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

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Author contributions:

H.T. and S. Takagi are the principal investigators and take primary responsibility for the paper. H.T. and S. Takagi wrote the manuscript. H.T. and S. Takagi, K. Kato, O.W., K.Y., K. Kageyama, D.K., Y.T., A.N., K.I., H.Y., Y.A-M., G.Y., A.W., S. Taniguchi, and N.U. treated the patients and reviewed the final version of the manuscript. S. Takagi designed the research, while S. Taniguchi and N.U. organized the project.

Data sharing statement:

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

Subject ontology

Philadelphia chromosome, *BCR::ABL1*, B-ALL, deletion mutations

To the editor

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 (TKIs), 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 TKIs.[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 no. 2418), and was conducted in accordance

with the Declaration of Helsinki. The requirement for informed consent was waived owing to 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 10 males (66.6%) and 5 females (33.3%), with a primary diagnosis was Ph^+ B-ALL in 8 patients (53.3%) and Ph^+ MPAL (B and myeloid) in 7 (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 [IQR], 56 - 512 days). Chromosomal abnormalities at the time of mutation detection included the following: isolated t(9;22)(q34;q11.2) in 8 patients (53.3%), complex karyotype with t(9;22)(q34;q11.2) in 3 patients (20.0%), and t(9;22)(q34;q11.2) with additional aberrations in 4 patients (26.6%). Disease status at the time of mutation detection was as follows: newly diagnosed primary disease in 4 patients (26.6%) (total tested at this stage: 6), first remission in 2 (13.3%) (total tested: 17), first relapse in 7 (46.6%) (total tested: 39), and second relapse in 2 (13.3%) (total tested: 13). Four patients (26.6%) were evaluated post-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 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 exon 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's plot (Figure 2), with detailed clinical information retained in Supplementary Table 1. Following the discovery of the mutations, 12 patients (80.0%) achieved a molecular complete response (mCR). mCR was defined as undetectable *BCR::ABL1* transcript by reverse transcriptase (RT)-PCR with a detection limit of 10□ □. The treatments leading to mCR included TKI and prednisolone (PSL) in 3 patients (20.0%), TKI and chemotherapy in 4 (26.6%), and allogeneic HCT in 5 (33.3%). The 3-year survival rate for these 15 patients with deletion mutations from diagnosis was 65.5% (95% confidence interval [CI], 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, 4 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 4 cases. These findings indicate that, like point mutations, *ABL1* deletion mutations do not necessarily require prior exposure to TKIs or transplantation.

TKIs 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 mCR with a combination of TKI and PSL, supporting the clinical efficacy of TKIs 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 RT-PCR 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, TKIs 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 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. TKIs 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.

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Total Patients with deletion mutation, n	15
Sex, n (%)	
Male	10 (66.6%)
Female	5 (33.3%)
Median age, years (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%)
Median interval between diagnosis and deletion mutation detection, days (range)	242 (56 - 512)
Disease status at deletion mutation detection, n (%)	
Untreated	4 (26.6%)
CR1	2 (13.3%)
Rel1	7 (46.6%)
Rel2	2 (13.3%)
post 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%)

Table 1. Summary of clinical features of patients with deletion mutations in *BCR::ABL1*.
Abbreviations: CR1: first complete remission; Rel1: first relapse; Rel2: second relapse; post SCT: after stem cell transplantation.

Figure Legend

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

Figure 2. Swimmer's plot of the clinical courses of 15 patients with *ABL1* deletion mutations.
Abbreviations: 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: hematological complete remission; nonCR: non-complete remission; PD: progressive disease; REL: relapse; AE: adverse event.

