Original Article / Özgün Makale

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.735979
J Health Sci Med 2020; 3(3): 307-311

P210 breakpoint is associated with less minimal residual disease compared to p190 breakpoint in acute lymphoblastic leukemia patients with Philadelphia chromosome

Philadelphia kromozomu olan akut lenfoblastik lösemi hastalarında p210 kırılma noktası P190 kırılma noktasına göre daha az minimal kalıntı hastalığı ile ilişkilidir

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Cite this article as / Bu makaleye atıf için: Yiğenoğlu TN, Bahsi T, Erdem HB, et al. P210 breakpoint is associated with less minimal residual disease compared to p190 breakpoint in acute lymphoblastic leukemia patients with Philadelphia chromosome. J Health Sci Med 2020; 3(3): 307-311.

ABSTRACT

Introduction: The Philadelphia chromosome is the most common cytogenetic abnormality in adult patients with acute lymphoblastic leukemia. In addition to its role in treatment choice, evaluation of Philadelphia chromosome is also important to monitor the minimal residual disease. In this study, we aim to study the differences of minimal residual disease status between 2 breakpoint regions (p190 and p210) in adult patients with acute lymphoblastic leukemia.

Material and Method: The data of 205 acute lymphoblastic leukemia patients whose genetic evaluations were performed at our center between March 2010 and February 2019 were retrospectively analyzed.

Results: Philadelphia chromosome was observed in 30 (14.6%) patients. In 75% of the patients who had p210 breakpoint at the time of diagnosis, minimal residual disease was negative after 2 cycles of chemotherapy whereas only 42.8% of the patients who had p190 at the time of diagnosis, minimal residual disease was negative after 2 cycles of chemotherapy. The frequency of Philadelphia chromosome was the highest in 51-60 years age group and it was the least in 18-39 age group in adult B cell acute lymphoblastic leukemia patients.

Conclusion: To the best of our knowledge, this is the first study which evaluated the minimal residual disease status of Philadelphia positive acute lymphoblastic leukemia patients by classifying them into 2 groups according to 2 breakpoints (p190 and p210) in the BCR locus. In our study, we found that p190 breakpoint is associated with less minimal residual disease negative status compared to the patients with p210 breakpoint, therefore more augmented therapies may be preferred in patients with p190 breakpoint compared to therapies of patients with p210 breakpoint.

Keywords: Philadelphia chromosome, minimal residual disease, p210 breakpoint, p190 breakpoint

ÖZ

Giriş: Philadelphia kromozomu, akut lenfoblastik lösemili erişkin hastalarda en sık görülen sitogenetik anormalliktir. Philadelphia kromozomunun değerlendirilmesi, tedavi seçimindeki rolüne ek olarak minimal rezidüel hastalığı izlemek için önemlidir. Bu çalışmada akut lenfoblastik lösemili yetişkin hastalarda 2 kırılma noktası (p190 ve p210) arasındaki minimal rezidüel hastalığı durumu farklılıklarını araştırmayı amaçladık.

Gereç ve Yöntem: Mart 2010-Şubat 2019 tarihleri arasında merkezimizde genetik tetkikleri yapılan 205 akut lenfoblastik lösemili hastasının verileri retrospektif olarak incelendi.

Bulgular: 30 hastada (%14,6) Philadelphia kromozomu gözlendi. Tanı anında p210 kırılma noktası olan hastaların %75'inde 2 siklus kemoterapi sonrasında minimal rezidüel hastalığı negatif hale gelirken, tanı anında p190 kırılma noktası olan hastaların sadece %42,8'inde 2 siklus kemoterapi sonrasında minimal rezidüel hastalığı negatif hale geldi. Philadelphia kromozomu sıklığı 51-60 yaş grubunda en yüksek, 18-39 yaş grubunda en az idi.

