CLINICAL RESEARCH

Hyperfibrinolysis Is an Important Cause of Early Hemorrhage in Patients with Acute Promyelocytic Leukemia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCEF 1 **Yu-Hua Song**
ABG 2 **Chun Qiao**
B 2 **Li-Chan Xiao**
BD 2 **Run Zhang**
AFG 2 **Hua Lu**

1 Department of Hematology, The Second Hospital of Nanjing, Nanjing, Jiangsu, P.R. China
2 Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, Jiangsu, P.R. China

Corresponding Author: Hua Lu, e-mail: luhua1956@aliyun.com
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Background: The objective of the current study was to guide the early clinical treatment strategies by assessing the recovery of abnormal coagulation in acute promyelocytic leukemia (APL) patients during induction therapy.

Material/Methods: Retrospective analysis was performed in 112 newly-diagnosed patients with APL during induction treatment.

Results: The early death (ED) rate in our study was 5.36% and the main cause was fetal hemorrhage. The presence of bleeding symptoms was significantly correlated with low platelet and fibrinogen levels. The values of white blood cell (WBC), lactate dehydrogenase (LDH), prothrombin time (PT), fibrinogen, and bone marrow leukemic promyelocyte in the high-risk group were significantly different from those in the low/intermediate-risk groups. Coagulation variables significantly improved after dual induction therapy. No significant difference was found in changes of platelet (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimers, and fibrinogen among different risk groups after induction therapy. D-dimer levels were initially high and remained well above normal after 4 weeks of induction therapy.

Conclusions: Aggressive prophylactic transfusion to maintain high platelet and fibrinogen transfusion thresholds could reduce hemorrhage in APL patients. Immediately starting induction therapy effectively alleviated coagulopathy in APL patients. Hyperfibrinolysis was a more important event in the APL hemorrhagic diathesis.

MeSH Keywords: Fibrinolysis • Hemorrhage • Leukemia, Promyelocytic, Acute

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Background

Acute promyelocytic leukemia (APL) is a distinct clinical and biological subtype of acute myeloid leukemia (AML). The disease is identified by the predominance of abnormal promyelocytes in the bone marrow and a specific chromosomal translocation – t(15;17) – resulting in a fusion transcript between the promyelocytic (PML) gene presented on chromosome 15 and the retinoic acid receptor alpha (RARα) gene found on chromosome 17 as PML-RARα [1]. ATRA (all-trans retinoic acid) and ATO (all-trans retinoic acid) are the cornerstones of APL therapy at present and have dramatically improved outcomes, but APL is still has a high incidence of early hemorrhagic death mainly due to the presence of coagulopathy, including disseminated intravascular coagulation (DIC), fibrinolysis, and proteolysis. The coagulopathy in APL is different from classical DIC, with relatively preserved levels of protein C and antithrombin III. Fibrinolysis is demonstrated by increased urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA), as well as decreased plasminogen activator inhibitor-1 (PAI-1) and a2-antiplasmin [2]. The management of coagulopathy associated with APL remains a clinical challenge. Changes in clinical and laboratory parameters before and during induction therapy were examined in this study in order to guide early clinical treatment strategies.

Material and Methods

Patients and ethics statement

A total of 112 newly diagnosed APL patients were treated at Jiangsu Province Hospital, the first affiliated hospital to Nanjing Medical University (Nanjing, China) from May 2009 to April 2016, including 66 males and 46 females aged 12–75 years and with a median age of 41 years. The diagnostic criteria of APL were based on the World Health Organization Classification of Tumors-Pathology and Genetic of Tumors of Haematopoietic and Lymphoid Tissue (2008) and FAB (1976) [3]. Molecular diagnosis was confirmed by cytogenetic analysis of t(15;17), and/or positivity of PML-RARα in fluorescence *in situ* hybridization or reverse transcription-polymerase chain reaction (RT-PCR) analysis. The immune phenotype diagnosis of APL was identified as positive for CD33, CD9, CD13, and CD117 and low expression of HLA-DR and CD34. Early death (ED) was defined as death for any cause within 30 days after diagnosis. Other criteria were no serious underlying liver disease or cardiovascular disorders or other hemorrhagic diseases, without use of anticoagulants during induction therapy. We collected data from May 2009 to April 2016 and identified the information during and after data collection. The Medical Ethics Committee waived the need for informed consent because the study was an observational retrospective study using a database. All clinical investigations were conducted in accordance with the principles expressed in the Declaration of Helsinki.

