Thrombosis in Acute Promyelocytic Leukemia: The Current Understanding

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Abstract

Despite enormous improvement in the management of patients with acute promyelocytic leukemia (APL), the distinctive coagulopathy observed at presentation in affected patients is often life-threatening. While hemorrhagic manifestations are well known and described in this setting, APL-related thromboses are underappreciated. Data regarding this complication are scarce showing variable incidence. Furthermore, risk factors for thrombosis are inconsistent and unreliable; so, differentiation of increased risk of hemorrhage from an increased thrombotic risk is quite difficult in the absence of adequate predictive scores. Besides, prophylactic use of anticoagulants and recombinant thrombomodulin are a matter of ongoing debate. Also, due to the common feature of thrombocytopenia and other hemorrhagic risks, patients with APL are excluded from trials analyzing anticoagulant prophylaxis in cancers; so, data from prospective trials are lacking. A detailed analysis of thrombotic risks in APL with the development of a reliable risk stratification model is needed to further improve the care of APL patients.

Keywords

- acute promyelocytic leukemia
- thrombosis
- hypercoagulability

Introduction

Acute promyelocytic leukemia (APL) is a rare type of acute myeloid leukemia (AML), characterized by distinctive biological and clinical features. Tremendous progress has been achieved in its management in that APL has transformed from a highly lethal condition to highly curable cancer in the era of all-trans retinoic acid (ATRA), and arsenic trioxide (ATO), with complete remission achievement of >90% and 10-year survival of >80%.[1–3] In spite of evolving therapeutic strategies, the rate of early death (ED) still remains as high as 21.3%.[3] A unique pattern of coagulopathy observed in APL, however, continues to be an impediment in managing patients with this condition.[2] The most frequented clinical feature of APL is bleeding, commonly mucocutaneous and/or gastrointestinal, with the reported rates varying between 76 and 89%.[4,5] Moreover, novel data have shown that intracranial hemorrhage has been the most significant contributor of early treatment failure and has led to ED in 42%.[6] Although hemorrhagic complications have always received the most attention in APL, the rate of thrombotic complication, at the opposite end of the spectrum, has been overlooked. It is thought that the incidence of thrombosis in APL is higher than in all other types of AML, but there are still little data on this complication.[2,7] Both arterial and venous thromboses have been described in APL patients. But the focus on bleeding, and measures to prevent this complication coupled with lack of reliable risk assessment models to identify increased thrombotic risk, might be responsible for underdiagnosis of thrombotic complications. In this article, in addition to reviewing the available data on the incidence, and risk factors for thrombosis in APL, we aim to discuss the

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role of alternate laboratory tests and possible therapeutic targets in its management.

Incidence of Thrombosis in APL

Underrecognition

A common but underrecognized problem in APL is thrombosis. The incidence of thrombosis in APL in post-ATRA era varies from 5.1 to 20.6% as shown in ►Table 1. [8–17] Both venous and arterial thromboses are observed.[9–13,16,17] The reported incidence of arterial thromboses is 2.3 to 6.3% and most common types are cerebral ischemia and acute myocardial infarction.[8–13,16,17] Observed incidence rates of venous thromboembolisms (VTE) reported are between 3 and 14.3% with deep vein thrombosis (DVT) and pulmonary embolism being the most common types.[8–14,16,17] According to the reported data, thromboses most frequently occur at presentation or during the induction of chemotherapy and are rare during the consolidation phase.[10–16,18,19] The heterogeneity in the reported incidence could be due to the retrospective nature of the studies, variable and usually small sample sizes, a mix of patient population. While majority of trials were focused only on presentation and therapy induction period, some studies also analyzed thrombotic incidence during post-induction and consolidation.[9,10,17] Also, follow-up period was not systematically reported in trials and only few of them contain the follow-up data.[9,11,13,16] Besides, the above studies included patients who received different therapeutic approaches: ATRA with chemotherapy and ATRA in combination with ATO. Moreover, in some cases the use of tranexamic acid during induction was common practice, while it is not in other cases.[8,9] In occasional cases, pulmonary thromboembolism was considered as arterial thrombosis which could affect the actual incidence rate of both arterial and venous thrombosis in this cohort.[17]

Above-mentioned studies were mainly focused on thrombotic complications, but some authors also reported the bleeding incidence which varied between 18 and 89%.[8,12–15] The reason for this discrepancy could be in the fact that articles with lower incidence reported only the rate of severe bleeding, while others reported overall bleeding incidence. It is worth mentioning that thrombotic complications are not exclusively happening in patients without bleeding. Concomitant occurrence of thrombosis and bleeding in a patient has been described in few studies; so, it is not surprising that in some articles thrombotic and hemorrhagic complications are named with one word *thrombohemorrhage*.[12,13,15]

