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Poor prognostic implication of *CDKN2* deletion in adult patients with Philadelphia chromosome-positive ALL

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TO THE EDITOR:

Advancements in tyrosine kinase inhibitors [1], novel agents such as blinatumomab [2], and allogeneic hematopoietic cell transplantation (allo-HCT) have improved the survival of patients with Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) [3]; however, outcomes remain poor for those who experience relapse, especially after HCT [4]. Recent advancements in genetic techniques have deepened insights into gene mutations linked to ALL development and resistance [5]. Key genetic alterations in lymphoid differentiation, tumor suppression, and cell cycle regulation suggest their potential as prognostic markers. Among these, *IKZF1* deletions (*IKZF1*del) have attracted significant attention due to their association with impaired lymphoid development and a high relapse rate [6]. Another notable genetic alteration is the deletion of cyclin-dependent kinase inhibitor 2 (*CDKN2*) [7], a known tumor suppressor gene. However, while most studies report a negative clinical impact, some discrepancies remain.

We aimed to evaluate the prognostic significance of *IKZF1*del and *CDKN2*del in a well-defined cohort of adults with Ph-positive ALL who underwent allo-HCT after receiving imatinib-based intensive chemotherapy as described in previous studies [8]. Between April 2018 and December 2022, a total of 156 adult patients were retrospectively analyzed. Genetic profiling included MLPA to detect deletions in *IKZF1, CDKN2A, CDKN2B, PAX5, BTG1, EBF1, ETV6, JAK2, RB1*, and the *PAR1* region, as well as NGS targeting 73 genes. Measurable residual disease (MRD) monitoring for *BCR::ABL1* transcript was conducted by RT-qPCR at key treatment milestones, with a sensitivity of 10^{-5}. Relapses included a significant MRD increase of at least 1-log. Poor molecular response (PMR) was defined with values exceeding 0.1% of detected MRD, while complete molecular response (CMR) was defined as absence of detectable MRD. Major molecular response (MMR) was characterized by values between these CMR and PMR criteria. Allo-HCT was the standard post-remission therapy for high-risk adult ALL including Ph-positive ALL and other cytogenetics like complex karyotype and MLL rearrangement, and delayed remission after at least 2 cycles of induction chemotherapy. Thus, all patients in this study were candidates for allo-HCT, but it was not performed when a suitable donor was unavailable or when the patient's performance status was insufficient. The primary end points were overall survival (OS), disease-free survival (DFS), cumulative incidence of relapse (CIR), and non-relapse mortality (NRM) in patients who underwent allo-HCT after successful chemotherapy. All patients provided written informed consent approved by the Institutional Review Board of The Catholic University of Korea (KC16TISI0438, KC23RASI0119, KC24RISI0772). This study was conducted in accordance with the Declaration of Helsinki.

Baseline characteristics of the entire cohort are detailed in Supplementary Table 1. The most frequent gene deletion detected by MLPA was *IKZF1*del (80.8%), followed by *CDKN2*del (39.1%), and *PAX5*del (38.5%). Among the 73 targeted genes analyzed by NGS, the most frequently observed gene mutation was in *SETD2* (7.1%), followed by *RUNX* (5.8%) and *IKZF1* (5.8%). One hundred and twenty-seven patients (81.4%) underwent allo-HCT, all of whom were in complete remission (CR) at the time of allo-HCT. Pre-HCT MRD assessment showed CMR in 69 (54.3%), MMR in 31 (24.4%), and PMR in 27 (21.3%). Among those genetic alterations, our data revealed *CDKN2*del was the only genetic alteration associated with poor survival outcomes (Supplementary Fig. 1). Also, we identified that the survival outcome of *IKZF1*del was poor only when it was combined with *CDKN2*del (Supplementary Fig. 2).