Treatment strategies

The treatment followed the Shanghai APL protocol, which underwent minor adjustments during the induction period [4]. Intravenous ATO (10 mg/d) daily was started immediately at the time APL was suspected, then oral ATRA (25 mg/m²/day) was prescribed according to genetic confirmation until complete remission (CR) of induction therapy. Additional chemotherapy was administered to control hyperleukocytosis (idarubicin 8 mg/m²/day for 3–4 days or daunorubicin 45 mg/m²/day for 3–4 days was added if peripheral WBC was greater than 10×10^9/L or on the second day in patients with high risk (initial WBC count $>10 \times 10^9$/L). Differentiation syndrome (DS) result from the use of differentiating agents (such as ATRA or ATO) in APL patients during induction therapy. The clinical manifestations were unexplained fever, bone pain, weight gain, hypotension, edema, dyspnea, heart failure, and renal failure. After we diagnosed DS clinically, we immediately suspended ATRA and gave 10 mg dexamethasone twice daily for at least 3 days until symptoms subsided. Patients underwent central nervous system (CNS) prophylaxis, including 6 intrathecal injections of 50 mg cytosine arabinoside (Ara-C), 10 mg methotrexate, and 5 mg dexamethasone, in addition to systemic treatment. Treatment with platelets, fresh frozen plasma (FFP), or cryoprecipitate transfusion was provided when clinically-associated bleeding occurred. Prophylactic platelet transfusion strategy was available when the platelet count was less than 50×10^9/L. In China, 1 apheresis unit is standardized with 2.5×10^{11} platelets or more, with less than 5×10^8 leucocytes. Patients only received random ABO-identical (non-HLA-typed) apheresis platelets for platelet transfusions. Prophylactic transfusion of fresh frozen plasma (FFP) or cryoprecipitate was predominantly based on fibrinogen level below 1.5 g/L.

Laboratory studies and clinical outcomes

The obtained information included case mix (age, sex), clinical (initial bleeding events, early hemorrhagic death events, laboratory variables [white blood cell (WBC) counts, hemoglobin (HB) levels, platelet(PLT) counts, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fbg), D-dimer (D-D), lactate dehydrogenase(LDH) and bone marrow leukemic promyelocyte (BMP) percentage]. Routine blood tests were carried out using a Sysmex XT-4000i Hematology Analyzer (Sysmex, Kobe, Japan) on EDTA-anticoagulated blood samples. The Sysmex CS-2000i Automated Hemostasis Analyzer (Sysmex, Kobe, Japan) was used for detecting coagulation parameters such as PT, APTT, fibrinogen level (Clauss method), and D-dimer (Immuno-turbidimetric method). Blood biochemical tests were done on a Beckman Coulter AU5800 biochemical

analyzer (Beckman Coulter, USA) on heparin-anticoagulated blood samples. Bone marrow leukemic promyelocytes were microscopically examined by 2 experienced physicians separately. Fusion gene transcript of chromosome aberrations was analyzed by reverse transcription polymerase chain reaction. PML-RARα gene fusion was performed on bone marrow (BM) samples collected at diagnosis of APL.

Statistical analysis

The prognostic risk stratification of APL is based on widely accepted risk assessment criteria derived from Italian GIMEMA and Spanish PETHEMA trials: WBC $\leq10\times10^9$/L and PLT >40×10^9/L for low risk, WBC $\leq10\times10^9$/L and PLT $\leq40\times10^9$/L for intermediate-risk, and WBC>10×10^9/L for high-risk group [1]. Statistical analysis was performed using SPSS software 16.0 (SPSS Inc, Chicago, IL, USA). The results are presented as the median ± standard deviation (SD) of normally distributed data, and as the median of non-normally distributed data. Comparisons were made using the *t* test, chi-square test, Fisher's exact test, and analysis of variance. P values were bilateral, and P<0.05 was considered as statistically significant.

