

Risk factors of thrombosis in chinese subjects with acute promyelocytic leukemia

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Research

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Abstract

Acute promyelocytic leukemia (APL) is a kind of malignant hematologic disease. Thrombosis is a rare manifestation of APL. However, the risk factors of thrombosis related to Chinese APL patients are not fully understood. Clinical and laboratory data of 44 consecutively Chinese APL patients were collected and analyzed. 1 arterial and 6 venous thrombosis occurred in 44 patients, including 22 males and 22 females, with a median age of 44 years (range 18–74 years). The ratio of male and female gender ($P = 0.68$), age ($P = 0.823$), white blood cell count ($P = 0.077$), hemoglobin ($P = 0.409$), platelets ($P = 0.334$), disease risk stratification ($P = 0.475$), CD2 ($P = 0.737$), Khorana score ($P = 0.52$), differentiation syndrome (DS) ($P = 0.562$) and gene mutation related to prognosis of APL, including DNMT3A ($P = 0.44$), TET2 ($P = 0.43$), IDH1 ($P = 0.6$), IDH2 ($P = 0.66$), NRAS ($P = 0.66$), ASXL1 ($P = 0.9$) in the two groups with and without thrombosis were not statistically significant. The detection rate of PAI-1 genotype 4G4G was 71.4% (5/7) in 7 patients with thrombosis, while the detection rate of PAI-1 genotype 4G4G in 37 patients without thrombosis was 8.1% (3/37). The differences between the two groups in WT-1 ($P = 0.01$), PAI-1 4G4G ($P = 0.0009$), bcr3 ($P = 0.027$), CD15 ($P = 0.005$), and FLT3-ITD mutation ($P = 0.0008$) were statistically significant. The results suggested the PAI-1 gene 4G4G type, PML/RAR α (bcr3), CD15, WT-1 and FLT3-ITD mutations excluding DNMT3A, TET2, IDH1/2, NRAS and ASXL1 are risk factors of thrombotic events in Chinese APL patients.

Introduction

Acute promyelocytic leukemia (APL) is a special type of acute myeloid leukemia with cytogenetic characteristics of t(15;17)(q22;q21) formation the PML/RAR α fusion gene [1–3]. APL is a kind of leukemia with dangerous prognosis in early phase [4]. The disease has common clinical manifestations of acute leukemia, including anemia, hemorrhage, infection, hepatosplenomegaly, lymphadenopathy and bone pain and so on [5–6]. Among them, bleeding tendency is the most significant clinical manifestation of APL patients, and also the primary factor for early death of APL patients [7–10]. In addition, the incidence of thrombotic events (TE) in APL is higher than in other types of leukemia, and the incidence of arterial and venous thrombosis is reported to be between 2 % and 10–15 % according to previous data documented [11–14]. APL venous thrombosis can occur in deep veins, cerebral venous sinus, portal vein, and hepatic vein. APL arterial thrombosis occurs mostly in peripheral arterial occlusion, myocardial infarction and ischemic stroke [15].

Therefore, it is very important to evaluate the risk of thrombus in the early stage of acute promyelocytic leukemia, especially in the process of induced differentiation and other treatment, and actively give intervention treatment to reduce complications.

At present, as respect to the risk factors of APL related thrombotic events, limited research results showed that they could be related to high leukocyte, CD2/CD15 positive, FLT3/ITD positive, PML/RAR α fusion gene variant, retinoic acid syndrome, high platelet count and male [16–18]. However, the epidemiology and risk factors of APL related thrombotic events are still uncertain. Thus, through a single center retrospective study, we characterized the clinical information of 44 patients with newly diagnosed APL, analyzed the risk factors of APL related thrombotic events, and provided strategies for better clinical treatment of APL patients.