Figure 1

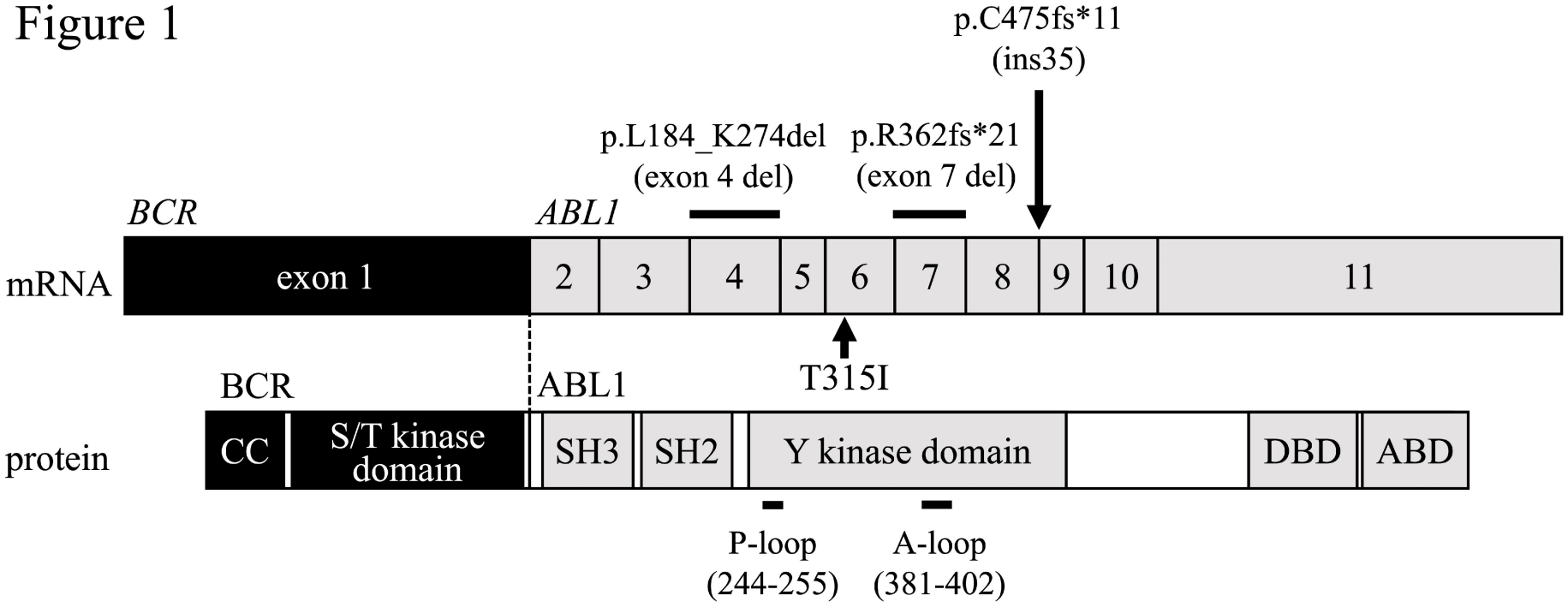
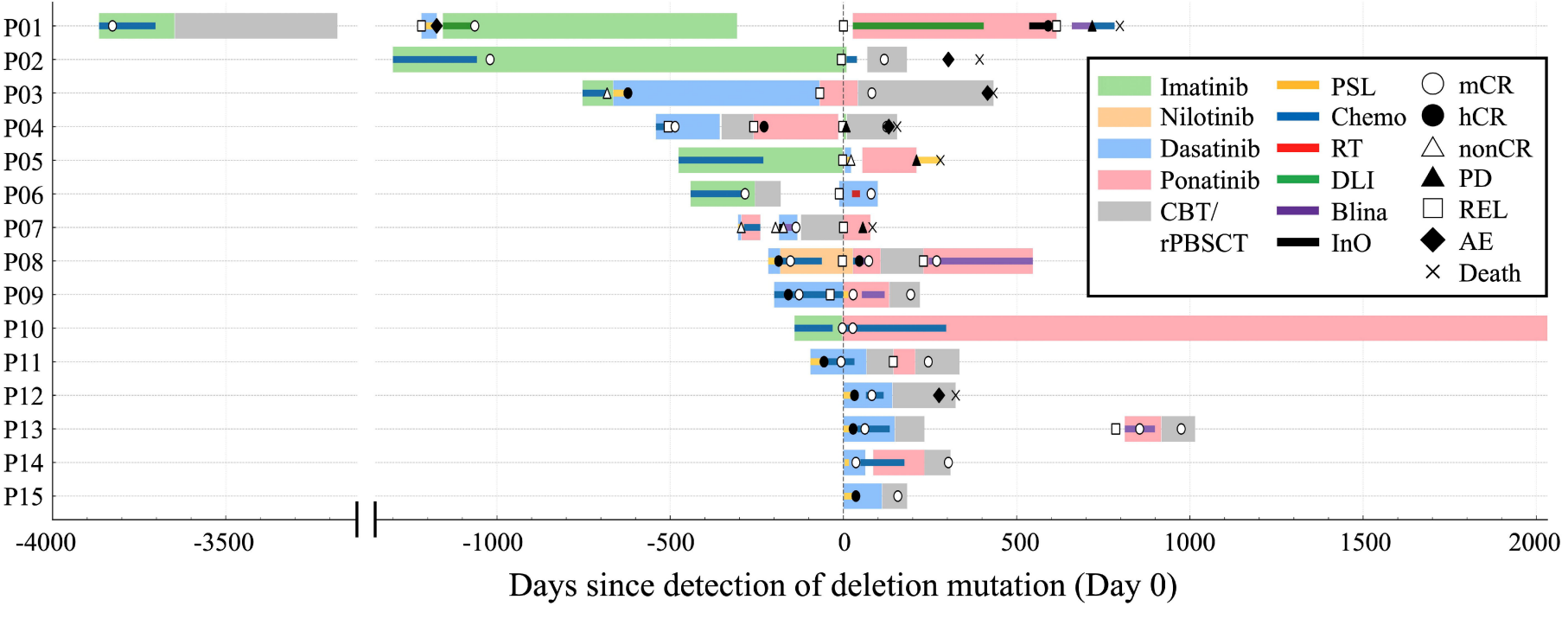

p.C475fs*11
(ins35)
p.L184_K274del
(exon 4 del)
p.R362fs*21
(exon 7 del)
BCR
ABL1
mRNA
exon 1
2
3
4
5
6
7
8
9
10
11
T315I
BCR
ABL1
protein
CC
S/T kinase domain
SH3
SH2
Y kinase domain
DBD
ABD
P-loop
(244-255)
A-loop
(381-402)

