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Association between *FLT3-ITD* and additional chromosomal abnormalities in the prognosis of acute promyelocytic leukemia

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Abstract

Objectives: Internal tandem duplications of the Fms-like tyrosine kinase 3 gene (*FLT3-ITD)* and additional chromosomal abnormalities (ACA) are prognostic factors in patients with acute promyelocytic leukemia (APL). This study aimed to determine the effect of the association between *FLT3-ITD* and ACA in the prognosis of APL.

Methods: This was a retrospective cohort study including 60 patients with APL treated with all-trans retinoic acid (ATRA) and chemotherapy. Five-year overall survival (OS) and progression-free survival (PFS) were analyzed in patient groups according to the presence of *FLT3-ITD* and ACA.

Results: *FLT3-ITD* was an independent adverse factor for 5-year PFS, and ACA was an independent adverse factor for 5-year OS. There were significant differences in OS and PFS among the groups: *FLT3-ITD*-negative without ACA, *FLT3-ITD*-positive without ACA, *FLT3-ITD*-negative with ACA, and *FLT3-ITD*-positive with ACA. The OS times were 52.917, 45.813, 25.375, and 23.417 months, and the PFS times were 48.833, 38.563, 23.250, and 17.333 months, respectively.

Conclusion: *FLT3-ITD* and ACA are associated with the poorest OS and PFS outcomes in patients with APL treated with chemotherapy plus ATRA.

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FLT3-ITD, additional chromosomal abnormalities, acute promyelocytic leukemia, prognosis, survival, all-trans retinoic acid

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Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia characterized by the proliferation of abnormal promyelocytic cells, with rearrangements involving the retinoic acid receptor alpha (*RARα*) located at 17q21. About 95% of patients with APL show the translocation (15;17)(q22;q21) including promyelocytic leukemia (*PML*)/*RARα*,[1] while the remaining patients show the nucleophosmin1 (*NPM1*)/*RARα* translocation (5;17)(q35;q21) or the promyelocytic leukemia zinc finger (*PLZF*)/*RARα* translocation (11;17)(q23;q21).[2] Abnormal promyelocytic cells with the (15;17)(q22;q21) translocation are considered to be susceptible to all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), and APL is thus considered to be a curable malignant disease.[3] However, in addition to this major translocation, patients with APL may have other chromosomal abnormalities that may interfere with the therapeutic efficacy of these specific drugs. Previous studies found that these additional chromosomal abnormalities (ACA) were associated with poorer treatment outcomes and survival times.[4–6] Unfortunately, a relatively high percentage of patients with APL (29%–43%) may have ACA at diagnosis.[7]

Internal tandem duplication of the Fms-like tyrosine kinase 3 gene (*FLT3-ITD*) is associated with increased survival and proliferation of hematopoietic progenitors and is related to leukocytosis in patients with APL, and thus plays a role in the pathogenesis of APL.[8–10]Given the high incidence of *FLT3-ITD* in APL (13%–40%), it is important to understand its potential effect on patient survival.[11,12] However, few studies have investigated the association between *FLT3-ITD* and ACA and their effect on survival in patients with APL. The current study aimed to determine the role of the association between *FLT3-ITD* and ACA in the prognosis of APL.

Materials and Methods

Patients

This was a retrospective cohort study conducted at the Center for Hematology and Blood Transfusion, Bach Mai Hospital, Hanoi, Vietnam, from January 2015 to December 2019. The study enrolled all consecutive patients diagnosed with new APL according to the FAB classification with positive *PML*/*RARα*, who were treated with chemotherapy plus ATRA.[13]

The Institutional Review Board of Hanoi Medical University waived the need for approval and patient consent because of the retrospective observational nature of the study. All patient details were de-identified.

Reverse transcription polymerase chain reaction

Bone marrow samples obtained from all patients at the time of diagnosis were

analyzed by reverse transcription polymerase chain reaction to detect *PML/RARα* and *FLT3-ITD*.