Patients And Methods

44 newly diagnosed APL patients with or without thrombotic events in our center from January 2013 to December 2019 were consecutively enrolled based on the presence of t(15;17) (q22;q12) and/or PML-RARA fusion gene by standard cytogenetic analysis and reverse-transcriptase polymerase chain reaction (RT-PCR), respectively. The study

was approved by informed consent of patients and the Ethical Committee of Fujian Medical University Second Hospital. The FLT3/ITD and WT1 gene mutations were detected in 44 patients by PCR and the second generation sequencing. Four color flow cytometry (FACS-calibur, BD, USA) was used to detect the surface antigens of leukemia cells. Monoclonal antibodies were HLA-DR, CD2, CD3, CD4, CD5, CD7, CD8, CD9, CD10, CD11b, CD13, CD14, CD15, CD16, CD19, CD20, CD22, CD33, CD34, CD38, CD56, CD64, CD71, CD117, CD123, MPO and CD45.

All patients were treated with all-trans retinoic acid plus anthracyclines and/or arsenic trioxide. During the induction treatment, the platelet count was maintained above $30 \times 10^9/L$ by infusion of platelets, and the fibrinogen level was maintained above 1.5 g/L by fresh frozen plasma infusion. The patients did not use antifibrinolytic drugs such as tranexamic acid, and did not have a central venous catheter during the induction therapy.

Detection of Coagulation Related Parameters

The activated prothrombin time (APTT), prothrombin time (PT) and fibrinogen were detected by Automatic Coagulation Analyzer (Sysmex Corporation, Japan). D-dimer was measured by immunoturbidimetry. The normal range is as follows: PT 6-14s, APTT 25-35s, fibrinogen 2-4 g /L. D-dimer 0-0.5ug/ml.

Detection of plasminogen activator inhibitor-1 (PAI-1) gene polymorphism

Plasminogen activator inhibitor-1 (PAI-1) gene 4G/5G polymorphism was performed according to the previous reported [19] in 7 APL patients with TE and 37 APL patients without TE.

Detection of Thrombosis and Bleeding Events

From the day of admission to our department to the last day of follow-up, APL patients were evaluated for thrombotic events and bleeding. Bleeding in the central nervous system, lung or digestive tract is considered to be severe bleeding. Venous or arterial thrombosis was confirmed by Color Doppler Vascular Ultrasound and CT or MRI in APL patients.

Treatment of Thrombotic Diseases

In the acute phase of venous thrombosis, under the condition of ensuring platelets value $> 30 \times 10^9/L$ and fibrinogen $> 1.5g/l$, heparin was given intravenously for 2 weeks, and then warfarin sequential therapy for 3 months. During the treatment, the warfarin dosage was adjusted according to INR value. Antiplatelet drugs were used in the treatment of arterial thrombosis, and the platelet count was maintained $> 100 \times 10^9/L$ during treatment. Three months after anticoagulation and antiplatelet therapy, the recanalization of blood vessels was detected by Color Doppler Ultrasound.

Statistical Analysis

Using chi square and Fisher's exact method to analyze the relationship between variables, $P < 0.05$ is considered statistically significant. The differences between groups were analyzed by log rank test. Single factor Cox proportional regression model and multi factor Cox proportional regression model were used to identify risk factors. The odds ratio (OR) and 95% confidence interval (CI) were calculated by social science statistical software package.

Results

The study population included 44 APL patients, 22 (50%) males and 22 (50%) females with a median age of 42 years (range 18–74 years). These population were all newly diagnosed APL patients admitted to our department from January 2013 to December 2019, and received treatment according to the PETHEMA APL99 protocol. Among them, 7 APL patients had thrombotic events, none of them had previous history of thrombosis and family history of thrombosis. 1 patient had arterial thrombosis (2.3%) and 6 patients had venous thrombosis (13.6%). No APL patients existed bleeding and thrombosis simultaneously. The clinical characteristics of APL patients with thrombotic events were shown in Table 1.

