study was approved by the Ethical Committee of Adnan Menderes University encoded approval letter (dated 13/09/2012 and numbered 050.04-245). This study was undertaken at the Department of Hematology.

This is a review of 41 patients who were newly diagnosed with CLL and 18 patients who had benign hematological diseases. In the former group, the diagnosis of CLL was made according to the criteria of International CLL Study Group and it was made sure that the CLL patients did not receive any treatment during the study period. In the latter group, six patients (33.3%) had iron deficiency anemia, six patients (33.3%) had immune thrombocytopenic purpura, three patients (16.6%) had dimorphic anemia, one patient (5.6%) had megaloblastic anemia, one patient (5.6%) had autoimmune hemolytic anemia and one patient (5.6%) had hydatid disease. All patients with solid organ tumor and hematological malignancies except CLL were excluded from the study. The CLL patients were evaluated according to the Binet classification system. Bone marrow aspiration and biopsy were performed in all patients with CLL and benign hematological diseases.

Evaluation of Aurora Kinase A mRNA Expression: Aurora kinase A mRNA expression was assessed by quantitative reverse transcription polymerase chain reaction (RT-PCR) in bone marrow cells by using β-actin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA as internal controls. Total RNA was extracted from bone marrow cells by Trizol method (High Pure Isolation Kit, Roche Diagnostics, Mannheim, Germany) and cDNA was prepared by Transcriptor First Strand cDNA Synthesis Kit (Roche Diagnostics, Mannheim, Germany). Aurora kinase A cDNA was prepared by TaqMan Universal PCR Mastermix (Applied Biosystems, Foster City, CA, USA) and quantified by Aurora-A TaqMan Gene Expression Assay. The expression by β-actin was evaluated by TaqMan Universal PCR Mastermix using 400nM forward (CCCTGGCACCCAGCAC) and reverse (GCCGATCCACACGGAGTAC) primers and 100nM concentration probe (fam-ATCAAGATCATTGCT CCTCCTGAGCGC-bhq). RT-PCR was performed by LightCycler 480II (Roche Diagnostics). Relative RNA levels were obtained by standard delta/delta Ct (δ/δ Ct) method which normalized AURKA gene Ct values by β-actin and GAPDH and yielded δ Ct values. The patient groups were compared and δ/δ Ct values were estimated. The δ/δ Ct values over 2 were interpreted as AURKA positive expression and δ/δ Ct values less than -2 were regarded as down-regulation.

Immunohistochemical Staining for Aurora Kinase A: Bone marrow specimens that were fixed with formalin and embedded in paraffin were immunohistochemically stained for Aurora kinase A. The tissue sections were incubated with Aurora A antibodies in 1:100 dilution in 60 minutes (Novus Biologicals Inc., Littleton, CO, USA). An experienced pathologist who was blinded to the clinical characteristics of the patients evaluated the bone marrow specimens. The existence of >10% staining in bone marrow cells was addressed as positive staining while the existence of 1% to 10% staining in bone marrow cells was defined as weakly positive staining. The lack of any staining in bone marrow cells was identified to be negative staining.

Cytogenetic Analysis: Fluorescence in situ hybridization was used to determine cytogenetic abnormalities in bone marrow aspirates of CLL patients. Thirty-five of 41 patients were investigated for 17p13.1 deletion, while 32 patients and 31 patients for 13q14.3 deletion and for trisomy 12, respectively.

Statistical Analysis: Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS, SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum-maximum) whereas categorical variables were denoted as numbers and percentages. One way ANOVA, chi square test, Fisher's Exact Test and Mann Whitney U test were used for statistical comparisons. Two-tailed p values <0.05 were accepted to be statistically significant.

Results

Characteristics of the Patients: Fourty-one patients (22 men and 19 women) who were newly diagnosed with CLL and 18 patients (7 men and 11 women) with benign hematological disease were retrospectively reviewed. The patients with CLL had significantly higher age than that of the patients with benign hematological diseases (70.2±10.1 years vs 53.3±20.0 years, p=0.032). Twenty-eight patients with CLL (68.3%) had stage A disease while two patients with CLL (4.9%) had stage B disease and eleven patients (26.8%) had stage C disease according to Binet classification. Neither the expression of Aurora kinase A nor the immonuhistochemical staining for this enzyme was correlated with Binet classification of CLL in this study.