Cytogenetics

Bone marrow samples obtained at diagnosis were also subjected to chromosome analysis to detect t(15;17)(q21;q22) and ACA.

Treatment

Patients were treated with an induction, consolidation, and maintenance regimen. The induction regimen consisted of oral ATRA (twice daily, 45 mg/m^2/day) until complete remission, with daunorubicin (45 mg/m^2/days 1–3) in the low/intermediate-risk group or daunorubicin (45 mg/m^2/days 1–3) + cytarabine (100 mg/m^2/days 1–7) in the high-risk group. The consolidation regimen consisted of daunorubicin (45 mg/m^2/days 1–3) and ATRA (45 mg/m^2/day for 15 days) for two to three courses, monthly. Maintenance therapy with oral ATRA (45 mg/m^2/day for 15 days every 3 months) and oral mercaptopurine (60 mg/m^2/day) was administered for 2 years.

Definition

Risk groups were classified according to the Sanz score.[14] Disseminated intravascular coagulation (DIC) was defined according to the criteria of the International Society for Thrombosis and Hemostasis.[15] The response criteria to induction therapy were determined according to the International Working Group criteria.[16]

Statistical analysis

The patients were grouped according to the presence of *FLT3-ITD* and ACA. Patients were further divided into three groups based on the number of ACA: no ACA, one ACA, two or more ACA. Differences in quantitative variables (hemoglobin, white blood cells, platelets, fibrinogen, D-dimer, bone marrow cell count, bone marrow blast percent) among groups were analyzed by one-way ANOVA, and differences in qualitative variables (DIC and risk group) were analyzed by χ^2 or Fisher's exact test. Univariate and multivariate analyses were performed using the Kaplan–Meier method and Cox proportional hazards model to identify independent prognostic factors for overall survival (OS) and progression-free survival (PFS). OS was defined as the time from diagnosis to the last follow-up, or death, and PFS was defined as the time from remission to relapse or death.

There were no missing data in this study and the bias was therefore controlled. The reporting of this study conforms to the STROBE guidelines.[17]

Results

Clinical data

Sixty patients were included in the study and their data were analyzed retrospectively. There were 28 men (46.7%) and the mean age was 38.6 years (range: 15–68 years). The characteristics of the patients are presented in Tables 1 and 2. There were no significant differences in laboratory indices, except for Hb levels, including the distribution of risk groups or the frequency of DIC, between the groups of patients according to the presence of *FLT3-ITD* and ACA.

Survival analysis

Univariate analysis showed that both *FLT3-ITD* and ACA were associated with poor 5-year OS and 5-year PFS (*FLT3-ITD*: $P = 0.027$, $P = 0.008$; respectively; ACA: $P = 0.007$, $P = 0.015$; respectively) (Table 3). However, multivariate analysis

Table 1. Laboratory indices in patients according to presence of *FLT3-ITD* and additional chromosomal abnormalities.