Table 1
Presenting characteristics of APL patients who developed thrombotic events

Characteristics of Patients	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age(years)/sex	27/M	27/F	22/M	45/M	53/F	55/M	67/F
WBC($\times 10^9/L$)	3.7	2.5	3.7	106.8	14.5	0.6	3.9
HGB(g/L)	56	59	99	46	57	67	71
PLT($\times 10^9/L$)	9	36	2	7	24	62	19
Risk stratification	Intermediate	Intermediate	Intermediate	High	High	Low	Intermediate
PML/RAR α isoforms	Bcr1	Bcr3	Bcr1	Bcr3	Bcr3	Bcr3	Bcr3
Leukemic cell biomarks	CD2- CD15-	CD2- CD15+	CD2- CD15+	CD2- CD15+	CD2- CD15+	CD2- CD15+	CD2- CD15+
WT1 mutation status	negative	positive	negative	negative	positive	positive	positive
FLT3/ITD mutation status	negative	positive	positive	positive	positive	positive	positive
PAI-1 gene polymorphism	4G4G	4G5G	4G5G	4G4G	4G4G	4G4G	4G4G

Thrombotic events in patients with APL

The incidence of arterial thrombosis was 1/44 (2.3%), and the patient was a female, aged 53 years, when the disease was first diagnosed, she felt weakness of the limbs. There was no history of thrombosis, hypertension, diabetes and hyperlipidemia. Cerebral infarction was confirmed by CT and MRI, and antiplatelet drug was used. The incidence of VTE was 6/44 (13.6%), the ratio of male to female was 4/2, the median age was 37 years (22–67 years). Venous thrombosis occurred in 6 cases of lower extremity venous thrombosis, 4 cases on the left and 2 cases on the right, all of which occurred during the induction of all-trans retinoic acid after diagnosed. The median time for the treatment of venous thrombosis was 14 days (9–26 days). 6 patients with venous thrombosis were treated with heparin anticoagulation under the premise of platelet and fibrinogen supplementation, and then sequential administration of warfarin. The treatment of venous thrombosis had obvious effect and no serious bleeding occurred.

The clinical characteristics of the two groups of APL patients with thrombotic events were shown in Table 2. There was no significant difference between the two groups in gender ratio ($P = 0.68$), age ($P = 0.823$), white blood cell count ($P = 0.077$), hemoglobin ($P = 0.409$), platelet ($P = 0.334$), disease risk stratification ($P = 0.475$), CD2 ($P = 0.737$) and differentiation syndrome (DS) ($P = 0.562$). There were significant differences between the two groups in PAI-1 4G4G ($P = 0.0009$), bcr3 ($P = 0.027$) and CD15 ($P = 0.005$). In order to demonstrated whether additional gene mutations involved in thrombotic events in APL patients, we have analysed the results of gene mutation related to prognosis of APL. As shown in Table 3, there were significant differences between the two groups in WT-1 ($P = 0.01$) and FLT3-ITD muations ($p = 0.0008$), excluding DNMT3A ($p = 0.44$), TET2 ($p = 0.43$), IDH1 ($p = 0.6$), IDH2 ($P = 0.66$), NRAS ($p = 0.66$), ASXL1 ($p = 0.9$). In multivariate Cox proportional regression, the most significant risk factor for venous TE was the FLT3-ITD mutation ($P = 0.034$, RR 10.036, 95% CI 1.197–84.123). As shown in Table 4, a total of 2 (4.5%), 16 (36.4%), 24 (54.5%), 2 (4.5%) of APL patients had a khorana score of 0, 1, 2, 3, respectively. However, there were no statistically significant between two groups with thrombosis and without thrombosis.

