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

Prognostic Impact of TP53 Mutation in Adult Acute Lymphoblastic Leukemia Treated with Pediatric-Inspired Regimen

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Abstract

Background: TP53 is one of the most extensively studied genes in human cancer. However, the prognostic impact of TP53 mutations (TP53mut) in adult acute lymphoblastic leukemia (ALL) remained debatable, especially in those treated with pediatric-inspired regimen. Herein, we determined the characteristic of TP53mut in adult acute ALL patients and investigated the clinical significance of these TP53mut in newly diagnosed ALL.

Patients and Methods: We performed TP53 mutation analysis in 283 adult ALL patients (B-ALL n=227; T-ALL n=56) including 57 diagnose-relapse pairs using targeted next-generation sequencing (NGS). TP53 mutations were analyzed for their association with adult ALL enrolled in pediatric-inspired regimen evaluating clinical characteristics and treatment outcomes.

Results: A total of 35 TP53mut sites were detected in 31 diagnosed samples among 283 diagnosed patients and 17 among 57 paired diagnose-relapse samples, with a significant difference (11.0% vs 29.8%; c2=13.9, P<0.001). The major variant was missense mutation (n=32), followed by frameshift (n=11), nonsense mutation (n=4), in-frame (n=3), and splicing mutation (n=2). In paired diagnose-relapse samples, we identified acquired and/or loss of TP53mut in the samples at the time of relapse. In 283 newly diagnosed patients, patients with TP53mut had a higher proportion of the older population, complex karyotype, and MRD positivity before consolidation therapy (P=0.023, 0.002, 0.024). Survival analysis revealed that TP53mut was associated with inferior outcomes in the whole cohort of newly diagnosed ALL (4-year OS rates, 43.6% vs 63.6%, P=0.0086; 4-year EFS rates, 30.4% vs 52.2%, P=0.0056). Additional survival analysis showed that TP53mut did not confer poor outcomes in the AYA population (4-year OS rates, 60.6% vs 68.1%, P=0.55; 4-year EFS rates, 52.5% vs 55.5%, P=0.57). For the older patients, however, TP53mut predicted inferior OS and EFS in older patients (4-year OS rates, 18.2% vs 46.2%, P=0.0033; 4-year EFS rates, 0 vs 39.6%, P=0.00028).

Conclusion: Our data revealed that TP53mut was present at a low incidence at diagnosis and increase at relapse. TP53mut were potential biomarkers associated with poor prognosis in older patients with newly diagnosed ALL treated with pediatric-inspired regimen.

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Key words TP53; Acute lymphoblastic leukemia; Pediatric-inspired regimen; Next-generation sequencing; Prognosis

Disclosures No relevant conflicts of interest to declare.

Table 1. Comparison of clinical characteristics of patients with TP53mut or not.

Characteristic	*TP53*wt (n=252)	*TP53*mut (n=31)	*P*
Age (years)			
<40	200	19	0.023
≥40	52	12	
Gender			0.943
Male	148	18	
Female	104	13	
WBC, ×10^9/L [median(range)]	14.9 (0.4-775.7)	15.2 (0.6-222.6)	0.558
HGB, g/L [median(range)]	80 (28-171)	78 (32-140)	0.430
PLT, ×10^9/L [median(range)]	64 (6-534)	62 (8-236)	0.257
LDH, IU/L [median(range)]	449.5 (90-9899)	449 (130-13959)	0.574
BM blast (%) [median(range)]	94.2 (90.1-97.1)	93.4 (93.1-96.8)	0.623
Phenotype			0.568
B-ALL	201	26	
T-ALL	51	5	
Complex karyotype			0.002
Yes	29	11	
No	174	18	
Translocation			0.481
Negative	148	19	
Positive	104	10	
MRD1	104	12	0.758
≥1%	146	19	
<1%			
MRD2			0.183
≥0.1%	76	13	
<0.1%	176	18	
MRD3			0.024
≥0.01%	72	15	
<0.01%	180	16	
Relapse			0.050
Yes	85	16	
No	167	15	
Final survival status			0.051
Alive	174	16	
Dead	78	15	

*Karyotype was available for 166 patients in TP53wt group and 29 patients in TP53mut group.
†Fisher exact

Figure 1. Lollipop figure of TP53 mutations in ALL patients [http://www.cbioportal.org/]

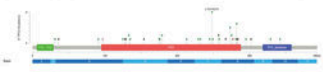
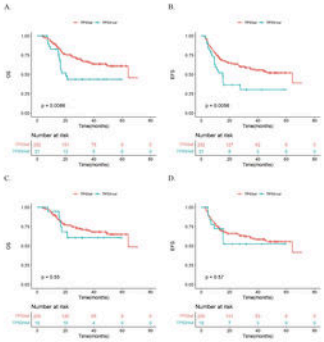


Figure 2. Kaplan-Meier overall survival (OS) and event-free survival (EFS) curves of ALL patients, stratified based on the presence of mutations in TP53. (A) In the whole cohort of ALL (n = 283); (B) In older ALL subset (n=64); (C) In AYA subset (n=219).



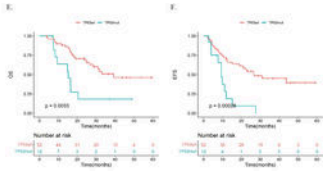


Figure 1

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