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POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

RUNX1 Mutation Does Not Significantly Impact the Outcome of Newly Diagnosedadult AML: A Retrospective Study of Chinese AML Patients

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Background

RUNX1 is one of the recurrent mutated genes in newly diagnosed acute myeloid leukemia (AML) with a frequency of 6%~15%. Although historically recognized as a provisional distinct entity, the AML subtype with *RUNX1* mutations (AML- *RUNX1* ^{mut}) was eliminated from the 2022 WHO classification system. With the update of AML diagnosis and treatment protocol, different outcomes of AML- *RUNX1* ^{mut}have been reported. However, an in-depth study about the prognostic value of *RUNX1* mutations, epecifically the classification change related to AML- *RUNX1* ^{mut} in a large well-annotated cohort is lacking.

Methods

The clinical data of 1065 AML (excluding acute promyelocytic leukemia and *RUNX1* germline mutations) patients according to WHO 2016 and treated from January 2017 to December 2021 at Jiangsu Institute of Hematology were retrospectively collected and analyzed after informed consent. All AML diagnosis samples were analyzed by targeted Next Generation Sequencing (NGS) panel covering 172 frequently mutated genes in hematological malignancies. Demographic and clinical data, disease characteristics at diagnosis, first-line treatment and clinical outcome data were available for all patients. The survival time of allogeneic hematopoietic stem cell transplantation patients was censored at the time of stem cell transfusion. Cytogenetic and molecular characteristics were used to classify patients into ELN2017 and ELN2022 risk groups (excluding the effect of *RUNX1* mutation).

Results

RUNX1 mutations were detected in 112 (10.5%) patients, namely, 66 (58.9%) male and 46 (41.1%) female. A total of 132 *RUNX1* alterations were detected with a medianvariant allelic frequency of 40% (3%~93%). *RUNX1* mutations were associated with older age (48.5 vs. 46.0 years old, *P*=0.087) and antecedent myeloid disorders (6.3% vs. 1.0%, P<0.001). One or more comutations were detected in 106 (94.7%) AML- *RUNX1* ^{mut} patients. The most frequent co-gene abnormalities were *FLT3-ITD* and *DNMT3A* mutations which represented the 23.2% and 18.7%. Mutations of *CEBPA* bZIP, *NPM1* and translocations of t(8;21), t(16;16)/inv(16) were uncommon in AML- *RUNX1* ^{mut} with a frequency of 6.3%, 1.8%, 2.7%, 0%, respectively **(Table 1).**
Compared with AML with wild-type *RUNX1* (AML- *RUNX1* ^{wt}), AML- *RUNX1* ^{mut} patients had a lower complete remission rate (19.6% vs. 29.7%, P=0.034), lower overall response rate (ORR) (73.5% vs. 84.3%, P=0.006) and higher no response rate (26.5% vs. 15.5%, P=0.021) in the first induction chemotherapy. When comparing groups based on the ELN2017 risk stratification criteria, no significant difference in ORR was observed between *RUNX1* ^{mut} and *RUNX1* ^{wt} patients in the favorable (91.2% vs. 94.0%, P=0.572), intermediate (75.0% vs. 78.4%, P=0.570) and adverse (63.3% vs. 71.4%, P=0.370) subgroups **(Table 2)**.
The median duration of follow-up of the entire cohort was 8.7 months (*RUNX1* ^{wt}: 8.4 months; *RUNX1* ^{mut}: 10.0 months). Comparing the two groups, patients with *RUNX1* mutations had a lower 5-year overall survival (OS) rate (35.4% vs. 42.3%; HR=1.563; 95% CI: 1.091~2.237, P=0.026), but no significant difference was observed in the 5-year event-free survival (EFS) rate (40.8% vs. 35.4%; HR=1.084; 95% CI: 0.750~1.570, P=0.098) **(Table 2)**. However, when patients were stratified according to the ELN2017 guidelines (excluding the effect of *RUNX1* mutation), outcomes did not differ between patients withor without *RUNX1* mutation in the favorable (OS: *P*=0.629, EFS: *P*=0.137), intermediate (OS: *P*=0.629, EFS: *P*=0.114) and adverse (OS: *P*=0.544; EFS: *P*=0.714) subgroups. Similar results were obtained according to the ELN2022 guidelines. In multivariate analysis, *RUNX1* was not an independent prognostic factor for OS (HR=1.353, 95% CI: 0.922~1.985, P=0.122) and EFS (HR=1.422, 95% CI: 0.975~2.075, P=0.068), while significantly worse OS and EFS were observed in patients with mutated *FLT3-ITD*, *TP53*, and *DNMT3A* (P-values were all less than 0.05).

