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POSTER ABSTRACTS

618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Adverse Prognostic Role of Copy Number Alterations and Mutations in Adults with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia

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Background: The impact of copy number alterations (CNAs) or mutations on outcomes has been broadly analyzed in pediatric acute lymphoblastic leukemia (ALL). However, the magnitude of the effect was often marginal, frequently restricted to specific genetic subtypes and rarely replicated across independent cohorts in adult ALL.
Aim: We tried to analyze the prognostic relevance of genetic copy number alterations and gene mutations in patients with Ph-negative ALL who were treated with modified hyper-CVAD based chemotherapy followed by allogeneic hematopoietic cell transplantation (alllo-HCT).
Methods: We investigated the role of CNAs or mutations to refine risk stratification in 128 adults with newly diagnosed Philadelphia chromosome (Ph)-negative B-cell precursor ALL treated with intensive chemotherapy followed by allo-HCT for post-remission therapy. We performed multiplex ligation-dependent probe amplification (MLPA) to detect deletions of 11 genes (*IKZF1, CDKN2A/B, EBF1, ETV6, PAX5, BTG1, JAK2, RB1, PAR1, ZFY*) and high throughput sequencing (HTS) of 70 gene mutations.
Results: MLPA analysis showed that *IKZF1* and *CDKN2A/B* deletions were observed in 54 (42.2%) and 52 (40.6%) patients, respectively. The remaining gene deletions were: *PAX5* in 29 (22.6%), *ETV6* in 22 (17.2%), *BTG1* in 15 (11.7%), *EBF1* in 14 (10.9%), *RB1* in 13 (10.1%), *JAK2* in 8 (6.2%), and *PAR1* in 4 (3.1%). By HTS, *NRAS* (n=21, 16.4%), *KRAS* (n=11, 8.6%), *TP53* (n=14, 10.9%), and *PTPN11* (n=12, 9.4%) mutations were frequently detected. Overall, multivariate analysis for disease-free survival (DFS) and cumulative incidence of relapse (Table 1) showed that *TP53* mutations (HR 5.04, 95%CI 2.29-11.30, $P<0.001$) and *CDKN2A/B* deletions (HR 1.88, 95%CI 1.10-3.31, $P=0.026$) were significantly associated with a poorer DFS. Patients with *TP53* mutations (HR 5.64, 95%CI 1.95-16.20, $P<0.001$) and *IKZF1* deletions (HR 1.91, 95%CI 1.09-3.31, $P=0.022$) had a higher relapse risk. To better define the prognostic role of CNAs, further analyses were restricted to patients excluding 14 *TP53* mutations (n=114). Here, we classified patients into 4 subgroups; (1) No deletions (n=45, 39.5%), (2) *IKZF1* deletion-alone (n=11, 9.6%), (3) *IKZF1* ^{plus} (n=40, 35.1%), and (4) *CDKN2A/B*±other deletions without *IKZF1* deletions (n=18, 15.8%). Patients with *IKZF1* ^{plus} or *CDKN2A/B*±other deletions had an inferior DFS ($P=0.023$) and higher relapse incidence ($P=0.002$) than patients having no deletions. The results were similarly reproduced in patients receiving allo-HCT in first complete remission.
Conclusions: Our data showed that *IKZF1* or *CDKN2A/B* deletions and *TP53* mutations may confer a poor prognosis for adult Ph-negative B-cell precursor ALL in the setting of intensive chemotherapy and allo-HCT. The combination of genomic abnormalities and minimal residual disease response may further refine risk stratification and better select patients who could benefit from novel therapeutic approaches.

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Table 1. Multivariate analysis of affecting factors for DFS and cumulative incidence of relapse.				
	DFS		Cumulative incidence of relapse	
	HR (95% CI)	P value	HR (95% CI)	P value
TP53 mutations	5.04 (2.29-11.30)	<0.001	5.64 (1.95-16.20)	<0.001
CDKN2A/B deletions	1.88 (1.10-3.31)	0.026	1.35 (0.73-2.53)	0.340
IKZF1 deletions	1.02 (0.61-1.71)	0.934	1.91 (1.09-3.31)	0.022
Delayed CR	3.37 (1.86-6.11)	<0.001	2.74 (1.41-5.33)	0.003
Allo-HCT (Time-dependent co-variate)	0.06 (0.03-0.13)	<0.001	0.39 (0.15-0.98)	0.045

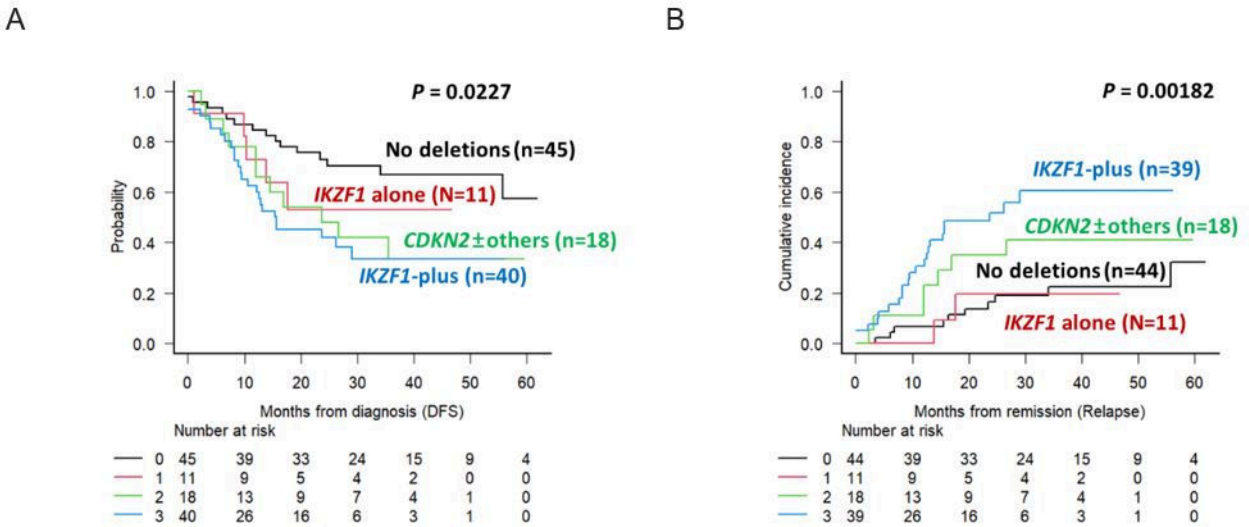

Figure 1. DFS and cumulative incidence of relapse based on the profile of copy number alterations.

Figure 1

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