Table 2
Comparison of characteristics in APL patients with and without thrombosis

Characteristics	APL patients with thrombosis(7)	APL patients without thrombosis(37)	P values
Gender			
Female	3	19	0.68
Male	4	18	0.68
Age(years)	42.3	40.9	0.823
WBC($\times 10^9/L$)	26.240	10.846	0.077
HGB(g/L)	63.40	81.21	0.409
PLT($\times 10^9/L$)	15.60	33.71	0.334
Risk stratification			
Low-risk	1(14.3%)	10(27%)	0.475
Intermediate-risk	4(57.1%)	24(64.9%)	0.697
High-risk	2(28.6%)	3(8.1%)	0.245
PML-RARα gene type			
Bcr1	2(28.6%)	26(70.3%)	
Bcr2	0(0%)	0(0%)	
Bcr3	5(71.4%)	10(27.0%)	0.027
Rare	0(0%)	1(2.7%)	
Leukemic cell biomarks			
CD2 positive	2(28.6%)	13(35.1%)	0.737
CD15 positive	6(85.7%)	11(29.7%)	0.005
PAI-1 gene polymorphism			
4G4G	5(71.4%)	3(8.1%)	0.0009
4G5G	2(28.6%)	25(67.6%)	
5G5G	0(0%)	9(24.3%)	
Differentiation syndrome	2(28.6%)	7(18.9%)	0.562

Table 3

Comparison of gene mutation related to prognosis of APL patients with and without thrombosis

Gene mutations	APL patients with thrombosis(7)	APL patients without thrombosis(37)	P values
WT-1	5(71.4%)	9(24.3%)	0.01
FLT3-ITD	6(85.7%)	8(21.6%)	0.0008
DNMT3A	0(0%)	3(8.1%)	0.44
TET2	2(28.6%)	6(16.2%)	0.43
IDH1	1(14.3%)	3(8.1%)	0.6
IDH2	0(0%)	1(2.7%)	0.66
NRAS	0(0%)	1(2.7%)	0.66
ASXL1	1(14.3%)	6(16.2%)	0.9
TP53	0(0%)	0(0%)	—
RUNX1	0(0%)	0(0%)	—
NPM1	0(0%)	0(0%)	—
CEBPA	0(0%)	0(0%)	—
C-kit	0(0%)	0(0%)	—
dupMLL	0(0%)	0(0%)	—

Table 4

Comparison of Khorana score in APL patients with and without thrombosis

Khorana score	APL patients with thrombosis(7)	APL patients without thrombosis(37)	P values
0	0(0%)	2(5.4%)	0.52
1	3(42.9%)	13(35.1%)	0.7
2	4(57.1%)	20(54.1%)	0.88
3	0(0%)	2(5.4%)	0.52

The detection rate of PAI-1 genotype 4G4G was 71.4% (5/7) in 7 APL patients with thrombotic events, while the detection rate of PAI-1 genotype 4G4G in APL patients without thrombotic events was 8.1% (3/37). There was significantly statistical difference between the two groups regarding whether thrombotic events occurred or not ($P = 0.0009$).

Discussion

Our results showed that the incidence of APL arterial thrombus was lower than that of venous thrombus (2.3% vs 13.6%). Venous thrombus occurred in the disease induction treatment phase. The median time of thrombotic events occurred 14 days (range 9-26). 6 patients with venous thrombosis were given heparin anticoagulant therapy under the premise of platelet and fibrinogen supplementation, so that the vein was completely recanalized, and no serious bleeding events were observed. The incidence of venous thrombosis is

consistent with the data reported in the previous literature (11%). Other studies showed that the incidence of APL related thrombotic events increased from 2% before All trans retinoic acid (ATRA) used to 4.5-15% after ATRA used [20-22].

Currently, the risk factor of thrombosis in APL patients is not fully clear. Previous studies reported that these factors increasing the risk of APL thrombosis, including male, high score performance status (PS), high white blood cell count and platelet count, low fibrinogen levels, hypoalbuminemia, PML/RAR α fusion gene variant, CD2/CD15 and FLT3-ITD positive.

