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REVIEW ARTICLE

Hemorrhage in acute promyelocytic leukemia—fibrinolysis in focus

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Abstract

Coagulopathy continues to be a major challenge in the management of patients with acute promyelocytic leukemia (APL). Novel differentiating agents have led to improved survival in these patients, but perturbations in coagulation continue to have an impact on their prognosis. The most worrisome of coagulation disturbances is bleeding, which is not an uncommon cause of early death in APL. Despite this, there are no consistent predictors of this high risk of fatal hemorrhage in APL. In this context, the fibrinolytic system has been identified as a crucial role player in APL coagulopathy. However, the current guidelines for the management of APL give little regard to tests that measure the fibrinolytic system while giving more importance to close monitoring of conventional coagulation tests and platelet counts to identify the coagulopathy. More recently, viscoelastic tests have come to usefulness in determining global hemostasis and have been widely used for "diagnosing" hyperfibrinolysis in selected clinical settings. In this review, we attempt to describe risk assessment models for diagnosing APL coagulopathy, describe the possible application of viscoelastic tests in this setting, and persuade clinicians to reconsider the use of antifibrinolytics to improve survival of APL patients.

KEYWORDS
acute promyelocytic leukemia, bleeding, fibrinolysis

Essentials

- Severe hemorrhage is a major complication in patients with acute promyelocytic leukemia (APL).
- Fibrinolysis plays a central role in pathogenesis of APL coagulopathy.
- Viscoelastic tests might be useful in the coagulopathy of APL.
- There is a need for reconsideration of the use of antifibrinolytic drugs in APL patients.

1 | INTRODUCTION

Unique pathophysiological, clinical, prognostic, and therapeutic features make acute promyelocytic leukemia (APL) a distinctive type of acute myeloid leukemia. The introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) has transformed APL from a highly fatal to a curable disease [1,2]. Despite the widespread use of these differentiating agents achieving complete remission of >90% and 10-year survival of >80% in APL, coagulopathy continues to be a serious complication in these patients [2,3]. For example, severe hemorrhage accounts for most of the early deaths (EDs) occurring in the first 30 days from diagnosis [3–5]. A population-based study analyzing

epidemiologic changes in the different therapeutic eras in APL pointed out that the ED rate due to differentiation syndrome and infections has been decreasing over time, but the incidence of hemorrhagic ED (HED) remains the same [3]. Although clinical trials reported HED rate between 3% and 5%, severe bleeding represents a more common problem in the real-world settings with very high reported incidences [4,6–8]. Currently, there is a dearth of models that can help in discriminating patients at high risk for severe hemorrhage [9]. In this article, we review the available data on the incidence, types, pathophysiology, and prognostic factors of life-threatening bleeding in APL and also discuss the current consensus and controversies around the most appropriate management of this complication.

2 | TYPES OF BLEEDING IN APL

The most common bleeding manifestations in APL patients are skin and mucosal bleeding. However, severe bleeding, defined as "bleeding associated with moderate hemodynamic instability requiring red blood cell transfusion or bleeding associated with severe hemodynamic instability, fatal bleeding, or central nervous system bleeding," is responsible for the majority of HEDs [10,11]. The most common *severe* hemorrhage types in APL are intracranial and pulmonary hemorrhage, accounting for 65% and 32% of all HEDs, respectively [4,12]. Data from the 2 subsequent Programa Español de Tratamientos en Hematología trials, LPA96 and LPA99, reported that the majority of these fatal hemorrhages occurred during the first week of therapy. Majority of these hemorrhages had a fulminant course, with death occurring within 24 hours [12]. An important point of note is that although thrombocytopenia and disseminated intravascular coagulation (DIC), well-known risk factors for severe hemorrhage, can develop in all types of leukemia, pulmonary and intracranial hemorrhage are more frequent in patients with APL.

What may be the reason why there is high incidence of pulmonary and intracranial hemorrhages in APL? Kwaan et al. [13], analyzing the expression of receptors for plasminogen activators on endothelial cell surface, found that normal human cerebral microvascular endothelial cells had almost 3-fold higher expression of annexin II in comparison with endothelial cells originating from other organs, as well as from other human macrovascular endothelial cells (iliac, coronary artery, and aorta). The same authors also confirmed that normal human cerebral endothelial cells were more potent plasmin generators [13]. Annexin II acts as a receptor and cofactor for tissue plasminogen activator (tPA) and plasminogen, which further helps plasminogen to be activated to plasmin, resulting in fibrinolysis [14]. The high baseline expression of annexin II on the surface of intracranial endothelial cells may explain the high incidence of intracranial hemorrhage in APL [2,15,16]. In relation to pulmonary hemorrhage, increased secretion of interleukins acting chemotactically, as well as ATRA-induced upregulation of integrins with adhesion potential, have been shown to enhance neutrophils entrapment in the pulmonary vascular bed and induce alveolar hemorrhage [17,18].

