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Impact of insertion/deletion mutations affecting the *ABL1* gene in Ph-positive leukemias

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In this issue of *Haematologica*, Takano et al. report on the unexpectedly frequent occurrence of *ABL1* insertion/deletion (in-del) mutations in adult patients with Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) (1). In their cohort of 62 patients, all expressing the minor BCR::ABL1 (e1a2) transcript isoform, in-del events were identified in 15 patients (24.2%) either at diagnosis or during therapy. The predominance of exon 4 deletions (13 of 15 cases) aligns with earlier observations in chronic myeloid leukemia (CML), where such deletions were found to abolish kinase activity without compromising sensitivity to tyrosine kinase inhibitors (TKIs) (2). Two additional aberrations observed in individual patients - deletion of exon 7 and the 35-base insertion (INS35) between exons 8 and 9 - have likewise been described in CML and appear to generate kinase-inactive variants that do not mediate TKI resistance (3,4).

Although single and compound kinase domain (KD) point mutations remain the most recognized mechanism of TKI resistance in Ph-positive leukemias, structural alterations involving the *ABL1* or *BCR* genes have long attracted interest. One prominent category is the deletion of genetic material on the reciprocal ABL1-BCR gene on derivative chromosome 9 [der(9)], seen in >10% of patients with Ph-positive leukemias (5). These deletions likely arise concurrently with the initial t(9;22) translocation and were historically associated with inferior prognosis (5). In the TKI era, however, the adverse prognostic effect appears largely mitigated (6).

Deletion events are also more frequent in cases with variant or complex Ph rearrangements, supporting the interpretation that they reflect broader genomic instability rather than isolated disruption of the BCR::ABL1 transcript. Mechanistically, internal *ABL1* deletions differ from der(9) losses: deletions involving exons 4 or 7, as well as the INS35 insertion, predominantly arise from missplicing rather than genomic instability (2,4).

Several case reports have expanded the known repertoire of internal deletions (Figure). A 231-bp in-frame deletion spanning exons 7–8 was observed in a patient with CML blast crisis and likely resulted from alternative splicing, removing critical regulatory elements of the activation loop (7). Another case of CML with an atypical e12a2 fusion displayed partial deletion of exon 2 with a 39-bp insertion, which remained responsive to TKI therapy (8). These examples underscore the heterogeneity of such events and their variable clinical relevance.

Of interest are rare BCR::ABL1 variants lacking exon 2 and affecting the SH3 regulatory domain, which destabilize the kinase conformation and influence responsiveness to asciminib (9). A recent case report presented a patient harboring a T315I mutation, who developed a rare b6a3 transcript lacking SH3 residues, resulting in hyperactive signaling and resistance to ponatinib and asciminib (10). Although rare, such variants can have profound therapeutic consequences, especially when combined with high-risk point mutations.

Co-occurrence of point mutations and in-del events is increasingly recognized. Simultaneous presence of point mutations in the ABL1 kinase domain with deletion events has been described in various reports including the study by Takano et al. in the present issue of *Haematologica*, in which four patients harbored the point mutation T315I in addition to the in-frame deletion of ABL1 exon 4. Whether the two events coexist on the same molecule or represent separate subclones mostly remains unclear. A similar phenomenon has been previously demonstrated with the L248V mutation in the P-loop of the ABL1 kinase domain, which activates a cryptic splice site in exon 4, generating an 81-nucleotide in-frame deletion. The splice variant may not possess any kinase activity due to loss of the ATP binding pocket and was responsive to treatment with dasatinib (11). The deletion associated with the point mutation L248V is not uncommon and has been observed at different centers including ours.

Diagnostic pipelines mostly focus on point mutations, and structural variants including internal deletions, insertions, and splice-derived fusions could therefore be under-reported. Their contribution may be underestimated particularly in patients with unexplained resistance in the absence of KD point mutations.

Deletion events may also carry broader biological significance. Der(9) deletions have been proposed to remove regulatory elements or tumor suppressors adjacent to the breakpoint, potentially affecting disease progression (5). Internal deletions affecting SH3/SH2 or other regulatory sequences may alter kinase autoinhibition, protein stability, or interactions with signaling partners. Together, these data indicate that the impact of deletions may not be limited to disruption of coding sequences alone but may extend to more global effects on genomic architecture and cell biology.

In Ph+ ALL, the frequency of in-del events reported by Takano et al. is notable. Blasts in ALL exhibit higher proliferative stress and a greater tendency toward genomic instability than chronic-phase CML cells, which may partly explain the increased occurrence of deletions. Although many variants appear kinase inactive and may not directly mediate resistance, their coexistence with high-risk mutations such as T315I highlights their potential role in clonal evolution.

Even when not immediately clinically relevant, documenting in-del mutations remains valuable. These events may uncover hidden structural complexity, reveal genomic instability, or help explain atypical responses to therapy. Integrating deletion and splice-variant profiling with standard KD mutation analysis may refine risk stratification and enhance understanding of resistance mechanisms - particularly as treatment strategies evolve to include allosteric inhibitors and combination approaches (12).

Overall, the study by Takano et al. underscores the importance of expanding molecular monitoring beyond canonical point mutations. A more comprehensive approach that includes structural variants of *ABL1* may provide deeper insights into clonal

architecture, therapeutic resistance, and individualized treatment planning in Ph-positive leukemias.

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Figure 1. Schematic representation of insertion-deletion mutations affecting the BCR::ABL1 fusion gene in Ph-positive leukemias.