	N	Mean	SD	SE	P
Hb (g/L)					
FLT3-ITD-negative without ACA	24	78.3333	16.38309	3.34419	<0.05
FLT3-ITD-positive without ACA	16	68.8125	16.35530	4.08882	
FLT3-ITD-negative with ACA	8	91.6250	15.68382	5.54507	
FLT3-ITD-positive with ACA	12	78.4167	19.87899	5.73857	
Total	60	77.5833	17.98520	2.32188	
WBC ($\times 10^9$/L)					
FLT3-ITD-negative without ACA	24	10.9592	9.96506	2.03411	>0.05
FLT3-ITD-positive without ACA	16	15.5769	23.53658	5.88415	
FLT3-ITD-negative with ACA	8	12.6225	15.69540	5.54916	
FLT3-ITD-positive with ACA	12	13.5267	15.18278	4.38289	
Total	60	12.9258	15.97878	2.06285	
Platelets ($\times 10^9$/L)					
FLT3-ITD-negative without ACA	24	35.5833	26.05165	5.31777	>0.05
FLT3-ITD-positive without ACA	16	29.8750	21.93589	5.48397	
FLT3-ITD-negative with ACA	8	46.6250	56.11707	19.84038	
FLT3-ITD-positive with ACA	12	35.6667	33.98217	9.80981	
Total	60	35.5500	31.64176	4.08493	
Fibrinogen (g/L)					
FLT3-ITD-negative without ACA	24	2.0986	1.28843	0.26300	>0.05
FLT3-ITD-positive without ACA	16	2.3056	1.39051	0.34763	
FLT3-ITD-negative with ACA	8	2.6255	1.75769	0.62144	
FLT3-ITD-positive with ACA	12	1.8882	1.38827	0.40076	
Total	60	2.1820	1.38412	0.17869	
D-dimer (mg/L FEU)					
FLT3-ITD-negative without ACA	24	26.9240	17.89542	3.65289	>0.05
FLT3-ITD-positive without ACA	16	27.8965	29.33780	7.33445	
FLT3-ITD-negative with ACA	8	54.6998	40.70744	14.39225	
FLT3-ITD-positive with ACA	12	26.0148	27.20613	7.85373	
Total	60	30.7050	27.72660	3.57949	
Bone marrow cell count ($\times 10^9$/L)					
FLT3-ITD-negative without ACA	24	266.4433	186.09443	37.98637	>0.05
FLT3-ITD-positive without ACA	16	167.9500	159.93318	39.98329	
FLT3-ITD-negative with ACA	8	154.5275	119.96823	42.41518	
FLT3-ITD-positive with ACA	12	204.5825	155.01628	44.74934	
Total	60	212.8842	168.46741	21.74905	
Blasts in bone marrow (%)					
FLT3-ITD-negative without ACA	24	77.3333	20.17029	4.11724	>0.05
FLT3-ITD-positive without ACA	16	86.0625	6.63796	1.65949	
FLT3-ITD-negative with ACA	8	85.3750	8.17553	2.89049	
FLT3-ITD-positive with ACA	12	86.6667	11.85774	3.42304	
Total	60	82.6000	14.92944	1.92738	

ACA, additional chromosomal abnormalities; SD, standard deviation; SE, standard error; Hb, hemoglobin; WBC, white blood cells; FEU, fibrinogen equivalent units.

Table 2. Characteristics of patients according to the presence of FLT3-ITD and additional chromosomal abnormalities.

	FLT3-ITD-negative without ACA	*FLT3-ITD*-positive without ACA	*FLT3-ITD*-negative with ACA	*FLT3-ITD*-positive with ACA	*P*
Risk group					
Low	5	2	2	3	>0.05
Intermediate	9	11	3	5	
High	10	3	3	4	
Total	24	16	8	12	
DIC					
No	6	2	2	3	>0.05
Yes	18	14	6	9	
Total	24	16	8	12	

ACA, additional chromosomal abnormalities; DIC, disseminated intravascular coagulation.

Table 3. Univariate and multivariate analyses of survival times.

	Univariate analysis (OS)	Multivariate analysis (OS)		
Factor	*P* value[a]	HR	95% CI	*P* value[b]
FLT3-ITD				
Negative	0.027			>0.05
Positive				
ACA				
No	0.007	2.905	1.090–7.746	0.033
Yes				
ACA				
No	0.02			>0.05
One				
≥2				
	Univariate analysis (PFS)	Multivariate analysis (PFS)		
Factor	P value[a]	HR	95% CI	P value[b]
FLT3-ITD				
Negative	0.008	2.854	1.095–7.437	0.032
Positive				
ACA				
No	0.015			>0.05
Yes				
ACA				
No	0.019			>0.05
One				
≥2				

ACA, additional chromosomal abnormalities; OS, overall survival; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival.
[a]Log-rank; [b]Cox regression.

indicated that *FLT3-ITD* was only an adverse prognostic factor for PFS ($P = 0.032$, hazard ratio [HR] = 2.854, 95% confidence interval [CI]: 1.095–7.437) while ACA was only an independent adverse prognostic factor for OS ($P = 0.033$, HR = 2.905, 95% CI: 1.090–7.746) (Table 3).