Figure 2


P01
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Imatinib
Nilotinib
Dasatinib
Ponatinib
CBT/
rPBSCT
PSL
Chemo
RT
DLI
Blina
InO
mCR
hCR
nonCR
PD
REL
AE
Death
-4000
-3500
-1000
-500
0
500
1000
1500
2000
Days since detection of deletion mutation (Day 0)

Case No.	Age/Sex	Disease	From diagnosis (days)	Status	*ABL1* mutations	Treatment (pre-deletion)	Treatment (post-deletion)	Best Response	OS from diagnosis (months)
1	56/F	MPAL	3978	Rel2 (post SCT)	p.L184_K274del	Ima+Chemo, mCR, rPBSCT, Rel, Dasa+PSL, Ima+DLI, mCR, Rel	Pona+DLI, InO, hCR, Rel, Blina, Chemo, PD, Death	hCR	Dead (15M)
2	68/M	MPAL	1299	Rel1	p.L184_K274del	Ima+Chemo, mCR, Rel	Chemo, hCR, CBT, mCR, VOD, Death	mCR	Dead (56M)
3	65/M	B-ALL	753	Rel1	p.L184_K274del, T315I	Ima+Chemo, nonCR, Dasa+PSL, hCR, Rel	Pona, CBT, mCR, BO, Death	mCR	Dead (27M)
4	39/M	MPAL	544	Rel2 (post SCT)	p.L184_K274del	Dasa+Chemo, CNS Rel, RT, mCR, rPBSCT, Rel, Pona, hCR, Rel	Ima, PD, CBT, mCR, IPS, Death	mCR	Dead (23M)
5	75/M	MPAL	480	Rel1	p.L184_K274del, T315I	Ima+Chemo, Rel	Dasa+PSL, nonCR, Pona, PD, PSL, Death	PR	Dead (25M)
6	35/F	B-ALL	441	Rel1 (post SCT)	p.L184_K274del	Ima+Chemo, mCR, CBT, CNS Rel	Dasa+IT+RT, mCR	mCR	Alive (66M)
7	70/M	MPAL	304	Rel1 (post SCT)	p.L184_K274del	Dasa+PSL, nonCR, Pona+Chemo, nonCR, Dasa+InO, nonCR, Blina, mCR, CBT, Rel	Pona, PD, Death	PR	Dead (13M)
8	50/M	B-ALL	242	Rel1	p.L184_K274del, T315I	Dasa+PSL, hCR, Nilo+Chemo, mCR, Rel	Pona+Chemo, hCR, Pona+Blina, mCR, CBT, Rel, Pona+Blina, mCR	mCR	Alive (24M)
9	64/M	MPAL	216	Rel1	p.L184_K274del, T315I	Dasa+Chemo, hCR, Chemo, mCR, Rel	Pona+PSL, mCR, Blina, CBT, mCR	mCR	Alive (28M)
10	55/F	B-ALL	138	CR1	p.L184_K274del	Ima+Chemo, mCR	Pona+Chemo, mCR	mCR	Alive (41M)
11	39/M	B-ALL	96	CR1	p.L184_K274del, p.C475fs*11	Dasa+PSL, hCR, Chemo, mCR	CBT, Rel, Pona, 2ndCBT, mCR	mCR	Alive (45M)
12	42/M	B-ALL	15	Untreated	p.L184_K274del	None	Dasa+PSL, hCR, Chemo, mCR, CBT, BO, Death	mCR	Dead (11M)
13	54/F	MPAL	11	Untreated	p.L184_K274del	None	Dasa+PSL, hCR, Chemo, mCR, rPBSCT, Rel, Pona+Blina, mCR, CBT, mCR	mCR	Alive (38M)
14	27/M	MPAL	10	Untreated	p.R362fs*21	None	Dasa+PSL, mCR, Pona+Chemo, CBT, mCR	mCR	Alive (41M)
15	25/F	B-ALL	4	Untreated	p.L184_K274del	None	Dasa+PSL, hCR, CBT, mCR	mCR	Alive (51M)

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

Abbreviations: CR1: first complete remission; Rel1: first relapse; Rel2: second relapse; post SCT: after stem cell transplantation; Ima: imatinib; Nilo: nilotinib; Dasa: dasatinib; Pona: ponatinib; PSL: prednisolone; Chemo: chemotherapy; RT: radiotherapy; IT: intrathecal injection; DLI: donor lymphocyte infusion; Blina: blinatumomab; InO: inotuzumab ozogamicin; CNS: central nervous system; mCR: molecular complete remission; hCR: hematological complete remission; nonCR: non-complete remission; PR: partial response; PD: progressive disease; Rel: relapse; CBT: cord blood transplantation; rPBSCT: related peripheral blood stem cell transplantation; VOD: veno-occlusive disease; BO: bronchiolitis obliterans; IPS: idiopathic pneumonia syndrome.