Conclusion

RUNX1 mutations were rarely isolated genetic abnormities that conferred inferior outcomes. However, on the basis of ELN prognosis risk stratification, *RUNX1*mutation had no impact on the clinical outcomes of AML patients in stratified subgroups. *RUNX1* was not an independent prognostic factor for survival. Overall, our findings agree with the updated WHO classification system for AML that AML- *RUNX1* ^{mut} should not be recognized as a distinct AML entity.

Disclosures No relevant conflicts of interest to declare.

Table 1. Patients' clinical characteristics

Characteristic	Mutated RUNX1 n=112	Wild-type RUNX1 n=953	*P*
Median age, years (range)	48.5 (18-79)	46.0 (18-78)	0.087
Male sex, n (%)	66 (58.9)	517 (54.2)	0.347
AML history, n (%)			
De novo	104 (92.9)	928 (97.4)	**0.009**
Secondary	7 (6.3)	10 (1.0)	**<0.001**
Therapy-related	1 (0.9)	15 (1.6)	1.000
Hematological parameters			
Median WBC count, $\times 10^9$/L (range)	9.7 (0.46-286.98)	15.2 (0.32-466.55)	**0.005**
Median Plt count, $\times 10^9$/L (range)	42.5 (5-332.4)	40.0 (2-813)	0.774
Median Hb, g/L (range)	75.5 (31-122)	81.0 (25-155)	**0.029**
Median bone marrow blasts, % (range)	55.0 (17-98.0)	57.0 (3-99.5)	0.635
ELN Risk 2017, n (%)			
Favorable	13 (11.6)	453 (47.5)	**<0.001**
Intermediate	67 (59.8)	290 (30.4)	
Adverse	32 (28.6)	210 (22.0)	
ELN Risk 2022, n (%)			
Favorable	13 (11.6)	381 (40.0)	**<0.001**
Intermediate	42 (37.5)	346 (36.3)	
Adverse	57 (50.9)	226 (23.7)	
Chromosomal aberration, n (%)			
Normal karyotype	73 (65.2)	587 (61.6)	0.460
t(8;21)	3 (2.7)	97 (10.2)	**0.009**
inv(16)/t(16;16)	0	45 (4.7)	**0.011**
del(7q)/-7 in noncomplex karyotype	2 (1.8)	15 (1.6)	0.697
del(5q)/-5 in noncomplex karyotype	1 (0.9)	5 (0.5)	0.487
t(v;11q23.3)	3 (2.7)	16 (1.7)	0.441
Complex karyotype	6 (5.4)	42 (4.4)	0.647
Comutations, n (%)			
CEBPA bZIP	7 (6.3)	184 (19.3)	**0.001**
NPM1	2 (1.8)	241 (25.3)	**<0.001**
FLT3-ITD	26 (23.2)	226 (23.7)	0.906
ASXL1	16 (14.3)	54 (5.7)	**<0.001**
TP53	6 (5.4)	40 (4.2)	0.568
U2AF1	8 (7.1)	47 (4.9)	0.317
SRSF2	7 (6.3)	17 (1.8)	**0.003**
SF3B1	7 (6.3)	10 (1.0)	**<0.001**
ZRSR2	3 (2.7)	7 (0.7)	0.078
BCOR	20 (17.9)	31 (3.3)	**<0.001**
EZH2	8 (7.1)	35 (3.7)	0.078

WBC: White blood cell, Plt: Platelet, Hb: Hemoglobin, ELN: European LeukemiaNet.
Risk stratification according to the ELN guidelines, excluding the effect of RUNX1 mutations.

Table 2. Univariate outcome analyses according to RUNX1 mutation status.

Clinical endpoint	Mutated RUNX1 n=102	Wild-type RUNX1 n=843	*P*
Response, n (%)			
CR	20 (19.6)	250 (29.7)	**0.034**
CRi	21 (20.6)	243 (28.8)	0.080
MLFS	19 (18.6)	126 (15.0)	0.330
PR	15 (14.7)	93 (11.0)	0.271
NR	27 (26.5)	131 (15.5)	**0.021**
ORR (CR/CRi/MLFS/PR), n (%)			
All	75 (73.5)	711 (84.3)	**0.006**
Favorable-risk	11 (91.2)	390 (94.0)	0.572
intermediate-risk	45 (75.0)	196 (78.4)	0.570
adverse-risk	19 (63.3)	125 (71.4)	0.370
OS	**n=102**	**n=843**	**0.026**
Median, years	25.9	40.4	
95% CI	6.1~45.7	24.1~56.8	
5-year OS (%)	35.4%	42.3%	
EFS	**n=87**	**n=748**	0.098
Median, years	21.3	23.1	
95% CI	0.69~42.0	16.3~30.0	
5-year EFS (%)	40.8%	35.4%	

CR: complete remission, CRi: CR with incomplete blood count recovery, MLFS: morphologic leukemia-free state, PR: partial remission, NR: no response, ORR overall response rate, OS: overall survival, EFS: event-free survival.

Figure 1

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