LETTER TO THE EDITOR

Turk J Hematol 2024;41:49-50

Importance of Rare Gene Alterations in the Prognosis of B-Cell Acute Lymphoblastic Leukemia

B-Hücre Akut Lenfoblastik Lösemi Prognozunda Nadir Gen Değişikliklerinin Önemi

Li Xiang[1#], Yongliang Wang[2#], Wei Pan[3]

[1]*Zhejiang Provincial People's Hospital Bijie Hospital, Department of Science and Education, Bijie, China*

[2]*Xinchang Hospital Affiliated to Wenzhou Medical University, Department of Thoracic Surgery, Xinchang, China*

[3]*Haiyan People's Hospital, Department of Clinical Laboratory, Haiyan, China*

[#]*These authors contributed equally to this work.*

To the Editor,

We read the recently published study by Ray et al. [1] with great interest. They reported amplification of the *BCR::ABL1* fusion gene as a rare phenomenon in B-cell acute lymphoblastic leukemia (ALL). In their study, *BCR::ABL1* and *ETV6::RUNX1* translocations, *TCF3* and *KMT2A* rearrangements, and the t(9,22)(q34;q11) *BCR::ABL1* translocation were revealed by fluorescent in situ hybridization (FISH) along with multiple copies of the fusion gene appearing separately in a patient with B-cell ALL as a rare case. This patient died within a month of the diagnosis.

However, the two major isoforms of the oncogenic *BCR-ABL1* tyrosine kinase, p210 and p190, were not mentioned in the context of this patient's case. p210 is the hallmark of chronic myelogenous leukemia, whereas p190 occurs in the majority of B-cell ALL cases [2]. The resulting fusion oncogene is a tyrosine kinase, which in turn results in the uncontrolled proliferation of cells. Importantly, the combination of chemotherapy with second- or third-generation tyrosine kinase inhibitors further improved the outcomes of *BCR-ABL1*-positive B-cell ALL patients [3]. However, in the case discussed here, the *BCR-ABL1* tyrosine kinase p210 and p190 status of the patient and the possible use of tyrosine kinase inhibitors such as imatinib or dasatinib remains unclear since the patient died within a month of diagnosis.

Besides the *BCR::ABL1* translocation, the *ETV6::RUNX1* translocation and *TCF3* and *KMT2A* rearrangements were also revealed in this patient. Among these genes, *ETV6-RUNX1* is the most frequent genetic fusion in pediatric B-ALL. The distinct *KMT2A* rearrangements are independent dismal prognostic factors, and *TCF3* gene rearrangements were also described as being associated with significant differences in ALL prognosis [4,5]. As we know, the molecular hallmark of ALL entails recurrent prognostic genetic alterations, many of which are cryptic by conventional cytogenetics [5,6]. Thus, Ray et al. [1] highlighted the need for FISH or other conventional cytogenetic approaches over reverse-transcriptase polymerase chain reaction studies to confirm disease progression. However, FISH only uses several commercial probes, resulting in limited results for rare genes. Therefore, besides FISH, we want to emphasize that whole-genome sequencing could provide standalone, reliable genetic testing to detect all subtype-defining genetic abnormalities in B-ALL, accurately classifying patients for risk-directed treatment stratification [7]. Moreover, RNA sequencing is also a powerful next-generation sequencing technology that can simultaneously identify cryptic gene rearrangements, sequence mutations, and gene expression profiles in a single assay, including genetic alterations not detected by conventional methods that confer potential prognostic and therapeutic impact [6]. Thus, in addition to FISH, we suggest that whole-genome sequencing or RNA sequencing could be better tools to more accurately classify ALL patients for risk-directed treatment stratification.

Keywords: Rare gene, Prognosis, B-cell acute lymphoblastic leukemia

Anahtar Sözcükler: Nadir gen, Prognoz, B-hücre akut lenfoblastik lösemi

Ethics

Informed Consent: Not applicable.

Authorship Contributions

Concept: L.X., Y.W., W.P.; Data Collection or Processing: L.X., Y.W., W.P.; Analysis or Interpretation: L.X., Y.W., W.P.; Literature Search: L.X., Y.W., W.P.; Writing: L.X., Y.W., W.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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