Results

In our study, 112 patients were diagnosed with APL based on morphology and detection of PML-RARA mutations and/or t(15;17)(q22;q21). The ratio of t(15;17) translocation was 83.96% (89/106) using conventional cytogenetic techniques. The presence of PML-RARα mutation was 99.01% (100/101) via fluorescence *in situ* hybridization or reverse transcription-PCR. The induction strategies of all patients were based on the Shanghai APL protocol. There were 66 (58.93%) men and 46 (41.07%) women and the ratio of males to females was 1.43: 1. The median age of patients was 41 (range, 12–75) years. The baseline laboratory test results of all patients are summarized in Table 1. Early death (ED) is defined as death within 30 days after diagnosis throughout this study. Among the 112 patients, 6 died within 30 days after diagnosis and the ED rate was 5.36%. Out of 6 deaths, 5 were even earlier deaths (<7 days after induction therapy). ED causes in 5 cases were: 3 cases of intracranial hemorrhage, 1 case of pulmonary hemorrhage, and 1 case of acute renal failure. There was 1 case of intracranial hemorrhage complicated with pulmonary hemorrhage. A sixth patient died of severe infection with type 2 diabetes and had poor glycemic control. Patients who survived more than 1 week were excluded. Thus, the complete remission (CR) rate was 95.53% (107/112). Hemorrhage remained the major cause of ED in 4 (66.67%) patients.

Six cases of early death were excluded to minimize interference, and the remaining 106 cases (61 males and 45 females) were

Table 1. Baseline laboratory parameters of acute promyelocytic leukemia cases.

Laboratory parameters	Values	
Age (years), median (range)	41	(12–75)
Gender, Male/Female	66/46	
WBC (×10⁹/L), median (range)	11.22	(0.30–89.98)
HB (g/L), median (range)	86.03	(29–146)
PLT (×10⁹/L), median (range)	33	(5–231)
LDH(U/L), median (range)	422.41	(121–3571)
BMP(%), median (range)	82.62	(47.6–97.2)
Sanz risk groups		
Low-risk group	22	(19.64%)
Intermediate-risk group	63	(56.25%)
High-risk group	27	(24.11%)

incorporated into the following analysis. Among the 106 newly diagnosed patients with APL, 15 had no obvious bleeding, 78 bled at skin or soft tissue, 61 at oral or nasal, 19 at genitourinary system, 4 at central nervous system, 9 at pulmonary, and 4 at gastrointestinal system. The 106 patients were divided into bleeding and no bleeding groups, and their clinical characteristics were analyzed. Out of the 91 bleeding patients, 49 were male and 42 were female, and there was no statistically significant difference when compared to the 15 non-bleeding patients (12 males and 3 females, P=0.058). The median age of the bleeding patients was 41.27 years, compared to 38.87 years for the non-bleeding patients (P=0.554). The platelet count at presentation was lower in bleeding patients (median, 27.80×10⁹/L) compared to non-bleeding patients (median, 68.07×10⁹/L, P=0.033). The mean fibrinogen concentration was lower in bleeding patients than in non-bleeding patients (1.24±0.79 *vs.* 1.86±0.94, P=0.007). However, the WBC counts, hemoglobin, LDH, PT, APTT, and D-dimer levels and bone marrow leukemic promyelocyte(BMP) percentage at presentation in bleeding patients exhibited no significant differences compared to those in non-bleeding patients (Table 2).

According to Sanz risk, we divided the patients into 2 groups: 81 (76.42%) as the low/intermediate-risk group and 25 (23.58%) as the high-risk group. The high-risk group was associated with high WBC, LDH, BMP, and PT levels (P=0.000, P=0.000, P=0.042, P=0.000), and low fibrinogen level (P=0.000) at presentation. However, there were no statistically significant differences in age, sex, or HB, PLT, APTT, and D-dimer values between high-risk and low/intermediate-risk groups at diagnosis (Table 3). We analyzed changes in hemostatic variables such as PLT, PT, APTT, fibrinogen, and D-dimer in 106 patients during induction

**Table 2.** Main characteristics of our series and comparison patients between bleeding and no bleeding.

Characteristics	No bleeding (n=15)	Bleeding (n=91)	P-value
Age, (years), median ±SD	38.87±13.69	41.27±14.69	0.554
Gender, Male/Female	12/3	49/42	0.058
WBC (×10⁹/L), median ±SD	5.39±16.63	11.50±18.97	0.243
HB (g/L), median ±SD	83.60±25.70	86.57±25.09	0.673
PLT (×10⁹/L), median ±SD	68.07±65.57	27.80±19.03	0.033
LDH (U/L), median ±SD	229.47±123.76	430.67±519.86	0.140
PT (s), median ±SD	13.21±1.70	14.85±3.67	0.094
APTT (s), median ±SD	27.41±5.59	27.07±4.62	0.794
Fbg (g/L), median ±SD	1.86±0.94	1.24±0.79	0.007
D-D (ug/ml), median ±SD	7.58±10.92	9.40±13.22	0.651
BMP (%), median ±SD	81.52±8.00	82.51±9.49	0.703

Table 3. Main characteristics of our series and comparison patients between low/intermediate-risk group and high-risk group.