3 | INCIDENCE OF BLEEDING IN APL

The Table summarizes the reported incidences of severe bleeding and HED in various clinical trials, including APL patients [4,6–8,19–27]. Results of a prospective trial conducted on 279 enrolled patients revealed the occurrence of severe bleeding in 18 (6.5%) patients, of whom half died, with an HED rate of 3.2% [6]. A more recent analysis of 995 patients treated in 5 large trials, including those treated with ATO plus ATRA, confirmed this observation, with an HED incidence of 3.7% [7]. Although the trial data note an HED incidence of 3% to 5%, real-world data show the absolute HED rate to be as high as 16% [8,20–23]. This significant discrepancy may be attributed to selection bias, which favored enrolment of patients with minimal comorbidities and preserved organ function. Also, to be included in the trials, these patients may not have required "urgent" intervention and thus would be considered less likely to have developed serious complications. Heterogeneity has also been noted among publications, where the HED rate varied from 4% to 16% [20–26]. It is possible that retrospective study designs with mixed patient populations, small sample sizes, different treatment regimens, and, in some studies, the use of prophylactic heparin may have accounted for this variation.

4 | INCIDENCE OF BLEEDING IN ATO ERA

There are limited data about severe bleeding and HED incidence from the ATO era. A noninferiority phase 3 trial comparing ATRA plus chemotherapy with ATRA plus ATO not only showed that a chemotherapy-free regimen is at least as effective as ATRA plus chemotherapy but also that none of patients in ATRA plus ATO arm experienced HED or ED. It should be mentioned that study population consisted only of patients with low- or intermediate-risk APL [28]. A study by Hou et al. [23] of patients treated with ATO only revealed an HED incidence of 14.3%, which is in line with incidences observed in the pre-ATO era. There is not much known about effects of ATO on hemostatic system, but some reports have shown that ATO solely cannot improve hemostatic parameters in these patients [29].

5 | PREDICTORS OF BLEEDING—CURRENTLY KNOWN LABORATORY MARKERS

There are no established risk models capable of stratifying patients with APL with risk for severe bleeding. The high rates of HED have led several investigators to try to detect predictors of severe bleeding and HED (Figure 1) [4,6–8,19–21,23–27]. Given that the leukemic APL cells are the predominant "procoagulant molecules" in APL, the majority of authors have identified high tumor burden characterized by increased white blood cell (WBC) and peripheral blast count as the most consistent and reliable predictors of severe bleeding and HED [4,6,7,19,20,23–25,27]. Reported cutoff values of WBC, predictive of

TABLE Incidence of severe bleeding and hemorrhagic early death and risk factors in published reports.

Author	HED	Predictors of HED	Severe bleeding	Predictors of bleeding
Dally et al. [19][a]	-	-	10/34 (29%)	Multivariate: WBC $\geq 30 \times 10^9$/L
Yanada et al. [6][a]	9/279 (3.2%)	-	18/279 (6.5%)	Multivariate: FIB < 1 g/L, WBC $\geq 20 \times 10^9$/L, PS 2-3
De la Serna et al. [4][a,d]	37/750 (4.9%)	Multivariate: serum creatinine, PB > 30×10^9/L, coagulopathy	-	-
Chang et al. [20][b]	13/116 (11.2%)	-	13/116 (11.2%)	Increased WBC, prolonged PT, and aPTT
Mitrovic et al. [21][a]	8/56 (14.2%)	Multivariate: ISTH DIC score ≥ 6	-	-
Silva et al. [22][a]	6/61 (9.8%)	-	-	-
Mantha et al. [7][b]	37/995 (3.7%)	Multivariate: WBC	-	-
Hou et al. [23][c]	53/364 (14.6%)	Multivariate: relapse, male sex, WBC > 10×10^9 /L, FIB < 1 g/L, D-dimer > 4 mg/L and increased creatinine level	-	-
Naymagon et al. [24][b]	3/43 (6.9%)	-	15/43 (34.9%)	DS, increased WBC and/or LDH with uptrend during first days of induction
Minamiguchi et al. [25][a,e]	14/344 (4.1%)	-	21/344 (6.1%)	WBC $\geq 20 \times 10^9$ /L, PLT < 30×10^9/L
Chu et al. [26][b]	-	-	14/198 (7.1%)	Multivariate: FIB < 1.6 g/L, PLT < 10×10^9/L
Sabljic et al. [8][a]	5/31 (16.1%)	Elevated D-dimer, prolonged EXTEM CT	9/31 (29%)	Increased D-dimer, decreased PLT, prolonged EXTEM CT, and decreased INTEM A10
Li et al. [27]	-	-	20/109 (18.3%)	Multivariate: increased WBC, low FIB and FDP level, FDP/FIB > 61.77

aPTT, activated partial thromboplastin time; CT, clotting time; DIC, disseminated intravascular coagulation; DS, differentiation syndrome; FDP, fibrin degradation products; FIB, fibrinogen; HED, hemorrhagic early death; ISTH, International Society on Thrombosis and Haemostasis; LDH, lactate dehydrogenase; PB, peripheral blasts; PLT, platelets; PS, Eastern Cooperative Oncology Group Performance Status; PT, prothrombin time; WBC, white blood cell.

