Deletion mutations of the *ABL1* gene in Philadelphia chromosome-positive acute lymphoblastic leukemia: high prevalence with limited clinical impact

The *BCR::ABL1* fusion gene is the primary driver of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukemia (Ph$^+$ B-ALL). Tyrosine kinase inhibitors (TKI), which block ATP binding to the ABL1 protein, have significantly improved the prognosis of these diseases. However, point mutations in the *ABL1* gene remain a major cause of drug resistance by altering kinase structure and preventing TKI binding.[1,2] In contrast, deletion mutations in the *ABL1* gene are rare and have been reported almost exclusively in CML, with no prior reports in Ph$^+$ B-ALL.[3-9] Several studies suggest that these mutations result in structural changes in the TKI-binding region, contributing to drug resistance and tumor progression.[3-6] However, other studies indicate that deletions within the kinase domain may lead to reduced kinase activity and diminished proliferative potential of leukemia cells in CML.[7-9] Recently, our group reported the first two Ph$^+$ B-ALL cases harboring a partial deletion mutation in the *ABL1* gene (p.L184_K274del [Δ184-274]), identified at relapse after allogeneic hematopoietic cell transplantation (HCT), both of which showed clinical resistance to TKI.[10] To further investigate this phenomenon, we analyzed Ph$^+$ B-ALL patients with *ABL1* deletion mutations across two hospitals.

Between 2012 and 2021, 62 patients with Ph$^+$ B-ALL or Ph$^+$ mixed phenotype acute leukemia (MPAL) underwent *ABL1* mutation analysis at Toranomon Hospital (Tokyo, Japan) and Toranomon Hospital Kajigaya (Kawasaki, Japan). This retrospective study was approved by the Institutional Review Board of Toranomon Hospital and Toranomon Hospital Kajigaya (approval N. 2418), and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived given the retrospective nature of the study. Among these 62 patients, 15 (24.2%) were identified with deletion mutations. The characteristics of the 15 patients with deletion mutations are summarized in Table 1: they comprised ten males (66.6%) and five females (33.3%), with a primary diagnosis of Ph$^+$ B-ALL in eight patients (53.3%) and Ph$^+$ MPAL (B and myeloid) in seven (46.6%). All patients had a minor *BCR::ABL1* fusion transcript, which may reflect the limited sample size in this cohort. The median follow-up duration from diagnosis to detection of the deletion mutations was 242 days (interquartile range, 56-512 days). Chromosomal abnormalities at the time of mutation detection included the following: isolated t(9;22)(q34;q11.2) in eight patients (53.3%), complex karyotype with t(9;22)(q34;q11.2) in three patients (20.0%), and t(9;22)(q34;q11.2) with additional aberrations in four patients (26.6%). Disease status at the time of mutation detection was as follows: newly diagnosed primary disease in four patients (26.6%) (total tested at this stage: 6), first remission in two (13.3%) (total tested: 17), first relapse in seven (46.6%) (total tested: 39), and second relapse in two (13.3%) (total tested: 13). Four patients (26.6%) were evaluated after allogeneic HCT (total tested: 25).

Regarding the mutation spectrum, four patients also harbored point mutations; in all cases, the identified mutations were p.L184_K274del and T315I (N=4). Among the 11 patients with deletion mutations only, the identified alterations were p.L184_K274del (N=9), p.L184_K274del and p.C475fs*11 (N=1), and p.R362fs*21 (N=1). According to previous reports

Table 1. Summary of clinical features of patients with deletion mutations in *BCR::ABL1*.

Characteristics	Values
Total patients with deletion mutation, N	15
Sex, N (%)	
Male	10 (66.6)
Female	5 (33.3)
Age, years, median (range)	54 (39.0-64.5)
Disease, N (%)	
B-ALL	8 (53.3)
MPAL (B/myeloid)	7 (46.6)
Major/minor *BCR::ABL1*, N (%)	
Major	0 (0.0)
Minor	15 (100.0)
Interval between diagnosis and deletion mutation detection, days, median (range)	242 (56-512)
Disease status at deletion mutation detection, N (%)	
Untreated	4 (26.6)
First complete remission	2 (13.3)
First relapse	7 (46.6)
Second relapse	2 (13.3)
After SCT	4 (26.6)
Deletion mutation, N (%)	
p.L184_K274del	9 (60.0)
p.L184_K274del, T315I	4 (26.6)
p.L184_K274del, p.C475fs*11	1 (6.6)
p.R362fs*21	1 (6.6)
Chromosomal abnormality, N (%)	
Complex karyotype with t(9;22)(q34;q11.2)	3 (20.0)
t(9;22)(q34;q11.2) with additional aberrations	4 (26.6)
Isolated t(9;22)(q34;q11.2)	8 (53.3)

B-ALL: B-cell precursor acute lymphoblastic leukemia; MPAL: mixed phenotype acute leukemia; SCT: stem cell transplantation.

on CML, p.L184_K274del corresponds to an exon 4 deletion, p.R362fs*21 corresponds to an exon 7 deletion, and p.C475fs11 (N=1) corresponds to INS35, which represents a 35-base insertion between exons 8 and 9.[6-8] We have summarized the affected regions and corresponding protein domains of these mutations in Figure 1.