Characteristics	Low/intermediate-risk group (n=81)	High-risk group (n=25)	P-value
Age, (years), median ±SD	40.28±14.05	43.04±16.05	0.409
Gender, Male/Female	45/36	16/9	0.455
WBC (×10⁹/L), median ±SD	2.55±2.04	36.85±24.08	0.000
HB (g/L), median ±SD	84.11±24.96	92.76±24.79	0.132
PLT (×10⁹/L), median ±SD	34.53±35.10	30.16±24.76	0.564
LDH (U/L), median ±SD	275.01±154.40	814.28±856.25	0.000
PT (s), median ±SD	13.71±1.68	17.54±5.73	0.000
APTT (s), median ±SD	26.83±4.52	28.03±5.41	0.273
Fbg (g/L), median ±SD	1.49±0.86	0.84±0.48	0.000
D-D (ug/ml), median ±SD	9.46±13.36	10.73±13.60	0.683
BMP (%), median ±SD	81.36±9.41	85.66±8.11	0.042

therapy. The recording time points were at diagnosis before initial treatment, and at 0.5, 1, 1.5, 2, and 4 weeks after initiating treatment with ATO+ATRA and/or chemotherapy. All observed variables had statistically significant differences over time (all P<0.001). The values of PLT, PT, APTT, and fibrinogen appeared significantly improved at 0.5 weeks after induction treatment and the D-dimers began to decrease at 1 week of therapy. The value of PLT plateaued until the end of the second week, then returned to almost normal after 4 weeks of induction treatment. The elevated D-dimers experienced a relatively slow downtrend and remained at a high level after 4 weeks of induction treatment. There were no significant differences