Accordingly, we moved our focus to *CDKN2*del. As a large proportion of *CDKN2*del co-occurred with *IKZF1*del, we classified all patients into three subgroups – Group 1 with *CDKN2*del(−)/*IKZF1*del(+) ($n = 72$), Group 2 with *CDKN2*del(−)/*IKZF1*del(−) ($n = 23$), and Group 3 with *CDKN2*del(+)±*IKZF1*del ($n = 61$) to validate the prognostic impact of the combinatorial effect of *IKZF1*del and *CDKN2*del. Among the three subgroups, CR rate and MRD response at the time of allo-HCT were not significantly different, whereas concurrent genetic alterations and mutations showed some differences (Table 1). The median follow-up of the entire cohort was 43.4 months (range 2.6-77.5). Significant differences in OS ($p = 0.010$) and DFS ($p = 0.049$) were observed among the three subgroups, primarily due to the poor outcomes of Group 3 (*CDKN2*del regardless of *IKZF1*del). The 4-year OS and DFS rates were 65.9% and 38.5% in Group 1, 52.6% and 22.0% in Group 2, and 33.8% and 11.8% in Group 3, respectively. A trend toward higher CIR in Group 3 was observed ($p = 0.156$), while no significant differences were found in NRM ($p = 0.599$) (Supplementary Fig. 3).

Since allo-HCT was recommended as a post-remission therapy for all eligible patients, we analyzed outcomes in the transplanted cohort. The estimated 3-year OS, DFS, CIR, and NRM rates were 63.4%, 42.9%, 40.8%, and 16.3% after allo-HCT, respectively. Survival outcomes were significantly different among the three groups (Supplementary Fig. 4) – 3-year OS rates of Group 1, 2, and 3 were 73.6%, 60.9%, and 43.5% ($p = 0.017$), and 3-year DFS rates were 56.4%, 46.3%, and 23.5% ($p = 0.006$), respectively. CIR was highest in Group 3 (57.0%) compared to Group 1 and 2 (28.4% and 43.7%, respectively; $p = 0.024$). To further assess the adverse impact of *CDKN2*del, we additionally analyzed the outcomes in patients who underwent allo-HCT in CMR (Fig. 1). Group 3 still showed significantly inferior DFS and higher CIR than the other groups, with 3-year DFS rate of 27.9% compared to Group 1 and 2 (64.2% and 60.6%; $p = 0.009$) and CIR rate of 47.2% compared to Group 1 and 2 (21.2%, 13.6%; $p = 0.013$).

We performed multivariate analyses in the entire cohort (Supplementary Table 2) and transplantation cohort (Supplementary

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Table 1. Baseline characteristics according to the *CDKN2*del and *IKZF1*del combinatorial subgroups.