[a]All-trans retinoic acid and chemotherapy.

[b]All-trans retinoic acid and chemotherapy and/or arsenic trioxide.

[c]Arsenic trioxide alone.

[d]Use of tranexamic acid.

[e]Use of prophylactic anticoagulant.

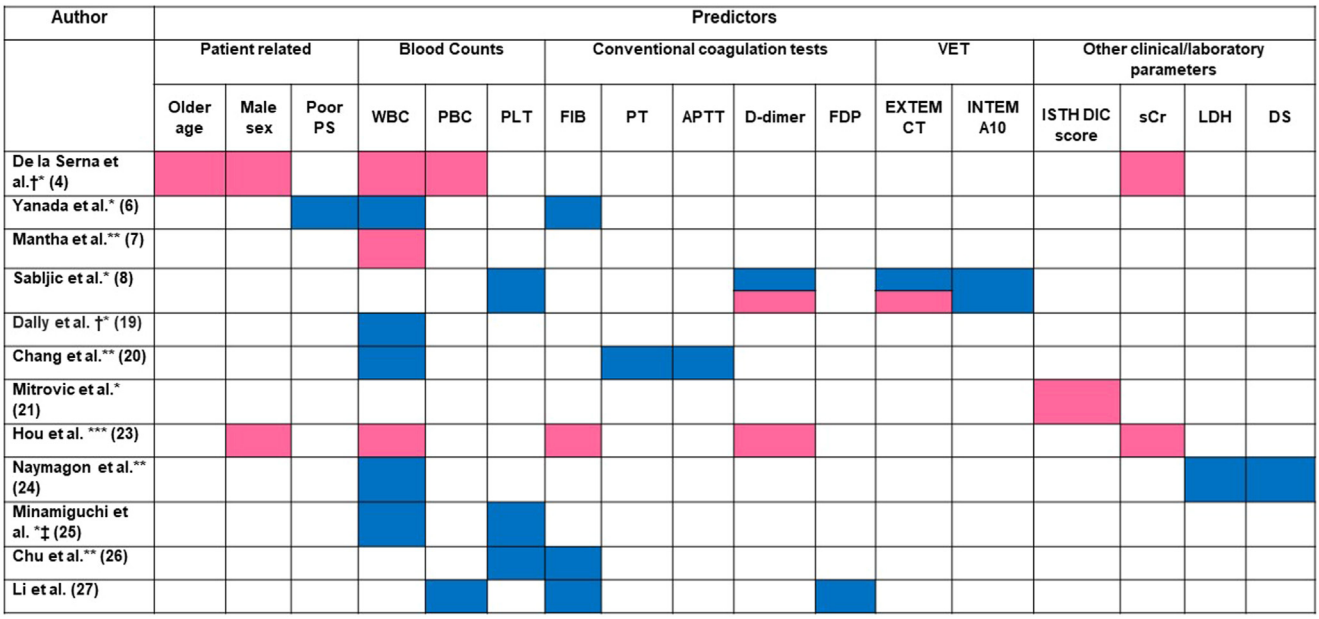


FIGURE 1 Risk factors for severe bleeding and hemorrhagic early death in reported papers. aPTT, activated partial thromboplastin time; CT, clotting time; DIC, disseminated intravascular coagulation; DS, differentiation syndrome; FIB, fibrinogen; FDP, fibrin degradation products; ISTH, International Society on Thrombosis and Haemostasis; LDH, lactate dehydrogenase; PBC, peripheral blast count; PLT, platelets; PS, performance status; PT, prothrombin time; sCr, serum creatinine; VET, viscoelastic tests; WBC, white blood cell. *All-trans retinoic acid and chemotherapy; **All-trans retinoic acid and chemotherapy and/or arsenic trioxide; ***Arsenic trioxide alone; †Use of tranexamic acid; ‡Use of prophylactic anticoagulants. Predictors for hemorrhagic early death; Predictors of severe hemorrhage.

severe hemorrhage and HED, vary between different studies from $>10 \times 10^9$/L to $\geq 30 \times 10^9$/L [4,6,7,19,23–25].

Other laboratory parameters such as serum lactate dehydrogenase or creatinine level have periodically emerged as predictive for severe/fatal bleeding [4,23,24]. Also, several other patient-related risk factors were noticed, like poor performance status, male sex, and older age [4,6,23]. Typically, these parameters are unrelated to hemostatic function but may represent sicker patients where HED is more likely.

Despite platelets playing a crucial role in primary hemostasis, only few reports showed decreased platelets correlating with severe bleeding [8,25,26]. Of course, low platelet count is observed in other types of leukemia where bleeding risk is not markedly raised, suggesting thrombocytopenia is not an independent risk factor for fatal hemorrhage. Prolonged prothrombin time, activated partial thromboplastin time, elevated fibrin degradation products (FDPs), and elevated D-dimer levels were predictive in individual studies, but a trial with the largest cohort observed no significance for these markers [7,8,19,21,23]. Some studies emphasized that a fibrinogen level lower than 1 g/L was a risk factor for severe bleeding and HED [6,23]. However, Chu et al. [26] showed that fibrinogen level ≤1.6 g/L rather than ≤1.0 g/L in combination with lower platelet counts may be a more appropriate predictor of moderate/severe hemorrhage.