Sonuç: Literatür taramamıza göre bu çalışma, Philadelphia pozitif akut lenfoblastik lösemili hastalarının minimal rezidüel hastalığı durumunu kırılma noktalarına göre (p190 ve p210) 2 gruba ayırarak değerlendiren ilk çalışmadır. Çalışmamızda BCR lokusundaki p190 kırılma noktasının, p210 kırılma noktasına sahip hastalara kıyasla daha az minimal rezidüel hastalığı negatif durum ile ilişkili olduğunu bulduk, bu nedenle p190 kırılma noktası olan hastalarda p210 kırılma noktası olan hastalarda kullanılan tedavilere kıyasla daha fazla yoğun tedaviler tercih edilebilir.

Anahtar Kelimeler: Philadelphia kromozomu, minimal rezidüel hastalık, p210 kırılma noktası, p190 kırılma noktası

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Received / Geliş: 12.05.2020 **Accepted / Kabul:** 08.06.2020

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a hematological malignancy characterized by abnormal proliferation of lymphoblasts and can be originated from B-cell lineage (B-ALL) or less commonly T-cell lineage (T-ALL). ALL is a heterogeneous disease that has different morphologic, cytogenetic, and molecular subgroups and becomes symptomatic in a short time due to its aggressive nature (1-3). ALL is the most common childhood malignancy, represents about 80% of all childhood leukemias; but only about 20% of adult leukemias. It has a bimodal distribution that has a peak at 4-5 years and 50 years. The incidence is up to 5/100,000 in children and 2/100,000 in adults (4). Diagnosis of ALL depends on the evaluation of morphology, flow cytometry, immunophenotyping, identification of cytogenetic and molecular abnormalities (4).

The pathogenesis of ALL patients involves a complex chain of events that block the proliferation and differentiation of lymphoid precursor cells and drive aberrant cell proliferation and survival. Improvements in the field of genetic revealed that several changes in the genome are required for leukemogenesis (4,5). The characterization of these genetic alterations that required for leukemogenesis has allowed the identification of the genes critical for pathogenesis and prognosis of ALL (6-8). Wiemels et al. (9) showed that there were chromosomal translocations and rearrangements of the TELAML1 fusion gene in neonatal blood cells of identical twin children with ALL, even several years before the onset of the disease and this may be the earliest evidence about the relation between genetic alterations and ALL pathogenesis. Currently, in more than 80% of ALL patients, numerical and structural chromosomal abnormalities can be identified due to the advances in conventional and molecular methods (5,10-12).

The evaluation of genetic alterations is crucial for diagnosis, risk classification and treatment choice (13). World Health Organization (WHO) classification of hematopoietic neoplasms, the category "B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities" has 7 recurrent genetic abnormalities including t(9;22) (q34.1;q11.2), BCR-ABL1; t(v;11q23.3), KMT2A rearranged; t(12;21) (p13.2;q22.1), ETV6-RUNX1; hyperdiploidy; hypodiploidy; t(5;14) (q31.1;q32.3), IL3-IGH; t(1;19) (q23;p13.3); TCF3-PBX1 and 2 provisional entities including BCR-ABL1–like and iAMP21 s14.

The Philadelphia (Ph) chromosome is the most common cytogenetic abnormality in adult patients with ALL and the incidence increases with age. It is observed in 3% of childhood ALL cases and up to 50% of ALL patients at the age of 50 years and older (15-20). Ph chromosome results from a reciprocal translocation between the Abelson (ABL-1) oncogene on the long arm of chromosome 9 and a breakpoint cluster region (BCR) on the long arm of chromosome 22. Because of this translocation, BCR gene is joined to the ABL oncogene and forms BCR-ABL fusion gene. This fusion gene encodes an oncogenic protein with constitutively active tyrosine kinase activity that interacts with RAS, AKT, and JAK/STAT pathways and contributes to proliferation and tumor growth (21-23). In adult ALL patients with Ph chromosome, approximately 25% have a p210 breakpoint and 75% have a p190 breakpoint in the BCR locus (23).