The clinical courses of the 15 patients with deletion mutations are summarized in a swimmer plot (Figure 2), with detailed clinical information retained in *Online Supplementary Table S1*. Following the discovery of the mutations, 12 patients (80.0%) achieved a molecular complete response, defined as undetectable *BCR::ABL1* transcript by reverse transcriptase polymerase chain reaction with a detection limit of 10^{-5}. The treatments leading to molecular complete response included TKI and prednisolone in three patients (20.0%), TKI and chemotherapy in four (26.6%), and allogeneic HCT in five (33.3%). The 3-year survival rate for these 15 patients with deletion mutations from diagnosis was 65.5% (95% confidence interval: 35.7%-84.0%), which was comparable to previously reported outcomes (56.8% in the JALSG 202 Ph-positive B-ALL study).[11]

This study represents the first retrospective analysis of Ph$^+$ B-ALL cases with *ABL1* deletion mutations. The frequency of *ABL1* deletion mutations was 24.2%, which is unexpectedly high in patients with Ph$^+$ B-ALL and Ph$^+$ MPAL. Although the number of patients analyzed at diagnosis was limited, these mutations were detected at various stages of the disease, from diagnosis to relapse/refractory disease. Some reports on deletion or insertion mutations in CML suggest that TKI treatment may induce these mutations.[6,12] Similarly, it is plausible that selection pressure from allogeneic HCT could promote the accumulation of mutations in leukemic cells. However, in this study, four of 15 patients (26.6%) harbored deletion mutations prior to any treatment. Although analysis of the remaining patients was not possible due to lack of diagnostic samples, additional cases may have already harbored deletion mutations at diagnosis. Notably, there are also reports of deletion mutations being detected at diagnosis in CML.[13] Furthermore, among the total 35 post-transplant analyses performed, deletion mutations were identified in only four cases. These findings indicate that, like point mutations, *ABL1* deletion mutations do not necessarily require prior exposure to TKI or transplantation. TKI were effective in some Ph$^+$ B-ALL cases with deletion mutations. In this analysis, the predominant deletion was p.L184_K274del [Δ184-274], which corresponds to a loss of exon 4 in the *ABL1* gene. A previous study using cell lines overexpressing this mutant concluded that it did not induce kinase phosphorylation or tumor growth, and that the mutant protein itself lacked kinase activity.[7] Furthermore, this mutation does not confer TKI resistance; leukemia cells co-expressing both native *BCR::ABL1* and mutated *BCR::ABL1* with Δ184-274 remained sensitive to TKI treatment. In our study, three patients with the Δ184-274 mutation achieved molecular complete response with a combination of TKI and prednisolone, supporting the clinical efficacy of TKI in this context. Although this analysis is based on a limited number of cases, no clear evidence of worsened prognosis was observed in patients with *ABL1* deletion mutations.

This study has a few limitations. First, the deletion mutations were detected using reverse transcriptase polymerase chain reaction targeting *BCR::ABL1* mRNA, followed by Sanger sequencing. Since DNA mutation analysis was not conducted, it remains unclear whether the deletion mutations arose from DNA aberrations or from mRNA splicing variants. Second, comprehensive genetic analysis was not performed, leaving genetic alterations outside of the *ABL1* gene unidentified. If the deletion mutations originate from DNA mutations, this would suggest the existence of clones capable of proliferating independently of *BCR::ABL1* signaling, potentially in conjunction with additional oncogenic events. In this scenario, if the proportion of clones harboring deletion mutations is relatively small, TKI may still be effective in suppressing native Ph-dependent leukemia cells. Alternatively, if the deletion mutations arise from abnormal mRNA splicing, as reported in CML with