Variables	***CDKN2*del (−) /*IKZF1*del (+) (*N* = 72)**	***CDKN2*del (−) /*IKZF1*del (−) (*N* = 23)**	***CDKN2*del ±*IKZF1*del (*N* = 61)**	***p*-value**
Median age, years (range)	44 (22–71)	51 (18–65)	46 (19–71)	0.837
Older age (≥50 years), *n* (%)	32 (44.4)	12 (52.2)	23 (37.7)	0.461
Male sex, *n* (%)	34 (47.2)	10 (43.5)	18 (29.5)	0.106
Median leukocyte count, /μL (range)	32,210 (1930–296,610)	5080 (1250–391,230)	25,400 (750–499,750)	0.025
High leukocyte count (≥30 × 109/L), *n* (%)	38 (52.8)	8 (34.8)	27 (44.3)	0.283
Transcript subtype, *n* (%)				0.149
$p190^{BCR::ABL1}$	60 (83.3)	15 (65.2)	50 (82.0)	
$p210^{BCR::ABL1}$	12 (16.7)	8 (34.8)	11 (18.0)	
Extramedullary involvement, *n* (%)	14 (19.4)	7 (30.4)	14 (23.0)	0.542
Delayed CR, *n* (%)	1 (1.4)	1 (4.3)	3 (4.9)	0.487
Combined genetic deletion (MLPA)				
IKZF1	72 (100.0)	0 (0.0)	54 (88.5)	<0.001
PAX5	15 (20.8)	1 (4.3)	44 (72.1)	<0.001
BTG1	15 (2.8)	0 (0.0)	22 (36.1)	0.002
EBF1	17 (23.6)	1 (4.3)	5 (8.2)	0.014
RB1	7 (9.7)	0 (0.0)	12 (19.7)	0.033
Combined gene mutation (NGS)				
SETD2	9 (12.5)	1 (4.3)	1 (1.7)	0.047
RUNX	2 (2.8)	6 (26.1)	1 (1.7)	<0.001
IZKF1	4 (5.6)	2 (8.7)	3 (5.0)	0.806
ASXL1	2 (2.8)	2 (8.7)	1 (1.7)	0.257
PAX5	3 (4.2)	0 (0.0)	1 (1.7)	0.466
Allogeneic HCT proceeding, *n*	57 (79.2)	20 (87.0)	50 (82.0)	0.698
Pre-HCT disease status, *n* (%)				0.377
First CR	48 (84.2)	19 (95.0)	41 (82.0)	
Second CR	9 (15.8)	1 (5.0)	9 (18.0)	
Pre-HCT MRD status, *n* (%)				
CMR	30 (52.6)	11 (55.0)	28 (56.0)	0.939
MMR	17 (29.8)	5 (25.0)	9 (18.0)	0.364
PMR	10 (17.5)	4 (20.0)	13 (26.0)	0.560
Donor type, *n* (%)				
Matched sibling donor	11 (19.3)	4 (20.0)	18 (36.0)	0.354
Unrelated donor	22 (38.6)	8 (40.0)	19 (38.0)	
Haploidentical donor	7 (12.3)	4 (20.0)	5 (10.0)	
Cord blood	17 (29.8)	4 (20.0)	8 (16.0)	
Conditioning intensity, *n* (%)				
Myeloablative	31 (54.4)	9 (45.0)	23 (46.0)	0.622
Reduced toxicity	26 (45.6)	11 (55.0)	27 (54.0)	0.622
Median time-to-HCT, days (range)	210 (130.00–508)	209 (123–277)	210 (126–364)	0.902

CBT cord blood transplantation, *CMR* complete molecular response, *CR* complete response, *Del* deletion, *HCT* hematopoietic cell transplantation, *LDH* lactate dehydrogenase, *MLPA* multiplex ligation-dependent probe amplification, *MMR* major molecular response, *MRD* minimal residual disease, *NGS* next-generation sequencing, *PMR* poor molecular response.

Table 3) to analyze the factors affecting survival outcomes. In the transplantation subgroup, high leukocyte counts at diagnosis (HR 2.02, 95% CI: 1.10–3.69, $p = 0.023$) and *CDKN2*del (HR 2.51, 95% CI: 1.27–4.95, $p = 0.008$) were significantly associated with poorer OS. Similarly, *CDKN2*del (HR 2.27, 95% CI: 1.34–3.84, $p = 0.002$) and pre-HCT PMR (HR 1.88, 95% CI: 1.06–3.33, $p = 0.030$) were associated with poorer DFS and higher CIR rates (*CDKN2*del – HR 2.29, 95% CI: 1.21–4.34, $p = 0.011$ and pre-HCT PMR – HR 3.01, 95% CI: 1.56–5.79, $p = 0.001$). Older age remained as a significant risk factor for high NRM (HR 3.13, 95% CI: 1.24–7.87, $p = 0.015$).