Central Venous Line Thrombosis—APL versus AML

Previous studies reported that thrombotic complications are more frequent in APL than in all other subtypes of AML, with 6-month cumulative incidence of 8.4 and 1.7%, respectively.[9] However, more recent articles showed similar 6-month cumulative incidence around 10% in all AML types excluding APL.[18] Also, studies showed that central venous line–related thromboses are the most frequent type of thromboses in AML, with incidence of 10%, while the incidences of DVT and pulmonary embolisms accounts for 2.63 and 0.01%, respectively.[19–22] On the contrary, central venous line–related thromboses in APL are less frequent than all other types of thromboses. Only few studies in APL reported central venous line–related thrombosis all occurring during induction of chemotherapy.[12,13] In this context, it should be noted that current guidelines for the management of APL advocate avoidance of central venous line insertion during induction of chemotherapy until coagulopathy has resolved.[23] Another consideration is that central venous lines are placed in APL during consolidation therapy after coagulopathy has resolved, there is lack of data on the incidence of this specific thrombotic type during this period. Also, current guideline proposes chemotherapy-free regimens in patients with low-risk APL; so, insertion of central venous line is not mandatory.[23] According to the observed data, despite 6-month cumulative thrombotic incidence in APL and other types of AML that appear similar, frequency of different types of thrombosis could indicate completely different pathophysiological mechanisms and different risk factors in APL and other AML.

Thrombosis Incidence in ATRA Era

While the introduction of ATRA in APL management reduced the bleeding risk and improved survival, it seems that this success has not translated to diminished thrombotic risk.[24] In pre-ATRA era, only few thrombotic complications were reported. In a study by Breccia et al, published in 2007, the authors analyzed retrospectively the incidence of thrombotic events in 80 APL patients treated with chemotherapy without ATRA and showed none of these patients developed thrombotic conditions, whereas three events occurred at the time of relapse in patients who were re-induced with ATRA.[10] Those results led to the idea that treatment with ATRA could increase the risk of thromboses and supported the previous hypothesis that ATRA induces imbalance effects in the hemostatic system leading to higher propensity of thromboses.[12–14,16] Some possible reasons for this discrepancy and the higher thrombosis incidence during the ATRA era are as follows: First, in the pre-ATRA era, except the analysis of Breccia, there are no trials concerning thrombosis but only case reports. Also, early mortality rate was higher (31 vs. 21.3%) which could further influence thrombotic occurrence.[3] Second, the standard treatment protocols now encourage ATRA initiation even in cases of suspected APL; so, the period from the first symptoms of APL to ATRA initiation is considerably shorter than period under ATRA treatment in which thrombosis can be identified.[23] Bearing all this in mind, previous assumptions of higher thrombotic incidence during ATRA therapy could be a misleading.

Thrombosis Incidence in ATO Era

Significant progress in APL treatment has been observed with the addition of ATO in the treatment protocols, with substantial decrement in ED rate in comparison with the ATRA plus chemotherapy era.[25] However, effects of ATO on potential thrombotic complications are not clear. There are only few studies on APL patients treated with ATRA and ATO combination examining thrombotic conditions in which thrombotic incidence is in line with other reported articles (7.9 and 15.9%, respectively).[12,16]

Table 1 Incidence of thrombosis and risk factors in published reports in post-ATRA era

Authors	Incidence	Localization	Time	Follow-up period	Bleeding incidence	Predictive factors
Dally et al[a,b,8]	4/34 (11.7%)	2 cerebral sagittal sinus, 1 PE, 1 subclavian vein thrombosis	At presentation and during induction	N/A	29%	N/A
De Stefano et al[a,b,9]	8.4% cumulative incidence at 6 mo	2 ischemic stroke, 3 DVT	Presentation: 3 During therapy: 2	6 mo	N/A	N/A
Breccia et al[a,10]	11/124 (8.8%)	5 DVT, 4 AMI, 2 intraventricular thrombosis	Induction: 7/11 After induction: 4/11	N/A	N/A	High WBC, PML/RARA bcr3 type, FLT3-ITD positivity, CD2 +, and CD15+
Montesinos et al[a,11]	39/739 (5.1%)	17 DVT, 5 PE, 4 cardiac, 10 intracranial	During induction	80 mo	N/A	N/A
Chang et al[c,12]	10/127 (7.9%)	1 AMI, 5 ischemic stroke, 5 CRT	Presentation: 4/10 Induction: 6/10	N/A	N/A (4 patients with concomitant thrombosis and bleeding)	No difference in WBC and CCTs
Mitrovic et al[a,13]	13/63 (20.6%), 4/63 (6.3%) ATE, and 9/63 (14.3%) VTE	2 AMI, 1 cerebral infarction, 7 DVT, 3 CRT, 1 BCS, 1 CRVO	Presentation: 2/13 Induction: 11/13	From admission until discharge from hospital	89% (1 patient with concomitant thrombosis and bleeding)	Multivariate for VTE: FLT3-ITD mutation and PAI-1 4G/4G
Bai et al[a,14]	6/33 (18.2%)	2 DVT, 4 intracranial	Presentation: 2/6 Induction: 4/6	N/A	81.8%	N/A
Xiao et al[a,15]	12/83 (14.5%) in high-risk APL	–	N/A	N/A	18%	High WBC/D-dimer > 5.12 and low D-dimer/FIB < 5.14
Zhang and Guo[c,16]	7/44 (15.9%), 1/44 (2.3%) ATE, and 6/44 (13.6%) VTE	1 intracranial, 6 DVT	Presentation: 1/7 Induction: 6/7	From admission until discharge from hospital	N/A	Multivariate for VTE: CD15, PAI-1 4G4G, WT-1, and FLT3/ITD
`Ben Salah et al[a,17]	10/90 (11%), 5/90 (5.5%) ATE, and 5/90 (5.5%) VTE	2 intracranial, 2 PE, 1 AMI, 4 DVT, 1 BCS	Presentation: 4/10 Induction: 4/10 Consolidation: 2/10	N/A	N/A	Multivariate analysis: older age and PT < 60%