References

1. Ray D, Sharma P, Jain A, Sreedharanunni S. Amplification of the *BCR::ABL1* fusion gene: a rare phenomenon in B-cell acute lymphoblastic leukemia. Turk J Hematol 2023;40:204-205.
2. Reckel S, Hamelin R, Georgeon S, Armand F, Jolliet Q, Chiappe D, Moniatte M, Hantschel O. Differential signaling networks of Bcr-Abl p210 and p190 kinases in leukemia cells defined by functional proteomics. Leukemia 2017;31:1502-1512.
3. Haddad FG, Sawyers J, Short NJ. Treatment de-escalation in Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia: the emerging role of chemotherapy-free regimens. Ther Adv Hematol 2023;14:20406207231151294.
4. Meyer C, Larghero P, Almeida Lopes B, Burmeister T, Gröger D, Sutton R, Venn NC, Cazzaniga G, Corral Abascal L, Tsaur G, Fechina L, Emerenciano M, Pombo-de-Oliveira MS, Lund-Aho T, Lundán T, Montonen M, Juvonen V, Zuna J, Trka J, Ballerini P, Lapillonne H, Van der Velden VHJ, Sonneveld E, Delabesse E, de Matos RRC, Silva MLM, Bomken S, Katsibardi K, Keernik M, Grardel N, Mason J, Price R, Kim J, Eckert C, Lo Nigro L, Bueno C, Menendez P, Zur Stadt U, Gameiro P, Sedék L, Szczepański T, Bidet A, Marcu V, Shichrur K, Izraeli S, Madsen HO, Schäfer BW, Kubetzko S, Kim R, Clappier E, Trautmann H, Brüggemann M, Archer P, Hancock J, Alten J, Möricke A, Stanulla M, Lentes J, Bergmann AK, Strehl S, Köhrer S, Nebral K, Dworzak MN, Haas OA, Arfeuille C, Caye-Eude A, Cavé H, Marschalek R. The *KMT2A* recombinome of acute leukemias in 2023. Leukemia 2023;37:988-1005.
5. Yin H, Wang J, Tan Y, Jiang M, Zhang H, Meng G. Transcription factor abnormalities in B-ALL leukemogenesis and treatment. Trends Cancer 2023;9:855-870.
6. Tran TH, Langlois S, Meloche C, Caron M, Saint-Onge P, Rouette A, Bataille AR, Jimenez-Cortes C, Sontag T, Bittencourt H, Laverdière C, Lavallée VP, Leclerc JM, Cole PD, Gennarini LM, Kahn JM, Kelly KM, Michon B, Santiago R, Stevenson KE, Welch JJG, Schroeder KM, Koch V, Cellot S, Silverman LB, Sinnett D. Whole-transcriptome analysis in acute lymphoblastic leukemia: a report from the DFCI ALL Consortium Protocol 16-001. Blood Adv 2022;6:1329-1341.
7. Ryan SL, Peden JF, Kingsbury Z, Schwab CJ, James T, Polonen P, Mijuskovic M, Becq J, Yim R, Cranston RE, Hedges DJ, Roberts KG, Mullighan CG, Vora A, Russell LJ, Bain R, Moorman AV, Bentley DR, Harrison CJ, Ross MT. Whole genome sequencing provides comprehensive genetic testing in childhood B-cell acute lymphoblastic leukaemia. Leukemia 2023;37:518-528.

Reply from the Authors:

To the Editor,

We thank Xiang et al. [1] for their interest in our article [2]. We would like to clarify that in our patient, only the *BCR::ABL1* translocation was detected along with the amplification of this fusion gene. The *ETV6::RUNX1*, *TCF3*, and *KMT2A* translocations were not detectable in our patient. It is very unlikely to have translocations of multiple types in the same patient as they are mutually exclusive, although we and a few other hematologists have seen the *CRLF2* rearrangement in patients with the *BCR::ABL1* translocation. However, we acknowledge their insights into the roles of different *BCR::ABL1* isoforms and their prognostic significance. Testing for p190 and p210 was planned on fresh samples, due to technical reasons, but could not be performed as the patient died soon after the initial diagnosis, even before tyrosine kinase inhibitors could be initiated. We acknowledge that whole-genome sequencing and RNA sequencing provide more comprehensive genetic assessment and may help unravel cryptic and novel aberrations not picked up by conventional approaches. However, the exorbitant cost and limited availability of these advanced techniques is a significant hindrance preventing their routine application for all patients in resource-constrained settings. The objective of our paper was simply to highlight the rarity of *BCR::ABL1* amplification and the utility of FISH testing in its diagnosis in the era of advanced molecular diagnostics.

Sincerely,

Debadrita Ray, Praveen Sharma, Arihant Jain, Sreejesh Sreedharanunni

References

1. Xiang L, Wang Y, Pan W. Importance of rare genes in the prognosis of B-cell acute lymphoblastic leukemia. Turk J Hematol 2024;41:49-50.
2. Ray D, Sharma P, Jain A, Sreedharanunni S. Amplification of the *BCR::ABL1* fusion gene: a rare phenomenon in B-cell acute lymphoblastic leukemia. Turk J Hematol 2023;40:204-205.

Address for Correspondence/Yazışma Adresi: Wei Pan, M.D., Haiyan People's Hospital, Department of Clinical Laboratory, Haiyan, China
Phone : +0086-13757368188
E-mail : sd1663220@163.com ORCID: orcid.org/0000-0003-2638-4615

Received/Geliş tarihi: October 29, 2023
Accepted/Kabul tarihi: January 4, 2024

DOI: 10.4274/tjh.galenos.2024.2023.0400

©Copyright 2024 by Turkish Society of Hematology Turkish Journal of Hematology, Published by Galenos Publishing House.
Licensed under a Creative Commons Attribution-NonCommercial (CC BY-NC-ND) 4.0 International License.