With the increasing availability of diverse treatment options for adult ALL, the assessment of genetic abnormalities has become more crucial in establishing a well-defined risk stratification system. Our study identified *CDKN2*del as a significant genetic alteration

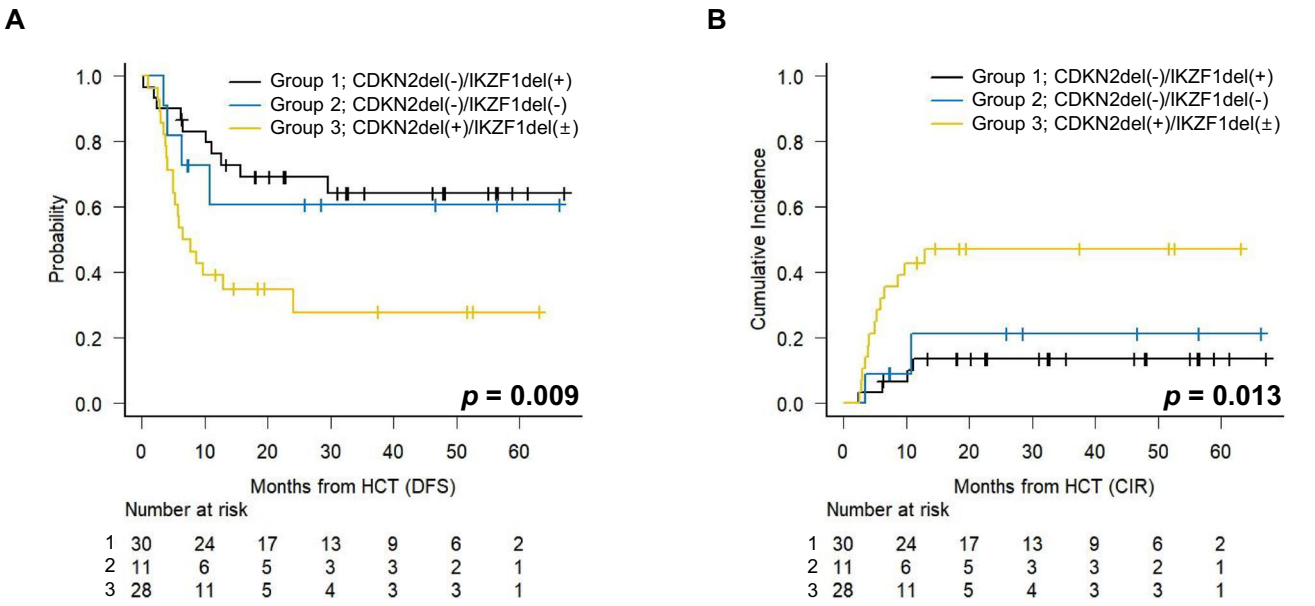

Fig. 1 Survival outcomes of the patients treated with allo-HCT in CMR according to the *CDKN2*del and *IKZF1*del combinatorial subgroups. **A** Disease-free survival. **B** Cumulative incidence of relapse.

associated with a higher relapse rate and poorer survival outcomes, even more than the well-recognized *IKZF1*del. Furthermore, we found that *IKZF1*del alone did not impact survival outcomes unless concomitant *CDKN2*del was present. This demonstrated that *CDKN2*del might be considered a primary prognostic indicator regardless of *IKZF1*del status, as reflected in Group 3. Also, this finding indicates that the adverse prognostic significance traditionally attributed to *IKZF1*del may actually stem from the frequent co-occurrence of *CDKN2*del, which appears to primarily drive the poor outcomes observed. Nevertheless, the clinical significance of *CDKN2*del should be interpreted with caution, as *CDKN2*del showed a higher frequency of concomitant deletions, including *PAX5, BTG1*, and *EBF1*. Although limited by a small number of patients, our data suggest concomitant genetic alterations did not substantially contribute to the poor survival outcomes observed in patients with *CDKN2*del (Supplementary Fig. 5). These findings highlight the prognostic relevance of *CDKN2*del.