Ph positive ALL has a high risk for relapse and central nervous system (CNS) involvement, patients typically present with an aggressive clinical course. Historically, patients with Ph positive ALL had an inferior outcome when compared to the patients with Ph negative ALL but the prognosis of Ph positive ALL patients had changed after the introduction of tyrosine kinase inhibitors (TKIs) into clinical practice (24,25). Therefore, evaluation of Ph chromosome at the time of diagnosis is very important since it has an important role in the treatment choice. In addition to its role in treatment choice, evaluation of Ph chromosome is also important to monitor the disease status and minimal residual disease (MRD). MRD monitoring is crucial for early relapse estimation and treatment decisions. Previous studies revealed that 2 breakpoint regions may be associated with different clinical phenotypes in adult ALL patients (26). In this study, we aimed to investigate the differences of MRD status between 2 breakpoint regions (p190 and p210) in adult patients with Ph positive ALL.

MATERIAL AND METHOD

The data of 205 ALL patients whose genetic evaluations were performed at our center between March 2010 and February 2019 were retrospectively analyzed. This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Permission granted /Decision number: 04.12.2019/475).

Patients aged between 18-40 years, received Danafarber chemotherapy protocol, those aged between 41-55 years received HyperCVAD chemotherapy protocol and those at the age of 56 and older and had good performance status received Ewall chemotherapy protocol whereas patients with poor performance status received vincristine and dexamethazone. Performance status was evaluated with Eastern Cooperative Oncology Group (ECOG) and Charlson Comorbidity Index (CCI). Good performance status was accepted as ECOG:0-2 or CCI:1-2 whereas poor performance status was accepted as ECOG:3-4 or CCI>2. MRD status was evaluated after 2 cycles of chemotherapy. 4 log reduction of abnormal transcript number after induction therapy was accepted as MRD negative.

Written informed consent was obtained from all patients before testing for the use of their ribonucleic acid (RNA) samples for research purposes. Total RNA from ethylenediaminetetraacetic acid (EDTA) -anticoagulated peripheral blood was extracted with an RNA extraction kit (QIAamp RNA Blood Mini Kit). RNA was reverse transcribed with an Ipsogen® RT Kit. cDNA was stored at -20 °C. BCR-ABL1 cDNA was performed on Qiagene Rotor-Gene-Q with TaqMan probes, according to manufacturer's instructions. Each Ipsogen BCR-ABL1 Mbcr Kit provides four standard dilutions for ABL and five standard dilutions for Mbcr. Use of the Ipsogen BCR-ABL1 Mbcr kits enables detection and quantification of BCR-ABL1 and ABL transcripts. The reaction was initiated according to the optimized protocols defined by the manufacturer.

The statistical analyses were performed with SPSS V21.0 (SPSS Inc., Chicago, IL) software. Descriptive statistics were used to summarize the data.

RESULTS

Two hundred five patients with B cell ALL were included in the study. Ph chromosome was observed in 30 (14.6%) patients. In adult ALL patients with Ph chromosome 14 (53.3%) had p210 breakpoint and 16 (46.7%) had p190 breakpoint in the BCR locus. There was not any patients who had both p190 and p210 breakpoints. Median age of the patients with Ph chromosome was 56. The characteristics of the patients with Ph positive ALL is given in **Table 1**. The frequency of Ph chromosome was the highest in 51-60 years age group and it was the least in 18-39 age group in adult B cell ALL patients. The frequency of Ph chromosome according to the age groups is given in **Table 2**. In 75% of the patients who had p210 at the time of diagnosis, MRD was negative after 2 cycles of chemotherapy whereas only 42.8% of the patients who had p190 at the time of diagnosis, MRD was negative after 2 cycles of chemotherapy.