in the changes of PLT, APTT, D-dimers, or fibrinogen (P=0.309, P=0.641, P=0.756, and P=0.392) between high-risk and low/intermediate-risk groups during 4 weeks of induction, but significant differences were found in changes of PT (P=0.014). Further comparison revealed that the differences in PT levels existed only at diagnosis (P<0.001), and there was no significant difference (P0.5W=0.075, P1W=0.349, P1.5W=0.138, P2W=0.897, P4W=0.847) between the 2 groups after therapy (Figure 1). The results show that prognostic stratification of APL did not affect the pace of coagulation recovery.
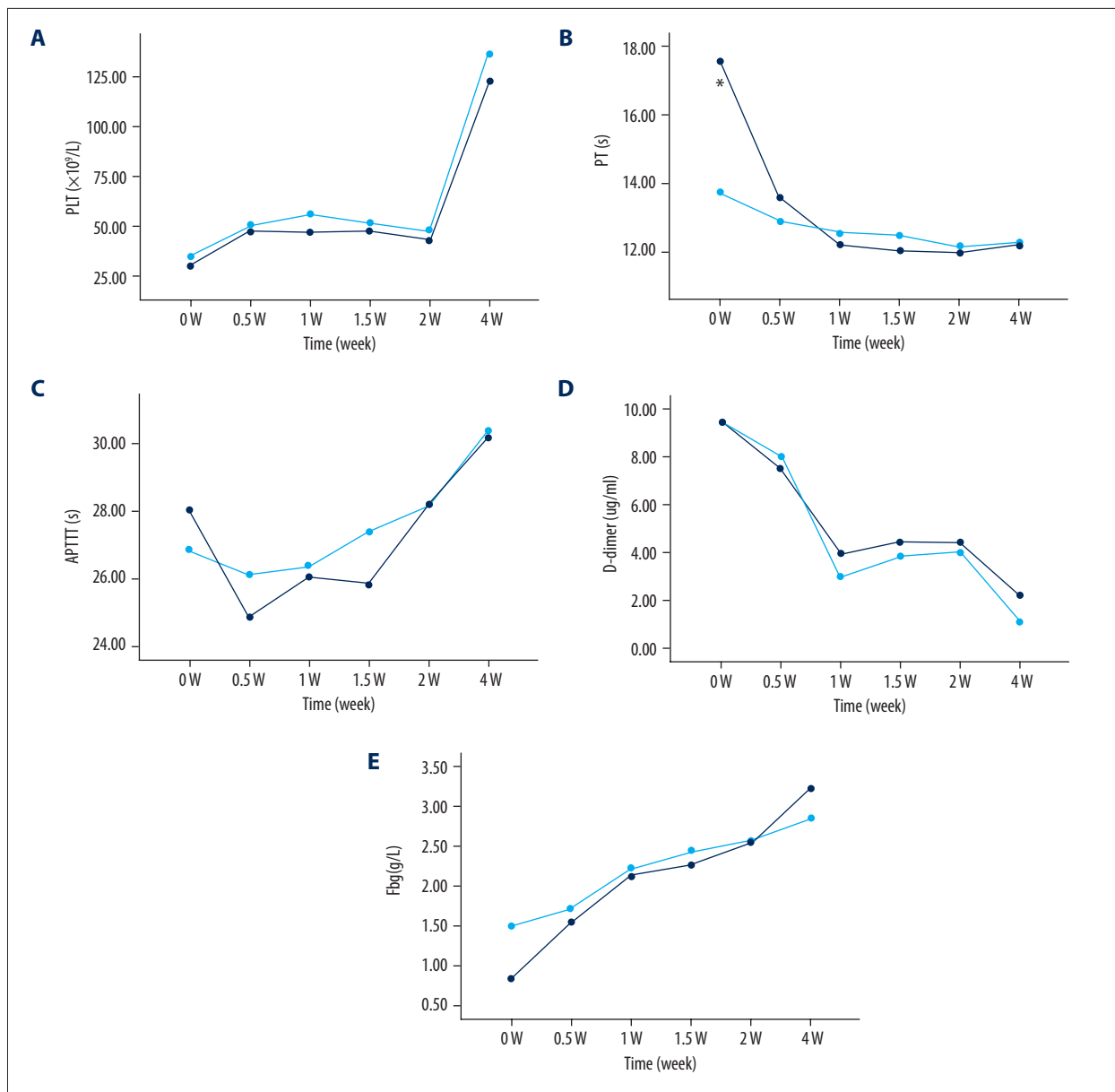
Figure 1. The changes of hemostatic variables over time in different risk patients. The high-risk graph is represented as ● and the low/intermediate-risk graph as ●. * The result of high-risk group was significantly different from low/intermediate-risk group at the same time. (**A**) PLT changes during 4 weeks of introduction, $P_{Times}<0.001$, $P_{Groups}=0.309$. (**B**) PT changes during 4 weeks of introduction, $P_{Times}<0.001$, $P_{Groups}=0.014$. (**C**) APTT changes during 4 weeks of introduction, $P_{Times}<0.001$, $P_{Groups}=0.641$. (**D**) D-dimer changes during 4 weeks of introduction, $P_{Times}<0.001$, $P_{Groups}=0.756$. (**E**) Fbg changes during 4 weeks of introduction, $P_{Times}<0.001$, $P_{Groups}=0.392$.

Discussion

Acute promyelocytic leukemia (APL) is now the most curable subtype of acute myeloid leukemia (AML). The primary cause of treatment failure in patients with APL is early death (ED), defined as death within the first 30 days after diagnosis. During the last 2 decades, the treatment of APL has undergone remarkable improvements due to the induction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), improved diagnostic tools and molecular monitoring, improved supportive care, and reduced doses of chemotherapy [5,6]. Therefore, ED remains a serious problem, and ED rates reportedly range from 7% to 14% [7,8]. In the present study, ATO was prescribed as the first induction treatment of APL and combined with ARTA and/or chemotherapy according to prognostic risk stratification and individual physicians' decisions. The ED rate in our study

was 5.36% (6/112), hemorrhages were the major reasons of ED, and the central nervous system (CNS) was the most common site of bleeding [9]. Other causes of ED in APL are infections, multiple organ failure, and differentiation syndrome [10]. Unfortunately, our data also demonstrated that hemorrhage remained the major cause of ED and hemorrhagic mortality was attributed to intracranial and pulmonary hemorrhages and occurred in the first week after diagnoses. Those 4 patients died very early after diagnosis and their deaths appeared to be difficult to prevent, but the time delay from the first symptom to seeking special medical care was not calculated, as the role of such delays in early death is difficult to evaluate.