Our data finally suggested that *CDKN2*del was associated with poor survival outcome regardless of the impact of *IKZF1* co-deletion. This result was based on the poor outcomes of both *CDKN2*del alone and *CDKN2*del(+)/*IKZF1*del(+) groups, showing that all *CDKN2*del alone relapsed even after allo-HCT with a higher CIR rate (Supplementary Fig. 6). However, the small number of patients with *CDKN2*del alone ($n = 7$) may limit clear conclusions and further studies are needed to validate the results by clarifying the role of *IKZF1* co-deletion. In a previous study by Pfeifer et al. [9], *CDKN2*del was identified as the sole genetic abnormality linked to poor survival outcomes and an independent predictor of a shorter remission duration, consistent with our findings. However, a notable distinction in our study is that the adverse prognostic impact of *CDKN2*del persisted even in patients who achieved pre-HCT CMR. Despite the favorable response to chemotherapy, the high relapse rate observed in patients with *CDKN2*del may be attributed to its role in promoting clonal evolution [10], enabling leukemic subclones with enhanced survival advantages to emerge and drive relapse. Additionally, the increased relapse rate following allo-HCT may be partially attributed to higher PD-L1 expression in patients with *CDKN2*del [11], potentially contributing to the immune escape process in ALL. Moreover, our study assessed MRD using RT-qPCR, but recent studies suggest that NGS-based detection offers superior sensitivity [12]. Further validation is needed to refine MRD assessment and better predict relapse risk in patients with *CDKN2*del.

In this study, *IKZF1*del did not correlate with prognosis, especially in patients without *CDKN2*del. This may suggest a weaker prognostic impact of *IKZF1*del in Ph-positive ALL in the Korean population or may be due to the lack of a detailed *IKZF1* isoform analysis in our study. Fedullo et al. [13] reported that only dominant-negative *IKZF1*del isoforms had prognostic significance, while a study from our institute [14] found no significant survival differences between dominant-negative and haplo-insufficient *IKZF1*del subtypes. Further research is needed to clarify the impact of *IKZF1*del through a more detailed isoform analysis.

In conclusion, this study underscores the substantial prognostic impact of *CDKN2*del in Ph-positive ALL. As our patients were treated with imatinib-based treatment, our results may not apply to a current ponatinib-based treatment era, but recent studies showed that *IKZF1del* alone did not affect survival even with ponatinib [15] Nevertheless, concomitant genetic alterations such as *CDKN2*del alongside *IKZF1*del, which is now defined as *IKZF1*-plus, was associated with significantly poor outcomes. These findings highlight the need for tailored strategies for this high-risk group with genetic alterations.

So Yeon Park[1], Daehun Kwag[1], Jin Jung[2,3], Gi June Min[1], Sung-Soo Park[1], Silvia Park[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Yonggoo Kim[2,3], Myungshin Kim[2,3], Seok Lee[4] and Jae-Ho Yoon[1]✉

[1]*Department of Hematology, Catholic Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.* [2]*Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.* [3]*Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.* [4]*Hematology, Mokdong Hospital, College of Medicine, Ewha Womans University, Seoul, Republic of Korea.*
✉*email: royoon@catholic.ac.kr*

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

SYP conceptualized and designed the study, contributed to statistical analysis and data interpretation, and wrote the manuscript as a first author. DHK, GJM, SSP, SP and SEL took care of the patients; BSC, KSE, YJK, HJK, CKM, and SGC provided patients and reviewed the manuscript; JJ, YK and MK provided laboratory work results and validations; SL contributed to study design and reviewed the manuscript; JHY designed and conducted the study, provided patients and materials, analyzed data, and wrote the manuscript; and all authors reviewed and gave final approval of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki and all patients provided written informed consent approved by the Institutional Review Board of The Catholic University of Korea. This research was approved by the Seoul St. Mary's Hospital Data Review Board and the Institutional Review Board of The Catholic University of Korea (KC16TISI0438, KC23RASI0119, KC24RISI0772).

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Jae-Ho Yoon.

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