We also analyzed the survival time of the patient groups based on the number of ACA (no ACA, only one ACA, ≥2 ACA). OS and PFS differed significantly among the three groups according to univariate analysis ($P = 0.02$, $P = 0.019$; respectively), but multivariate analysis found no significant difference (Table 3).

It should be noted that 5-year OS and 5-year PFS differed significantly among the following groups of patients: *FLT3-ITD*-negative without ACA, *FLT3-ITD*-positive without ACA, *FLT3-ITD*-negative with ACA, and *FLT3-ITD*-positive with ACA ($P = 0.006$, $P = 0.003$; respectively). The OS times were 52.917, 45.813, 25.375, and 23.417 months, respectively, and the PFS times were 48.833, 38.563, 23.250, and 17.333 months, respectively. *FLT3-ITD*-positive patients with ACA had the worst OS and PFS (Table 4, Figures 1 and 2).

Discussion

The *PML/RARα* fusion gene derived from translocation t(15;17)(q22;q21) generates the oncogenic PML/RARα fusion protein, which is considered to act as the main pathogenic factor in APL via deregulation of transcriptional control of the *RARα* gene and disruption of *PML* function.[18] ATRA is the main drug used to treat APL. Its mechanisms of action include relocalizing PML and degrading PML/RARα protein, and converting PML/RARα from a transcription inhibitor to a transcription activator.[3] However, ACA and/or *FLT3-ITD* may be associated with other comorbid mechanisms, resulting in reduced treatment efficacy and survival.

Pantic et al. showed that ACA was an independent adverse factor for survival time in patients with APL treated with ATRA,[19] and Wiernik et al. also suggested that APL patients without ACA had better OS and disease-free survival (DFS) than those with ACA, following treatment with ATRA.[20] Cervera et al. showed that ACA was associated with lower relapse-free survival according to univariate analysis, but there was no significant association in multivariate analysis.[21]

Epstein-Peterson et al. suggested that ACA was not always an adverse prognostic factor for event-free survival in patients with APL treated with ATO, but did have an adverse effect in cases with a complex karyotype,[22] while Chen et al. found that an abnormal karyotype was associated with a high risk of early mortality, even in patients treated with ATO.[23] Poiré et al. also suggested that patients with ACA had poorer OS, despite ATO therapy.[24]

Table 4. Overall and progression-free survival according to presence of *FLT3-ITD* and additional chromosomal abnormalities.

Group	OS (months)	*P*	PFS (months)	*P*
FLT3-ITD-negative without ACA	52.917	0.006	48.833	0.003
FLT3-ITD-positive without ACA	45.813		38.563	
FLT3-ITD-negative with ACA	25.375		23.250	
FLT3-ITD-positive with ACA	23.417		17.333	

ACA, additional chromosomal abnormalities; OS, overall survival; PFS, progression-free survival.