Table 1 compares the hematological parameters of CLL patients and patients with benign hematological diseases. The CLL patients had significantly higher leukocyte and lymphocyte counts than the patients with benign hematological diseases (p<0.001 for both).

Evaluation of Aurora Kinase A mRNA Expression: Table 2 shows the Aurora kinase A mRNA expression of two groups of the patients. The CLL patients and the patients with benign hematological diseases were statistically similar in aspect of Aurora kinase A mRNA expression through β-actin ve GAPDH housekeeping genes (respectively p=0.742 ve p=0.229).

Immunohistochemical Staining for Aurora Kinase A: Figure 1-3 displays the positive, weakly positive and negative immunohistochemical staining for Aurora kinase A in bone marrow tissues of the patients. Table 3 demonstrates the immunohistochemical staining for Aurora kinase A in bone marrow biopsies of CLL patients and patients with benign hematological diseases.

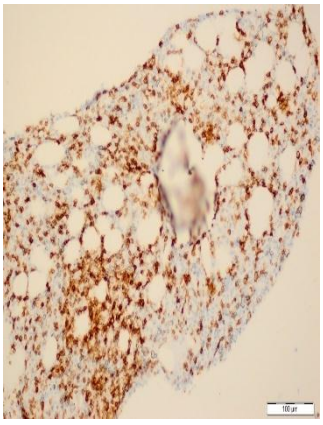

Figure 1. Positive immunohistochemical staining for Aurora Kinase A in bone marrow biopsy section of a chronic lymphocytic leukemia patient.

Positive immunohistochemical staining for Aurora kinase A was significantly more frequent in CLL patients (p<0.001).

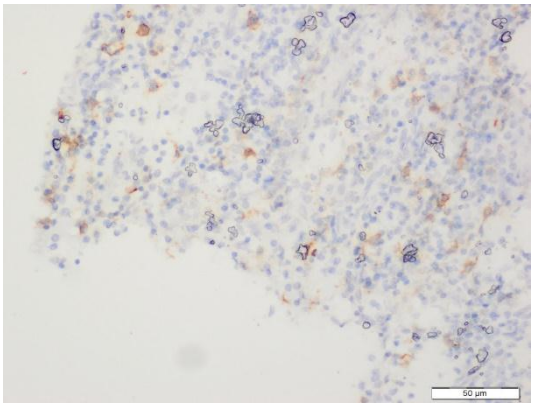

Figure 2. Weakly positive immunohistochemical staining for Aurora Kinase A in bone marrow biopsy section of a control group patient.

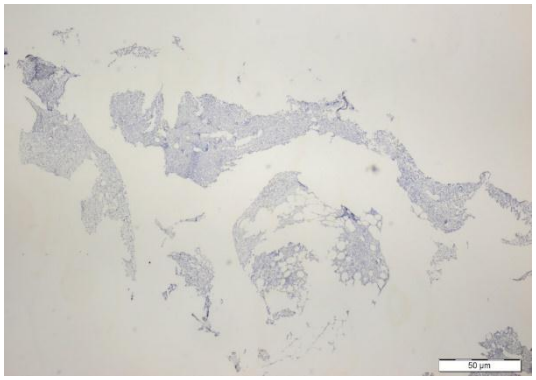

Figure 3. Negative immunohistochemical staining for Aurora Kinase A in bone marrow biopsy section.

Cytogenetic Analysis: Table 4 demonstrates that the immunohistochemical staining for Aurora kinase A in bone marrow biopsies of CLL patients does not change significantly with respect to cytogenetic abnormalities including 17p deletion, 13q deletion and trisomy 12 (p>0.05 for all).