In summary, the currently available laboratory markers, apart from severely reduced fibrinogen level, are not very helpful in predicting severe bleeding and HED in APL patients. It could be said that all mentioned laboratory markers are surrogate markers rather than indicators of bleeding in this disorder.

6 | CAN VISCOELASTIC TESTING BE HELPFUL?

Since predictive value of conventional coagulation tests (CCTs) was not consistent, we recently investigated the utility of rotational thromboelastometry (ROTEM) in APL patients based on its well-established role in patients with trauma or cardiothoracic surgery experiencing bleeding. We compared the effectiveness of ROTEM parameters and CCTs as predictors of HED in 31 APL patients and showed decreased INTEM amplitude 10 (A10), indicating that low clot firmness was a predictor for severe hemorrhage [8]. Prolonged EXTEM clotting time (CT) emerged as predictor for both severe bleeding and HED [8]. Interestingly, none of the CCTs was predictive of HED in this study [8].

In the mentioned study [8], all APL patients displayed hypocoagulable ROTEM pattern. More specifically, extended time to clot initiation and maximum stability achievement depicted by EXTEM/FIBTEM CT, EXTEM/INTEM clot formation time, as well as decreased clot stability represented by EXTEM, INTEM, FIBTEM A10, and maximum clot firmness (MCF), were observed in majority of patients [8]. Considering DIC plays a significant role in the mechanism of APL coagulopathy, reasonable question would be what happens with

ROTEM in DIC patients out of the context of APL. Studies conducted on DIC patient population demonstrated prolonged EXTEM/INTEM CT and clot formation time and decreased EXTEM/INTEM/FIBTEM MCF [30,31]. Of note, while all APL patients (100%) have prolonged FIBTEM CT, this observation is lacking in other types of DIC [8,30,31]. The FIBTEM assay measures the contribution of fibrinogen and clotting factors to clot formation, while platelets are inhibited by addition of cytochalasin D in the tube [32]. While patients with other types of DIC also have decreased clotting factors and fibrinogen due to consumption, one could speculate that something other than its consumption happens with fibrinogen in APL that makes an impediment in normal clot formation in FIBTEM.

Various CCTs and ROTEM parameter correlations have been reported in previous studies on patients with DIC, APL, chronic liver disease, and trauma [8,30,31,33–36]. However, these correlations have not been consistently observed, so the notion corroborated is that CCTs and ROTEM cannot be used interchangeably.

Exaggerated fibrinolysis is the cornerstone of APL coagulopathy. Conversely, to well-standardized and widespread CCTs, tests to assess fibrinolysis have lagged in this clinical scenario, probably due to technical difficulties, time-consuming laboratory processes, and challenges to achieve automation. Viscoelastic tests (VETs) such as ROTEM could give opportunity to analyze fibrinolysis. One of the ways to assess fibrinolysis is by the APTEM assay, in which plasmin inhibitor aprotinin is used to confirm whether the decrease in clot amplitude in EXTEM is caused by fibrinolysis [32,37]. In a previous study on APL patients, APTEM was evaluated in 17 patients' blood samples. In 7/17 patients (41.1%), decrement in EXTEM CT was observed, while in 5/17 (29.1%), clot stability in EXTEM A10 was improved [8]. Another proposed way to evaluate excessive fibrinolysis by ROTEM is by increasing maximum lysis (ML) by more than 15% [32]. Raza et al. [38] conducted a trial on trauma patients and compared results from ROTEM with other fibrinolysis markers (eg, D-dimer, plasmin-α2-antiplasmin complex, tPA, prothrombin fragments 1 + 2, and thrombin-activatable fibrinolysis inhibitor). They identified 3 major groups: a) a severe group in which raised fibrinolytic markers and EXTEM ML > 15% together indicated fibrinolysis; b) a moderate group in which ROTEM (ML < 15%) did not identify fibrinolysis but fibrinolytic markers were increased; and c) third small group in which EXTEM ML was > 15%, but there was no increase in fibrinolytic markers [38]. This study suggested that ROTEM could recognize only severe fibrinolysis. However, Harr et al. [39] showed that a better way to detect fibrinolysis is by FIBTEM ML > 15%. Both these studies were conducted on patients with trauma. In APL patients, only 7.2% of patients with EXTEM ML > 15% and 28.6% of patients with increased FIBTEM ML > 15% were observed [8].

In summary, there is some clear advantage to ROTEM compared with standard CCTs in its shorter turnaround times, which could contribute to timely hemostatic therapy. Furthermore, ROTEM parameters could be surrogates for HED and could be beneficial in identifying at least those patients with excessive fibrinolysis. Further exploration is needed to confirm advantage of ROTEM or similar VETs in APL.