The coagulopathy associated with APL is more complex than simple disseminated intravascular coagulation (DIC). It predominately includes activation of the clotting system, increased fibrinolytic activity and non-protease activity, and hyperfibrinolysis [11]. Risk factors for severe hemorrhage have been reported to be low initial fibrinogen level and performance status and high WBC counts [12]. Considering the important role of hemorrhage in early death, we excluded 6 patients with ED and analyzed the laboratory characteristics of patients with bleeding symptoms. We found that occurrence of bleeding was correlated with decreased levels of fibrinogen and platelets, but not with PT, APTT, or D-dimer. Thus, aggressive prophylactic transfusion is essential to control hemorrhage during the induction phase, and it was reported to reduce the incidence of fatal bleeding [13,14]; these reports also proved that hyperfibrinolysis is a more important cause of bleeding in APL. Recent reports also detailed the usefulness of thrombomodulin in treatment of APL-associated coagulopathy [15–17]; it binds to plasmin to activate thrombin-activatable fibrinolytic inhibitor (TAFI), thereby inhibiting fibrinolysis [18–20]. Administration of thrombomodulin might be an effective and feasible therapy for prevention of hemorrhage caused by coagulation abnormality in APL patients.

Multivariate analysis shows that WBC count is the most important prognostic factor in APL. High-risk patients had leucocytes >10×10^9/L, which is an important factor predictive of death during induction [21]. Early deaths are mostly attributable to the presenting coagulopathy [22]. In our study, high-risk patients had significantly higher values of lactate dehydrogenase (LDH), PT, fibrinogen, and bone marrow leukemic promyelocyte (BMP) than low/intermediate-risk patients. The high-risk patients in this study all had clinically significant bleeding symptoms; thus, high-risk patients are more prone

to hemorrhages. A recent study has shown that higher peripheral WBC counts are closely related to early death rate in APL patients, and control of peripheral WBC count may reduce the early death rate of APL patients [23]. We suggest that anthracycline or hydroxyurea to reduce WBC count might be beneficial if exceeding 10 000/µl before or after induction, which may ameliorate hemorrhages caused by coagulopathy.

Leukemic cells isolated from APL patients with typical t(15;17) chromosomal-balanced translocation manifest high levels of procoagulant activity (PCA), including tissue factor (TF) and cancer procoagulant (CP), and are associated with induction of hypercoagulability. All-trans retinoic acid (ATRA) induces cell differentiation of APL *in vitro*, which is associated with loss of expression capacity of cancer procoagulant (CP) or tissue factor (TF). Arsenic trioxide (ATO), another effective agent for curing APL, also decreases tissue factor (TF) expression and procoagulant activity (PCA) of APL malignant cells *in vitro* and *in vivo* [24]. In this study, after the aggressive treatment of induction regimen, hemostatic variables significantly restored in 0.5–1 week as compared to initial levels. No significant differences were found in changes of PLT, PT, APTT, D-dimers, or fibrinogen levels between high-risk and low/intermediate-risk patients after dual induction therapy. ATO+ATRA and/or chemotherapy as induction regimen effectively and quickly alleviate coagulopathy in all patients with APL. Based on cytologic criteria suspected of APL diagnosis, immediate induction of therapy is initiated even before definitive genetic confirmation has been made. The detection of elevated levels of D-dimer (the lysis product of fibrin) attracted particular interest and provides convincing proof that the typical hyperfibrinolysis in patients with APL is most likely secondary to activation of the coagulation system. Continued elevation of D-dimer suggests that hyperfibrinolysis was a more important event in the APL hemorrhagic diathesis.

Conclusions

The early hemorrhagic mortality of APL remains a therapeutic challenge. Immediate induction therapy with ARTA and ATO is a basic measure for effective relief of coagulopathy in APL patients. Prophylactic blood transfusion maintaining high platelet and fibrinogen transfusion thresholds is an important supportive measure to reduce early bleeding in APL patients. Hyperfibrinolysis was a more important event in the APL hemorrhagic diathesis.

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