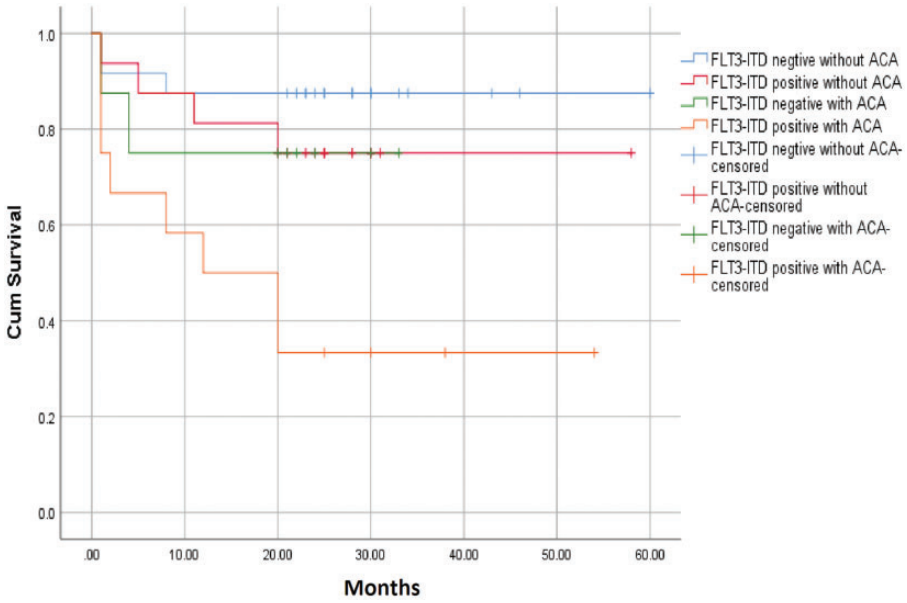

Figure 1. Cumulative overall survival (Cum Survival) according to the presence of *FLT3-ITD* and additional chromosomal abnormalities (ACA).

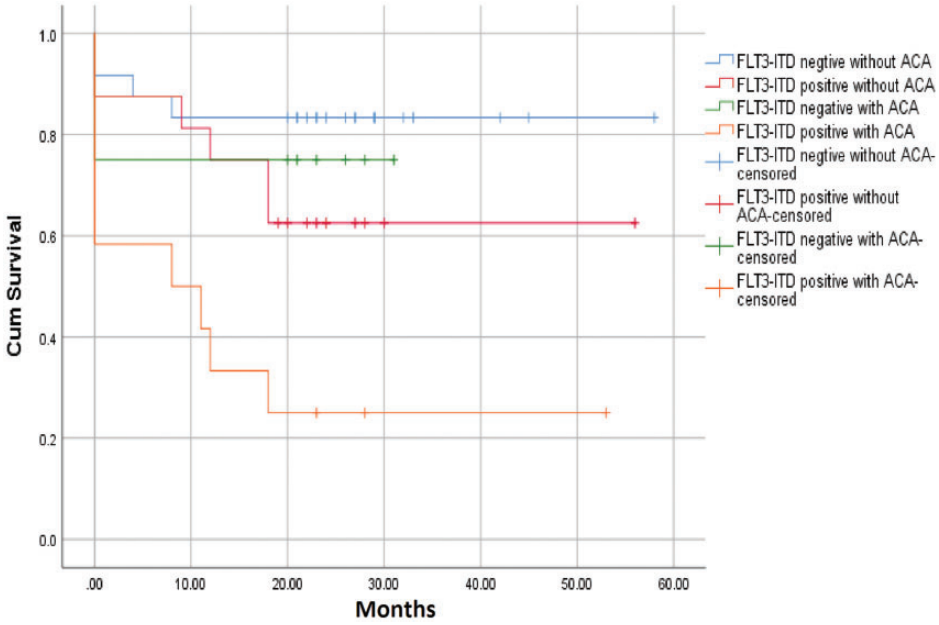

Figure 2. Cumulative progression-free survival (Cum Survival) according to the presence of *FLT3-ITD* and additional chromosomal abnormalities (ACA).

Overall, these studies suggest that ACA may be an adverse factor affecting survival time. The current multivariate analysis showed that ACA was an independent adverse prognostic factor for OS but not PFS in patients with APL treated with ATRA plus chemotherapy. This result appears to be similar to that of Pantic et al. and Wiernik et al.,[19,20] suggesting that ATRA has little effect on ACA.