7 | THE UNDERESTIMATED ROLE OF FIBRINOGEN AND FIBRINOLYSIS IN APL

Historically, secondary fibrinolysis as a part of DIC has been described to occur and contribute to the coagulopathy of APL [2,40]. However, the typical laboratory markers of DIC incorporated in DIC scores, including the platelet count and coagulation screen, demonstrated predictive value for HED in very few studies [21,26,27]. It is possible that primary fibrinolysis and fibrinogenolysis, in addition to secondary fibrinolysis, may be responsible for the hemorrhagic diathesis in APL [2]. A recent study by Li et al. [27] showed that an increased FDP/fibrinogen ratio has advantages in predicting the severity of bleeding, with higher ratio correlating with severe bleeding. Since FDPs are a marker of fibrinolysis, this indicates a role for the fibrinolytic process in APL, which is mostly underestimated. Yet, measurement of FDPs by polyclonal antifibrinogen antibodies does not differentiate whether the increase is due to fibrinolysis or fibrinogenolysis. A study of patients with DIC, including those with APL, evaluated FDPs and cross-linked FDPs (XDPs) using a monoclonal antibody. The results indicated that XDP/FDP levels in patients with APL were very low and even lower in comparison with patients with DIC secondary to other causes, indicative of primary fibrinogenolysis in APL [41].

8 | MECHANISMS OF HEMORRHAGE IN APL WITH FIBRINOLYSIS IN FOCUS

Fibrinolysis in patients with APL has always been described under the umbrella of DIC. Although secondary fibrinolysis in the context of DIC is important, previous studies have shown differences in DIC in APL patients and DIC related to other conditions [2]. Several findings indicate that primary rather than secondary fibrinolysis is instead the major constituent [40,42].

Plasminogen activation system consists of 2 activators, tPA and urokinase-type plasminogen activator (uPA), and 2 inhibitors, plasminogen activator inhibitor-1 and α2-antiplasmin [43]. Pretreatment levels of plasma tPA and uPA in APL patients are shown to be comparable with those of healthy individuals. On the other hand, tPA and uPA expression on peripheral leukemic cells and levels of their receptors were increased in APL patients in comparison with their expression on blood granulocytes and monocytes in the control group [44]. Annexin II, cell-surface protein functioning as a receptor and cofactor for tPA and plasminogen, helps plasminogen to be activated to plasmin [40,42]. Studies have shown that annexin II expression is greater in APL cells with the specific translocation 15;17 in comparison with other leukemic cells, increasing the efficacy of plasmin formation and fibrinolysis [14,45]. More recent data, however, showed no difference in annexin II level in APL subjects in comparison with healthy controls but showed greater levels of uPA receptor in the plasma of APL patients compared with healthy individuals [43]. In conjunction with the effects on the plasminogen activation system, there was also decrease in the levels of endogenous fibrinolysis inhibitors levels. Plasma of APL patients lacks α2-antiplasmin, which further facilitates uncontrolled fibrinolysis [46]. This acquired α2-

antiplasmin deficiency is thought to be due to consumption by a DIC process as well as direct digestion by some proteases like leucocyte esterase [46,47]. Besides, it has been observed that treatment with anthracyclines can further decrease the levels of this inhibitor [46]. Other studies have suggested that a decrease in the specific activity of plasminogen activator inhibitor-1 in APL patients further promotes the hyperfibrinolytic state [44,48]. Proteases, such as elastase and metallopeptidase, released from APL cells can enhance the breakdown of fibrinogen and, thus, fibrinogenolysis [15,49]. In support of fibrinogenolysis, patients with APL have overall increased FDP production but relatively low XDPs assessed by monoclonal antibody that specifically recognizes and binds to cross-linked fibrin and not fibrinogen [41].

In summary, fibrinolysis and fibrinogenolysis can contribute significantly to the high rate of bleeding complications in APL but cannot be identified by CCTs [2,40,42]. Specific aspects of fibrinolysis in APL are illustrated in Figure 2.

9 | EFFECTS OF ATRA AND ATO ON FIBRINOLYTIC SYSTEM

Prompt initiation of treatment in APL is mandatory, although the bleeding risk may not be immediately diminished as ATRA is commenced. This could possibly be because of the dual effects of ATRA on the hemostatic and fibrinolytic systems. Although ATRA can downregulate annexin II expression, it does not influence level and activity of nonspecific proteases, including granule elastase, which is responsible for fibrinogenolysis [2,17]. Furthermore, ATRA can potentiate production and expression of t-PA on endothelial cells and promote fibrinolysis [17].

Not much is known about the effects of ATO on hemostatic system. However, Wang et al. [44] showed that during ATO therapy, plasma levels of tPA, as well as that of uPA receptor and annexin II, increased in the leukocytes. Other parameters gradually tended to remain in the normal range [44].