Our results showed that there was no significant difference between thrombotic events and gender ratio ($P = 0.68$), age ($P = 0.823$), white blood cell count ($P = 0.077$), hemoglobin ($P = 0.409$), platelets ($P = 0.334$), disease risk stratification ($P = 0.475$) and CD2 ($P = 0.737$). In addition, PML/RAR α (bcr3) ($P = 0.027$), CD15 ($P = 0.005$), WT-1 ($P = 0.01$) and FLT3-ITD mutation ($P = 0.0008$) were statistically significant. In multivariate Cox proportional regression, the most significant risk factor for venous thrombosis was FLT3-ITD mutation ($P = 0.034$, RR 10.036, 95% CI 1.197-84.123), suggesting a high risk factor associated with thrombotic event. However, there is no literature to confirm whether the gene mutations related to prognosis of APL and differentiation syndrome are related to the occurrence of APL thrombotic events. Our data confirmed that DNMT3A ($P = 0.44$), TET2 ($P = 0.43$), IDH1 ($P = 0.6$), IDH2 ($P = 0.66$), NRAS ($P = 0.66$), ASXL1 ($P = 0.9$) and differentiation syndrome (DS) ($P = 0.562$) did not increase the risk of thrombosis in APL patients.

PAI-1 is a key regulator of endogenous fibrinolytic activity [23]. It is reported that the 4G/5G polymorphism of the PAI-1 gene affect plasma levels of PAI-1 [24]. The 4G/4G genotype is associated with higher plasma PAI-1 activity, which can lead to impaired fibrinolysis, thus increasing the risk of thrombosis [25-26]. Previous study reported that PAI-1 gene 4G/4G in APL patients received ATRA treatment, which showed high PAI-1 level in vivo and increased APL related thrombotic events [8]. Our results showed that PAI-1 4G/4G was detected in 71.4% (5/7) of 7 patients with thrombosis, and PAI-1 gene polymorphism was 4G/5G (28.6%, 2/7) in 2 patients. The detection rate of PAI-1 4G/4G in the patients without thrombotic events was 8.1% (3/37), the difference was statistically significant ($P = 0.0009$).

Thrombotic events are significant complications in malignant patients. Thrombosis risk is well defined for patients with solid tumors, and Khorana score is well validated for these patients, however, the value of Khorana scoring system in predicting the thrombotic events risk of hematological malignant diseases remains to be evaluated [27-28]. We conducted a retrospective study to validate the use of the Khorana score for thrombotic events in APL patients. The results of our study showed that the Khorana score of all APL patients with thrombotic events were 1 and 2, and there was no significant difference between the two groups.

Lee YG et al [29] suggested that advanced age and increasing cytogenetic risk were the independent risk factors of VTE from retrospectively analysed 811 consecutive AML patients. The expression of additional gene mutations were correlated with the pathogenesis and prognosis of acute myeloid leukemia. Recently, APL patients with epigenetic modifier genes (EMG) mutations may exert negative impact on the overall survival and disease free survival [30]. However, the possible of EMG mutations on the risk of VTE in APL patients has not been confirmed. We have analysed the results of EMG mutations related to prognosis of APL. As shown in Table 3, there were significant differences between the two groups in WT-1 ($P = 0.01$) and FLT3-ITD mutations ($P = 0.0008$), excluding DNMT3A ($P = 0.44$), TET2 ($P = 0.43$), IDH1 ($P = 0.6$), IDH2 ($P = 0.66$), NRAS ($P = 0.66$), ASXL1 ($P = 0.9$). These results suggested that WT-1 and FLT3-ITD mutations were the independent risk of thrombotic events in APL patients.

In conclusion, our study showed that the incidence of thrombotic events in APL patients is extraordinary. The PML/RAR α fusion gene (bcr3), WT-1 and FLT3/ITD mutation, PAI-1 gene 4G4G, CD15 positive expression are the risk factors of thrombotic events in chinese APL patients. But due to the limitation of retrospective single center study. The incidence of thrombotic events in chinese APL patients remains to be further explored.

Declarations

Authors' Note

Conceived and designed the study: XYZ, XZG; Conducted study procedures (patient recruitment, blood sampling): XYZ; Collected data: XYZ; Analysed the data: XYZ; Interpreted the results: XYZ; Wrote the first draft of the manuscript: XYZ; Contributed to the writing of the manuscript: XYZ, XZG

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Statement of conflict of interest

The authors declared that they have no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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