The *FLT3-ITD* mutation is associated with a poor prognosis in patients with acute myelogenous leukemia with a normal karyotype.[8] However, *FLT3-ITD* is often present in patients with APL and is associated with hyperleukocytosis, suggesting that it is also an adverse risk factor for treatment and survival outcomes in APL.[1]

Breccia et al. showed that *FLT3-ITD* was an independent unfavorable factor for OS, relapse-free survival, and DFS in patients with APL treated with ATRA plus chemotherapy,[11] but Lucena-Araujo et al. suggested that this mutation only had an impact on OS, but not on DFS.[25] However, Singh et al. compared patients with *FLT3-ITD* and wild-type *FLT3* and concluded that *FLT3-ITD* was a poor prognostic factor for DFS, but not for OS.[26]

Poiré et al. and Deka et al. assumed that *FLT3-ITD* had no effect on OS or DFS in patients treated with ATO,[24,27] while Song et al. suggested that *FLT3-ITD* was an adverse factor in terms of OS and event-free survival, even after ATO therapy.[28]

These studies have thus produced controversial results regarding the role of *FLT3-ITD* as a poor prognostic factor, regardless of ATRA or ATO treatment. However, the current multivariate analysis suggested that *FLT3-ITD* was an independent adverse prognostic factor for PFS, but not for OS, in accord with the findings of Lucena-Araujo et al.[25]

It is generally difficult to treat patients with APL with ACA or *FLT3-ITD*. Furthermore, the prognostic effect of the combination of these two abnormalities is unclear, and studies examining the effects of these two factors on survival time using multivariate analysis are lacking. We therefore analyzed the effect of the association between *FLT3-ITD* and ACA on survival time using the Kaplan–Meier method and log rank test. We found significant differences in both OS and PFS among the groups: *FLT3-ITD*-negative without ACA, *FLT3-ITD*-positive without ACA, *FLT3-ITD*-negative with ACA, and *FLT3-ITD*-positive with ACA ($P = 0.006$, $P = 0.003$; respectively), with *FLT3-ITD*-positive patients with ACA having the worst OS and PFS. Appropriate treatment strategies thus need to be considered for patients with both *FLT3-ITD* and ACA.

Our study had some limitations. The European Leukemia Network 2019 considers normal chromosomal acute myelogenous leukemia with $NPM1^{mut}$, without *FLT3-ITD* or with low-level *FLT3-ITD*, as having a favorable prognosis.[29] Low levels of *FLT3-ITD* may thus not cause adverse effects, and the adverse prognostic influence of *FLT3-ITD* may also depends on its expression level. This may also help to explain some of apparently conflicting results regarding the prognostic significance of *FLT3-ITD*. Unfortunately, we did not quantify *FLT3-ITD* levels in the current study. As noted above, some studies showed that *FLT3-ITD* had no effect on survival time in patients treated with the ATO regimen.[24,27] The prognostic factors thus change in line with advancements and changes in treatments, and different prognostic factors should be analyzed and applied at different stages of treatment development. The current study is applicable to patients treated with the ATRA regimen; however, further studies are needed in patients treated with the ATO regimen. More research is also needed to analyze treatment outcomes in relation to *FLT3-ITD* levels.

Conclusion

FLT3-ITD may be an independent adverse prognostic factor for PFS and ACA may be an independent adverse prognostic factor for OS in APL patients treated with chemotherapy plus ATRA, with *FLT3-ITD*-positive patients with ACA having the worst OS and PFS times.

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Author contributions

Minh Phuong Vu: conceptualization, formal analysis, methodology, writing – original draft, writing – review & editing; Cuc Nhung Nguyen: formal analysis, investigation, methodology, writing – original draft; Hoang Vu: investigation, writing – original draft; Tuyet Mai Nguyen: formal analysis, writing – original draft; Tuan Tung Nguyen: methodology, writing – original draft; Phuong Thao Pham: formal analysis, investigation, Writing – original draft. All authors approved the version to be published

Data availability

The dataset used for this paper is available upon reasonable request.

Declaration of conflicting interests

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