Discussion

Bone marrow is an important site for the activation and proliferation of malignant B cells in CLL patients. These malignant B cells interact with the other cells located in bone marrow so that these cells survive and proliferate. The clarification of these interactions within a dynamic microenvironment is important for the identification of novel potential targets and, thus, the development of new treatment modalities (20,21). Aurora kinase A can be addressed as such a potential target because it is an enzyme which is needed for chromosomal segregation during mitosis. It has been reported that the overexpression of Aurora kinase A is related with chromosomal disturbance and tumor proliferation especially in rapidly progressive hematological malignancies such as acute leukemias and aggressive lymphomas (22,23).

Table 1. Hematological parameters of patient groups

	Chronic lymphocytic leukemia (n=41)	Benign hematological diseases (n=18)	p
Hemoglobin (g/dL)	11.5 ± 2.2	10.0 ± 3.1	0.098
Hematocrit (%)	36.4 ± 7.1	31.1 ± 9.2	0.059
Leukocyte count (/µL)	45054.4 ± 33156.5	6897.4 ± 3437.3	< 0.001*
Lymphocyte count (/µL)	34184.3 ± 25323.2	1601.1 ± 652.2	< 0.001*
Monocytes count (/µL)	2028.3 ± 9955.4	498.0 ± 421.1	0.469
Platelet count (/µL)	199341.1 ± 86517	198056 ± 156828	0.581

*p<0.05 was accepted to be statistically significant.

Table 2: Aurora Kinase A mRNA expression of patient groups

	Aurora Kinase A mRNA (β-actin)				Aurora Kinase A mRNA (GAPDH)			
	Min.	**Max.**	**Mean±SD**	**p**	**Min.**	**Max.**	**Mean±SD**	**p**
Chronic lymphocytic leukemia (n=41)	1.02	9.61	3.84±2.61	0.742	1	9.81	3.49±2.31	0.229
Benign hematological diseases (n=18)	1.09	9.88	3.91±2.71		1.21	7.73	4.29±2.42	

Table 3: Immunohistochemical staining for Aurora Kinase A in bone marrow biopsies of patient groups

	Immunohistochemical staining for Aurora Kinase A			p
	Positive	**Negative**	**Weakly positive**	
Chronic lymphocytic leukemia (n=41)	25 (61.0%)	16 (39.0%)	-	< 0.001
Benign hematological diseases (n=18)	0 (0.0%)	14 (%77.8)	4 (22.2%)	

Table 4: Immunohistochemical staining for Aurora Kinase A in bone marrow biopsies of chronic lymphocytic leukemia patients with respect to cytogenetic abnormalities

	Immunohistochemical staining for Aurora Kinase A		p
	Positive	**Negative**	
13q14.3 deletion (+)	12 (71.0%)	5 (29.0%)	0.314
13q14.3 deletion (-)	8 (53.0%)	7 (47.0%)	
17p13.1 deletion (+)	2 (50.0%)	2 (50.0%)	0.572
17p13.1 deletion (-)	20 (64.5%)	11 (35.5%)	
Trisomy 12 (+)	1 (33.3%)	2 (66.7%)	0.296
Trisomy 12 (-)	18 (64.0%)	10 (36.0%)	

On the other hand, Inamdar et al. were the first to investigate the expression of Aurora kinase A in CLL the disease with less proliferative capacity than leukemia and lymphoma. They compared the expression of Aurora kinase A in peripheral blood and bone marrow of 47 patients with CLL and 20 age-matched healthy subjects. Aurora kinase A levels were significantly higher in lymphocytes of CLL patients than those of healthy people. Immunohistochemical staining indicated the expression of Aurora kinase A in all CLL patients and this expression was significantly stronger in larger prolymphocytes and paraimmunoblasts than small lymphocytes. In contrast, normal bone marrow reactive lymphocytes were negative for Aurora kinase-A with positive histiocytes and immature myeloid cells. Moreover, chromosomal aberrations including trisomy 12 and deletion of ataxia telangiectasia-mutated gene were defined in two thirds of CLL patients with enhanced Aurora kinase A expression (24).