ETosis, a cell death pathway that is characterized by release of chromatin or even cell-free DNA from neutrophils and mast cells, can be promoted by differentiation agents ATRA and ATO [50–53]. It has been showed that around 10% of APL cells treated with ATRA undergo ETosis instead of differentiation [50]. Novel data showed that extracellular chromatin induced by ATRA treatment enhanced thrombin generation, which could further lead to secondary fibrinolysis. Furthermore, authors also showed negative correlation between cell-free DNA and fibrinogen, as well as markedly enhanced plasmin generation in ATRA-treated cells undergoing ETosis in comparison with nontreated cells [54]. Despite this increment in plasmin generation, clot lysis time was prolonged in ATRA-treated group due to a mechanism in which extracellular chromatin provided a platform for fibrin, making it more resistant to lysis [54].

These findings can partly explain why hemorrhagic diathesis still exists even after the introduction of ATRA and ATO, which are very effective drugs in APL.

10 | MANAGEMENT OF HEMORRHAGE IN APL IN RELATION TO FIBRINOLYSIS

Monitoring CCTs and platelet count, as well as adequate supportive measures in addition to antileukemic therapy, are recommended by the current APL coagulopathy management guidelines [55]. They

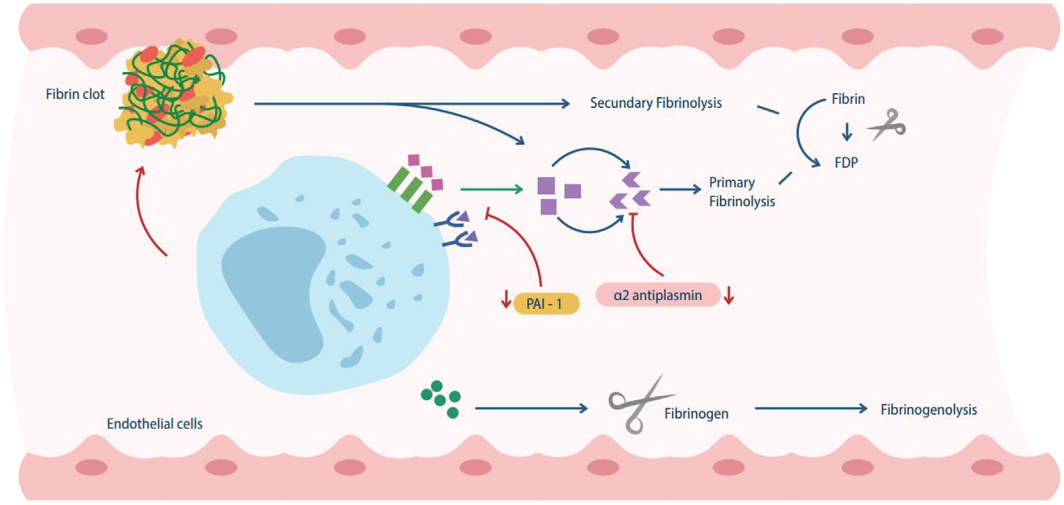


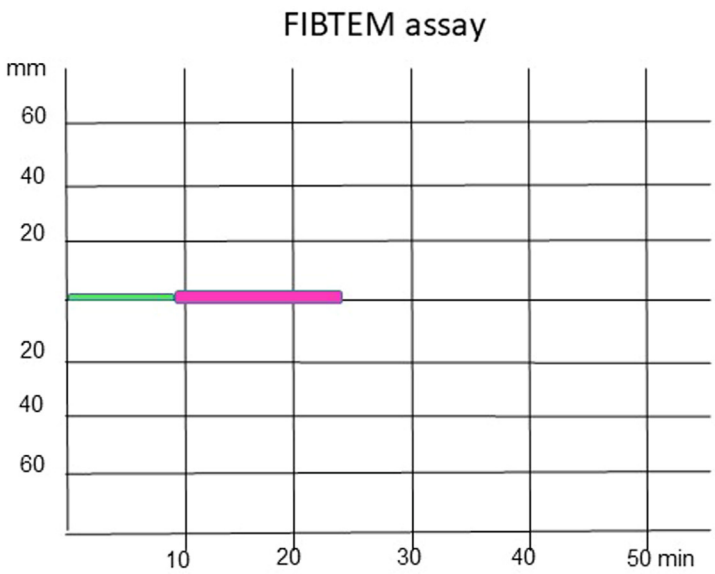
FIGURE 2 Illustration of fibrinolysis in acute promyelocytic leukemia (APL). Malignant APL cells highly expressing annexin II ( ) and urokinase-type plasminogen activator receptor ( ) are activating plasminogen ( ) in plasmin ( ) via tissue plasminogen activator ( ) and urokinase-type plasminogen activator ( ), and primary fibrinolysis starts. Natural fibrinolysis inhibitors, plasminogen activator inhibitor-1 (PAI-1) and α2-antiplasmin are decreased in APL patients, which further contribute to uncontrolled fibrinolysis. Released proteases ( ) are responsible for primary fibrinogenolysis. Altogether, fibrinogenolysis and primary and secondary fibrinolysis, as a consequence of DIC, are responsible for increased bleeding risk. FDP, fibrin degradation products.

recommend transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh frozen plasma with a goal to maintain fibrinogen level > 1 to 1.5 g/L, platelet count > 30 to 50 × 10^9/L, and international normalized ratio below 1.5, respectively. This approach should be continued until the signs of coagulopathy have abated [55]. Notably, these transfusion thresholds are empirically determined, and there is no data supporting it.

