To the Editor,

We read Purohit Debabrata’s paper [1] with great interest who reported amplification of the BCR::ABL1 Fusion Gene in a rare phenomenon in B-cell acute lymphoblastic leukemia (ALL). In this study, BCR::ABL1 and ETV6::RUNX1 translocations and the TCF3 and KMT2A rearrangements, and the t(9;22)(q34;q11) BCR::ABL1 translocation was revealed by fluorescent in situ hybridization (FISH) along with multiple copies of the fusion gene appearing separately in a rare B-cell ALL patient and 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 this patient. p210 is the hallmark of chronic myelogenous leukemia, whereas p190 occurs in the majority of B-cell ALL[2]. The resulting fusion oncogene is a tyrosine kinase, which in turn results in the uncontrolled proliferation of the cells. Importantly, the combinations of chemotherapy with second- or third-generation tyrosine kinase inhibitors further improved outcomes of these BCR-ABL1 positive B-cell ALL patients[3]. However, how about the BCR-ABL1 tyrosine kinase, p210 and p190 status in this patient, and did he use this tyrosine kinase inhibitor such as imatinib or...
dasatinib since this patient died within a month of the diagnosis. Except for the **BCR::ABL1** translocation, the **ETV6::RUNX1** translocations and the **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 is an independent dismal prognostic factor, and TCF3 gene rearrangements were also described that are associated with a significant difference in ALL prognosis[4,5]. As we know, the molecular hallmark of ALL is characterized by recurrent, prognostic genetic alterations, many of which are cryptic by conventional cytogenetics[5,6]. Thus, the author 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 commerical probes resulting in limited rare gene results. Therefore, except for the FISH, we also highlight that whole genome sequencing could provide a standalone reliable genetic test to detect all subtype-defining genetic abnormalities in B-ALL, accurately classifying patients for the 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, it also identified several genetic alterations not detected by conventional methods that confer potential prognostic and therapeutic impact[6]. Thus, in addition to the FISH, we also highlight that whole genome sequencing or RNA sequencing could be a better tool to more accurately classify ALL patients for risk-directed treatment stratification.

References


Reply:

Dear Editor,

We thank the authors for their interest in our article. We would like to clarify that in our patient, only BCR::ABL1 translocation was detected along with the amplification of this fusion gene. The ETV6::RUNX1, TCF3, KMT2A translocations were not detectable in our patient. It is very unlikely to have translocations of multiple types in the same patients as they are mutually exclusive; though we and a few other hematologists have seen CRLF2 rearrangement in patients with BCR::ABL1 translocation. We acknowledge their insights into the role 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 expired soon after the initial diagnosis even before tyrosine kinase inhibitors could be initiated. We acknowledge that whole genome sequencing and RNA sequencing provide a 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 performance in all patients in resource-constrained settings. The objective of our paper was just to highlight the rarity of BCR::ABL1 amplification and the utility of FISH testing in its diagnosis in the era of advanced molecular diagnostics.

Reference

Ray D, Sharma P, Jain A, Sreedharanunni S. Amplification of the BCR::ABL1 Fusion Gene: A Rare Phenomenon in B-cell Acute Lymphoblastic Leukemia. Turkish journal of haematology :official journal of Turkish Society of Haematology 2023;40:204-205.

Also please note that the first author's name is Ray Debadrita and not Purohit Debadrita as mentioned in the paper.