Later, an investigation was carried out to determine the gene expression profiles of B cells that were isolated from bone marrow and peripheral blood specimens of CLL patients. It was found out that the gene for Aurora kinase A was significantly up-regulated in B cells within the bone marrow. The down-regulation of Aurora kinase A by RNA interference suppressed the proliferation of CLL cells and mildly induced apoptosis. Therefore, it has been proposed that the overexpression of Aurora kinase A is related with chromosomal abnormalities which participate in the pathogenesis of CLL and effect its prognosis. Therefore, Aurora kinase A is a potential novel target in building up new strategies for CLL treatment (25). Indeed, MLN8237

(alisertib) has been developed as an inhibitor of Aurora kinase A and it has been tested for the treatment of advanced hematological malignancies.

As for the present study, Aurora kinase A mRNA expression through β-actin and GAPDH housekeeping genes was statistically similar in bone marrow specimens of 41 patients with CLL and 18 patients with benign hematological diseases. Although positive staining for aurora kinase A was significantly more frequent in bone marrow biopsies of CLL patients, the staining for Aurora kinase A was correlated with neither Binet classification nor cytogenetic abnormalities (including 17p deletion, 13q deletion and trisomy 12).

In the present study, aurora kinase A expression was increased in both the control group and the study group, unlike the previous study. Furthermore, no correlation was found between poor or good cytogenetic features and aurora kinase expression. Our findings appear to contradict the findings of the study mentioned above. The control group consisting of patients with benign hematological diseases can be regarded as a major reason for the aforementioned contradiction. That is, mitotic activity within bone marrow is somehow induced and the release of precursor cells is increased in case of anemia and/or thrombocytopenia (26, 27). Thus, the expression of Aurora kinase A may has been enhanced in benign hematological diseases as well. This could have led to the failure in detecting a significant difference between CLL patients and patients with benign hematological diseases in aspect of Aurora kinase A expression.

Another reason for the discrepancy between our findings and the previous report is that lymph nodes generate stronger stimuli for the proliferation of malignant B cells. That's why, the changes in Aurora kinase A expression of bone marrow cells may have been less marked than the changes in Aurora kinase A expression of peripheral blood cells (25, 28). This might be an explanation for the paradoxicality between molecular and immunohistochemical findings of our study.

Alternatively, the differences in the expression profiles could be related to technical issues, such as the dilution of the bone marrow aspirates with malignant B cells in peripheral blood or underrepresentation of malignant B cells in direct contact with the bone marrow stroma (25,29). In addition, ethnic and demographic variations in the study cohort and relatively small cohort size might have caused the variations in expression profiles for Aurora A kinase. The lack of any correlation between cytogenetic abnormalities and Aurora A kinase expression might be interpreted as an evidence for this hypothesis.

RT-PCR results may not always correlate with protein based methods such as western blot or Immunohistochemical staining (30,31); for reasons like mRNA half-life, translation efficiency, and protein stability, post transcriptional and post-translational regulatory mechanisms (32) and misclassification due to measurement errors (33, 34).

Although the study population is very low, another possible hypothesis is that the increased expression of aurora kinase A may not have clinical and prognostic significance in patients with chronic lymphocytic leukemia. We thought that the results of a recent phase I study with the aurora kinase inhibitor MLN8237 (alisertib) may support this hypothesis. No clinical response was observed in a small number of CLL patients in this study which investigated the efficacy and safety of MLN8237, an aurora kinase inhibitor in patients with hematological malignancies (35).

In conclusion, this study points out that Aurora kinase A may play a role in the pathogenesis of CLL. However, it may not have any clinical and prognostic relevance in these patients. However, the relatively small sample size and the absence of a control group made up by healthy individuals limit the power of this study. Further clinical trials with large number of patients should be conducted to understand whether the expression of Aurora kinase A have any clinical and prognostic significance in CLL patients.

Ethics Committee Approval: Adnan Menderes University Ethics Committee Permission was obtained with the letter dated 13.09.2012 and numbered 050.04-245.

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