10.1 | VETs over conventional blood tests

The recommendation of aggressive supportive care has not changed over a long period of time. But why, then, do we still have a high incidence of severe bleeding, leading to death in many cases? Are CCTs and platelet counts satisfactory for guiding transfusion support? It needs to be borne in mind that routine platelet counts and fibrinogen levels reveal only their quantitative values, with no indication of their functional impact. VETs may be a significant advantage in this regard. Our recent paper on the utility of ROTEM showed that almost all APL patients had protracted time to clot initiation in all assays and very poor clot stability and firmness. Interestingly, only 35% of patients had fibrinogen count below 1.5 g/L requiring cryoprecipitate transfusion as per the current practice, while almost 60% of them had very thin and unstable clots represented by FIBTEM MCF and A10 and 93.5% had prolonged EXTEM CT [8]. Thus, applying the cutoff values of ROTEM parameters (EXTEM CT and FIBTEM amplitude in 5 or 10 minutes) used in trauma or surgery patients to guide cryoprecipitate transfusion, we hypothesized that more APL patients could have received potentially life-saving transfusion support [8,56]. The explanation for this discrepancy in which FIBTEM parameters deviate from normal range more pronounced than CCTs is to be found, but potential interference of fibrin/fibrinogen breakdown products with fibrin polymerization could be the reason.

A sample case illustration of FIBTEM and CCTs at the time of APL diagnosis in 1 patient is shown in Figure 3. Despite the very pronounced hypocoagulable ROTEM pattern represented by extremely protracted time to clot initiation (FIBTEM CT more than 8-fold above the upper limit) and low clot firmness and stability (low FIBTEM A10 and MCF), this patient did not fulfill the criteria for cryoprecipitate transfusion nor fresh frozen plasma based on the conventional tests (fibrinogen 2.6 g/L and international normalized ratio 1.42). Furthermore, despite EXTEM ML being 0% in this case, a significant improvement in CT was observed in APTEM (EXTEM CT 646 seconds vs APTEM CT 444 seconds) but far from normalization. However, this



FIBTEM parameters (patient's and normal) at diagnosis		CCTs parameters (patient's and normal) at diagnosis	
CT	504 s (38-62 s)	PLT	25 x 10^9/L (150-450 x 10^9/L)
CFT	-	PT	56 % (75-120 %)
α	-	APTT	26 s (25.1-36.5 s)
A10	2 mm (7-23 mm)	Fib	2.6 g/L (2-4 g/L)
MCF	2 mm (9-25 mm)	INR	1.42

FIGURE 3 Illustration of initial FIBTEM and conventional coagulation tests (CCTs) in patients with newly diagnosed acute promyelocytic leukemia. As depicted, patient's clot in FIBTEM is very thin and unstable (very low amplitude 10 [A10] and maximum clot firmness [MCF]), and the time to clot initiation was extremely protracted (FIBTEM clotting time [CT]). On the other hand, the same patient had fibrinogen levels above the threshold indicative of transfusion support. Also, patient's international normalized ratio (INR) was below the cutoff in which transfusion of fresh frozen plasma is indicated. α, α angle; aPTT, activated partial thromboplastin time; CFT, clot formation time; Fib; fibrinogen level; PLT, platelets; PT, prothrombin time.

could suggest ongoing fibrinolysis. A similar observation was made by Bønløkke et al. [57], presenting a case of APL patient with normal fibrinogen concentration in CCTs but with no fibrin formed on the clot formation and lysis assay.

It is quite clear that in addition to quantitative value of fibrinogen, qualitative assessment based on the polymerization ability of fibrinogen is necessary for adequate coagulation in APL. Further analyses are needed, but these preliminary results using ROTEM suggest that it could be a promising tool for the management of patients with APL.

11 | USE OF TRANEXAMIC ACID

The use of tranexamic acid (TXA) or other antifibrinolytic agents with the aim to attenuate bleeding risk in APL patients is still debated. Even though their use appears logical, bearing in mind the high incidence of hyperfibrinolysis as a pathophysiological mechanism for bleeding, results from studies are conflicting. Several randomized trials reported that the use of antifibrinolytic agents demonstrated the cessation of bleeding and decreased need for blood transfusions, but all were performed in the pre-ATRA era [58,59]. Brown et al. [60] showed that 3 out of 7 patients treated with ATRA plus TXA died due to widespread thrombotic complications, raising concerns with the use of ATRA and TXA combination.