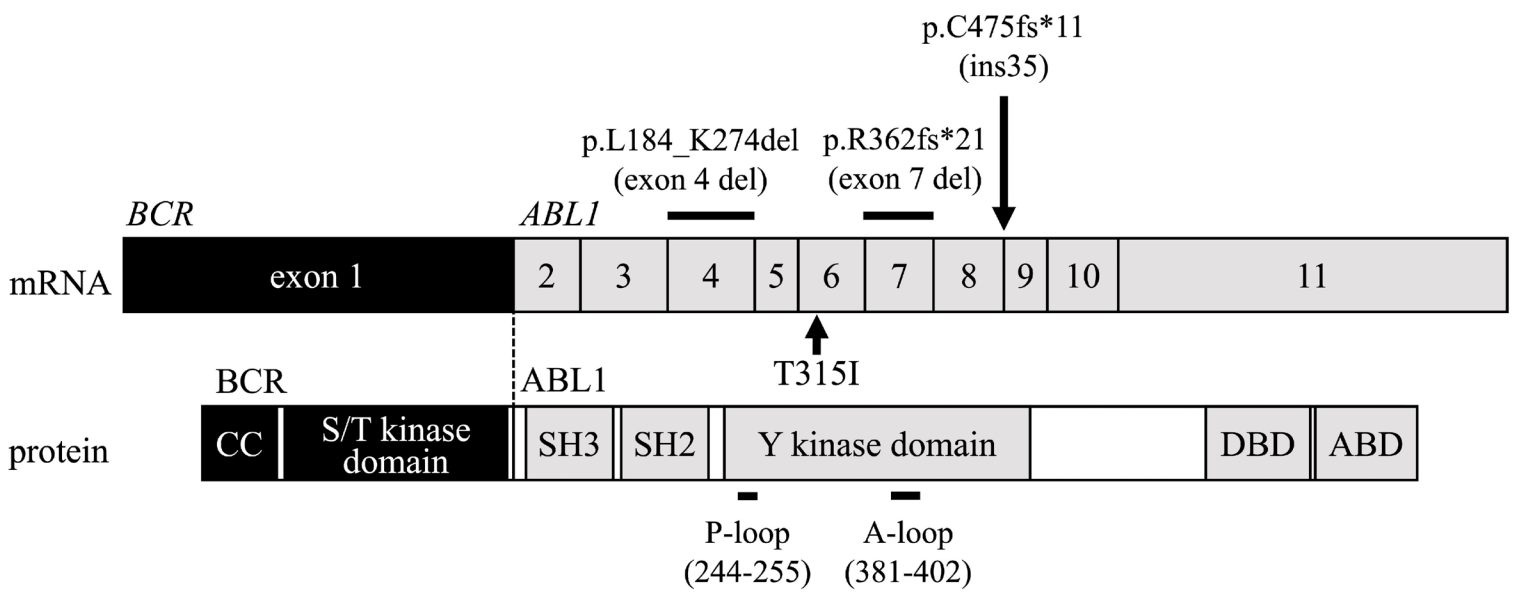

Figure 1. Exon composition of *BCR::ABL1* mRNA, major protein domains, and locations of *ABL1* deletion mutations. CC: coiled coil; DBD: DNA-binding domain; ABD: actin-binding domain.