Table 1. The characteristics of patients with Ph positive ALL

	p210 positive	p190 positive	Ph Chromosome
n	16	14	30
Gender	7 female	7 female	14 female
	9 male	7 male	16 female
Median age	55 (range 18-66)	56 (range 18-76)	56 (range 18-76)

Ph Chromosome: Philadelphia Chromosome

Table 2. The frequency of Ph chromosome according to age groups

Age group	n	p210 positive	p190 positive	Ph Chromosome
18-39	96	4	5	9 (9.3%)
40-50	39	3	2	5 (12.8%)
51-60	38	6	5	11 (28.9%)
>60	32	3	2	5 (15.6%)
≥18	205	16	14	30 (14.6%)

Ph Chromosome: Philadelphia Chromosome

DISCUSSION

ALL arises from recurrent genetic alterations that block precursor B and T cell differentiation (22). The etiology of ALL has been under investigation for decades but the exact cause is still unknown (27). Genetic alterations are observed in approximately 75% of patients with ALL (20). These genetic alterations influence the prognosis and therapeutic approach (20). ALL has a mean survival of 35% in patients aged between 18 and 60 years (28). Because of this poor survival, markers that can be translated to therapeutic targets are very important (29). Nowell and Hungerford (30) described the translocation between chromosomes 9 and 22 leading to the short chromosome 22. Observation of the role of BCR-ABL fusion gene in the leukemogenesis led to the development of a number of TKIs for the treatment of Ph positive B-ALL (31).

In the study conducted by Bartram et al. (3) Ph chromosome was found in 25% of adult ALL patients and up to 50% in older ALL patients. In the study conducted by Azevedo et al. (32) Ph chromosome was found in 34% of Brazilian adult patients with ALL. Gleier et al. (24) showed that 37% of 478 adult ALL patients had BCR-ABL fusion gene. In our study, Ph chromosome was found in 14.6% of adult ALL patients and 15.6% of B ALL patients over 60 years.

The prevalence of genetic alterations varies according to age groups (13). In our study, we observed that Ph chromosome was most common in 51-60 years age group (28.9%) and was observed only in 9.3% of ALL patients in 18-39 years age group.

Nashed et al. (23) observed that in adult ALL patients with Ph chromosome, approximately 25% had p210 breakpoint and 75% had a p190 breakpoint in the BCR locus. In the study conducted by Gleier et al. (24) in patients with Ph chromosome, 77% had p190 breakpoint, 20% had p210 breakpoint and 3% had both isoforms. Dombret et al. (33) found that in patients with Ph chromosome, 68% had p190 breakpoint, 28% had p210 breakpoint and 4% had both isoforms. In our study, in adult ALL patients with Ph chromosome 53.3% had p210 breakpoint and 46.7% had p190 breakpoint in the BCR locus. There was not any patients who had both p190 and p210 breakpoints.

MRD monitoring is very important for both pediatric and adult ALL (5). In our study, in 75% of patients who had p210 breakpoint in the BCR locus at the time of diagnosis, p210 breakpoint could not be detected after 2 cycles of treatment. In 42.8% of patients who had p190 breakpoint in the BCR locus at the time of diagnosis, p190 could not be detected after 2 cycles of treatment.

CONCLUSION

In conclusion, genetic evaluation of ALL patients is very important to plan treatment approaches. Ph chromosome can be observed in up to 1/3 of patients in 51-60 years age group. There is quite limited data about MRD evaluations in ALL patients with Ph chromosome and to our knowledge this is the first study which evaluated the MRD status of Ph positive ALL patients by classifying them into 2 groups according to 2 isoforms (p190 and p210). In our study, we found that p190 breakpoint is associated with less MRD negative status compared to the patients with p210 breakpoint in the BCR locus. As p190 breakpoint is associated with less MRD negative status compared to the patients with p210 breakpoint in the BCR locus, more augmented therapies may be preferred in patients with p190 breakpoint compared to therapies of patients with p210 breakpoint. Further prospective, randomized studies are needed about the relation between MRD status and Ph chromosome isoforms.

Abbreviations: ABL: Abelson; **ALL:** Acute lymphoblastic leukemia; **BCR:** Breakpoint cluster region; **CNS:** Central nervous system; **EDTA:** Ethylenediaminetetraacetic acid; **MRD:** Minimal residual disease; Ph: Philadelphia; **RNA:** Ribonucleic acid; **TKI:** Tyrosine kinase inhibitor; **WHO:** World Health Organization.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Permission granted: 04.12.2019, Decision number: 475).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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