A historical comparison of the 2 protocols of the Programa Español de Tratamientos en Hematología group showed that systematically used prophylaxis with TXA in the LPA99 trial did not impact decreasing bleeding mortality in comparison with the LPA96 trial, in which TXA was omitted. However, there was a trend toward a higher incidence of thrombosis in the LPA99 trial [12]. It is worth mentioning that while differentiation syndrome prophylaxis with corticosteroids was used only in cases of WBC $> 5 \times 10^9$/L in the LPA96 trial, all the patients in the LPA99 received corticosteroid prophylaxis regardless of the WBC count [61]. This may be relevant since corticosteroids are able to increase the risk of venous thromboembolism by increasing the levels of von Willebrand factor, thrombin, and blood velocity index, promoting a hypercoagulable state [62,63]. Thus, without prospective controlled trials, it remains unclear if the combination of ATRA and TXA is potentially harmful or if other prothrombotic factors may be responsible. One of the proposed approaches to the patient with newly diagnosed APL is depicted in Figure 4.

12 | CONCLUSION

The real revolution brought by ATRA and ATO made us feel that we can comprehend APL well. However, data are here to negate it, showing us that there still remains tremendous problem with hemorrhage in the management of patients with APL. There are still unanswered questions: can we design an adequate risk assessment model able to determine patients with high risk of fatal bleeding? Are we able to use VETs to better understand the role of fibrinogen and, more crucially, fibrinolysis in APL? How can we truly analyze the

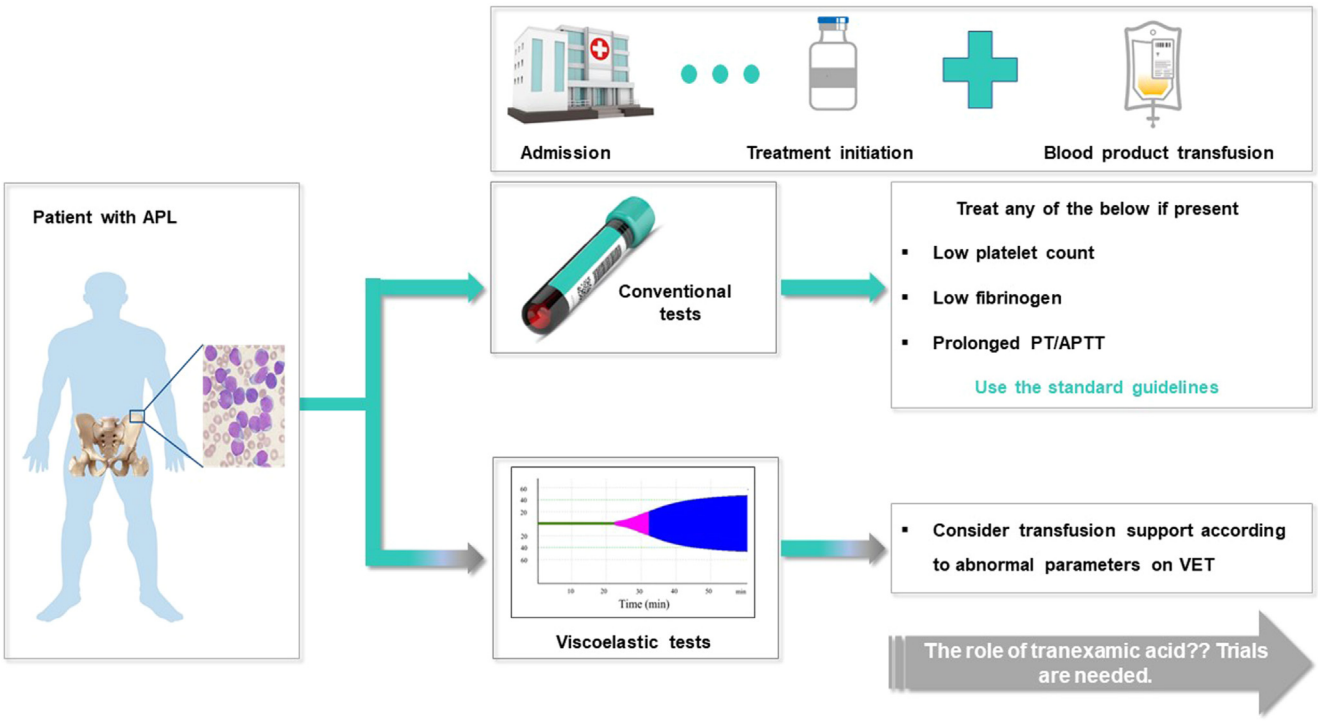


FIGURE 4 Illustration of potential approach to the patient with newly diagnosed acute promyelocytic leukemia. aPTT, activated partial thromboplastin time; PT, prothrombin time; VET, viscoelastic tests.

effectiveness with minimal harm with TXA use in APL patients? Future studies in these areas may lead to better understanding and management of APL coagulopathy, which will surely translate into improved survival.

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N.S. researched the literature, critically analyzed data, and drafted the manuscript. M.M. and J.T. brought up the idea, analyzed literature, and revised and critically appraised the manuscript. N.P. designed tables and figures and revised the manuscript.

RELATIONSHIP DISCLOSURE

The authors declare no potential conflicts of interest.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

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