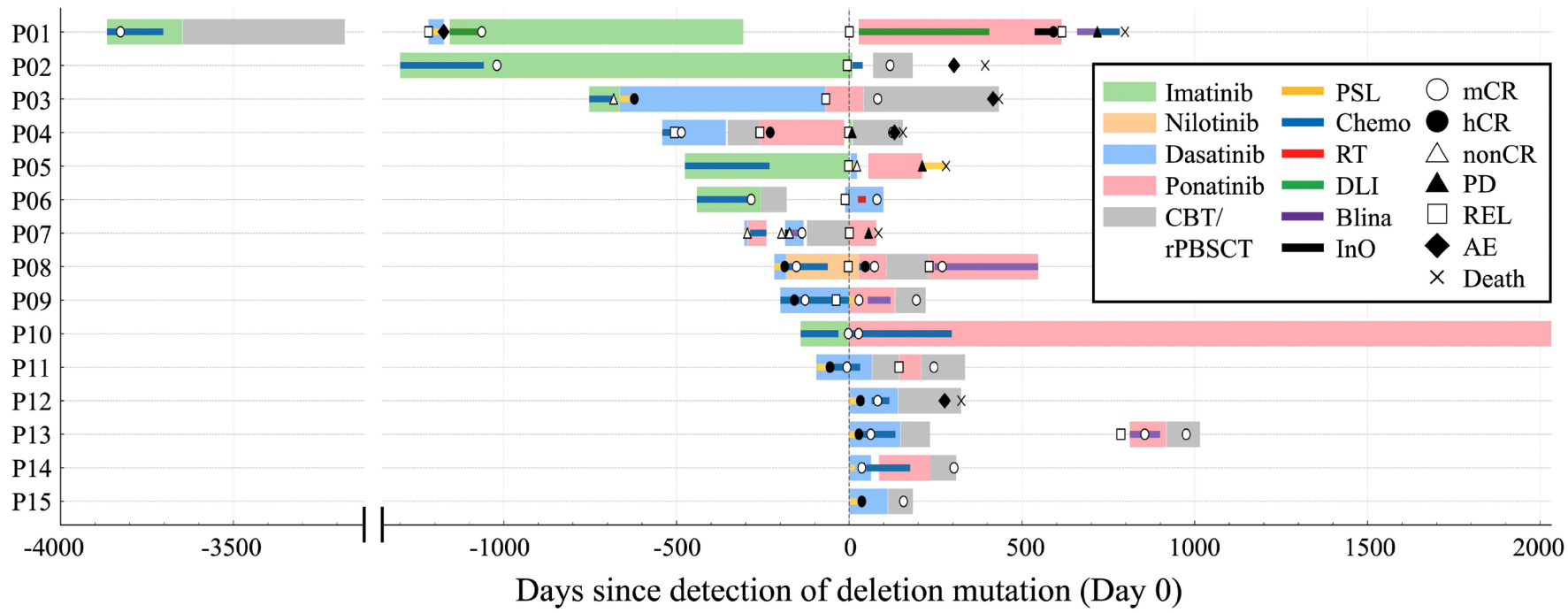

Figure 2. Swimmer plot of the clinical courses of 15 patients with *ABL1* deletion mutations. CBT: cord blood transplantation; rPBSCT: related peripheral blood stem cell transplantation; PSL: prednisolone; Chemo: chemotherapy; RT: radiotherapy; DLI: donor lymphocyte infusion; Blina: blinatumomab; InO: inotuzumab ozogamicin; mCR: molecular complete remission; hCR: hematologic complete remission; nonCR: non-complete remission; PD: progressive disease; REL: relapse; AE: adverse event.

deletion/insertion mutations,[3,7,8,14] both native and deletion mutant *BCR::ABL1* could coexist within a single leukemic cell.[7,14,15] This would imply that their proliferation remains dependent on native *BCR::ABL1*, making them vulnerable to TKI therapy.

In summary, *ABL1* deletion mutations are more frequently observed in Ph$^+$ B-ALL than previously expected. Their emergence does not require pre-treatment, such as TKI therapy or allogeneic HCT. TKI remain effective in Ph$^+$ B-ALL cases with these mutations, and no negative impact on prognosis was observed. Based on these findings, TKI therapy should not be avoided in cases with deletion mutations. However, the underlying mechanism driving the development of these mutations and their broader clinical implications remain unclear. Further studies are necessary to elucidate these aspects.

Authors

Hirofumi Takano,[1] Shinsuke Takagi,[1-3] Kana Kato,[1] Otoya Watanabe,[1] Kyosuke Yamaguchi,[4] Kosei Kageyama,[4] Daisuke Kaji,[1,5,6] Yuki Taya,[1,5,6] Aya Nishida,[1] Kazuya Ishiwata,[4] Hisashi Yamamoto,[1,2] Yuki Asano-Mori,[2,5,6] Go Yamamoto,[1,6] Atsushi Wake,[2,4] Shuichi Taniguchi[1] and Naoyuki Uchida[1,3]

[1]Department of Hematology, Toranomon Hospital, Tokyo; [2]Center for Long-Term Follow-Up after Hematopoietic Cell Transplantation, Toranomon Hospital, Tokyo; [3]Okinaka Memorial Institute for Medical Research, Tokyo; [4]Department of Hematology, Toranomon Hospital Kajigaya, Kanagawa; [5]Department of Transfusion and Cellular Therapy, Toranomon Hospital, Tokyo and [6]Center for Cellular Therapy, Toranomon Hospital, Tokyo, Japan

Correspondence:
H. TAKANO - htm.hoshi3@gmail.com

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Disclosures

No conflicts of interest to disclose.

Contributions

HT and STak are the principal investigators and take primary responsibility for the paper. HT and STak wrote the manuscript. HT, STak, KKat, OW, KY, KKag, DK, YT, AN, KI, HY, YA-M, GY, AW, STan and NU treated the patients and reviewed the final version of the manuscript. STak designed the research, while STan and NU organized the project.

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Data-sharing statement

Due to patient privacy concerns, no additional data are available.

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