Abbreviations: AMI, acute myocardial infarction; APTT, activated partial thromboplastin time; ATE, arterial thromboembolism; ATRA, all-trans retinoic acid; BCS, Budd-Chiari syndrome; CCT, conventional coagulation test; CRT, catheter-related thrombosis; CRVO, central retinal vein occlusion; DVT, deep vein thrombosis; DIC, disseminated intravascular coagulation; DS, differentiation syndrome; ISTH, International Society on Thrombosis and Haemostasis; FIB, fibrinogen; PE, pulmonary embolism; PT, prothrombin time; RAM, risk assessment model; VTE, venous thromboembolism; WBC, white blood cell.

[a]ATRA and chemotherapy.

[b]Use of tranexamic acid.

[c]ATRA and chemotherapy and/or arsenic trioxide.

Impact of Thrombosis on Early Death and Overall Survival

Thromboses are shown to be the second leading cause of death in patients with solid tumors.[26] However, novel data regarding the impact of thromboembolism on survival in AML patients stressed that VTE did not influence ED or overall survival rate.[27–29] Conversely, authors showed that arterial thromboses led to increased risk of early mortality and were associated with poorer overall survival.[30,31] Results of thromboembolic impact on mortality in the setting of APL are scarce. Reports by Mitrovic et al showed that both arterial and venous thromboses did not affect ED rate or 4-year overall survival.[13] Further analyses are needed in this area.

Risk Factors for Thrombosis in APL

Currently Known Risk Factors

Small sample sizes and retrospective nature of the above-mentioned studies have restrained the ability to identify the risk factors predictive for thrombosis in APL (►Fig. 1). An increased white blood cell count (WBC), shorter prothrombin time (PT), and activated partial thromboplastin time (APTT), were observed to associate with thrombotic complications, but contrary to the predictors of hemorrhage, cutoff values for these parameters were not calculated.[10,13,17] Even though some articles reported predictive value for PT, other authors showed that a combination of coagulation parameters (PT, D-dimer, fibrinogen) and platelet count incorporated in the International Society on Thrombosis and Haemostasis (ISTH) DIC score was also related to thrombotic complications.[13] Among molecular and immunophenotypic markers, the most consistently predictive were *PML/RARA* bcr3 type, *FLT3-ITD* mutation, as well as CD2 and CD15 expression.[10,13,16] It is worth mentioning that several authors posited that patients with underlying thrombophilic state, both inherited and acquired, were more prone to thrombotic complications during the course of APL. In a cohort of 379 patients with all types of acute leukemia including APL, among 24 patients with thrombotic complications, 10.5% had inherited thrombophilia.[9] Polymorphism in PAI-1 4G/4G has emerged as a predictor for thrombosis in APL patients especially for VTE in few studies, while other authors stressed that among APL patients diagnosed with thrombosis, some were carrier of prothrombin and factor V Leiden mutations.[8–10,13,16] Differentiation syndrome (DS), one of the leading causes of ED in ATRA era, was also observed as potential risk factor for thrombosis.[17] Additionally, Montesinos et al showed that patients with DS more frequently developed thrombotic complications and the more severe the DS, higher was the frequency of thrombosis.[11] In addition, corticosteroids, used for the prevention and treatment of DS, have been shown to increase a risk for new and recurrent VTE.[32] Moreover, it has been observed that even in healthy individuals, corticosteroids can increase the levels of von Willebrand factor, thrombin, and blood velocity index promoting a hypercoagulable state.[33]

Can We Use Risk Assessment Models in APL?

Risk assessment models (RAMs) could be very useful in identifying patients at higher risk of thrombotic complications. While Khorana score is one of the widely used thrombosis risk predictors in patients with malignancies, studies failed to validate its predictive ability in patients with AML.[34] Also, Zhang and Guo showed no statistical significance for the Khorana score values between two groups of APL patients with and without thrombosis.[16] Recently, Al-Ani et al conducted a study on 501 patients with diagnosis of acute leukemia, including 41 APL patients and designed a predictive RAM

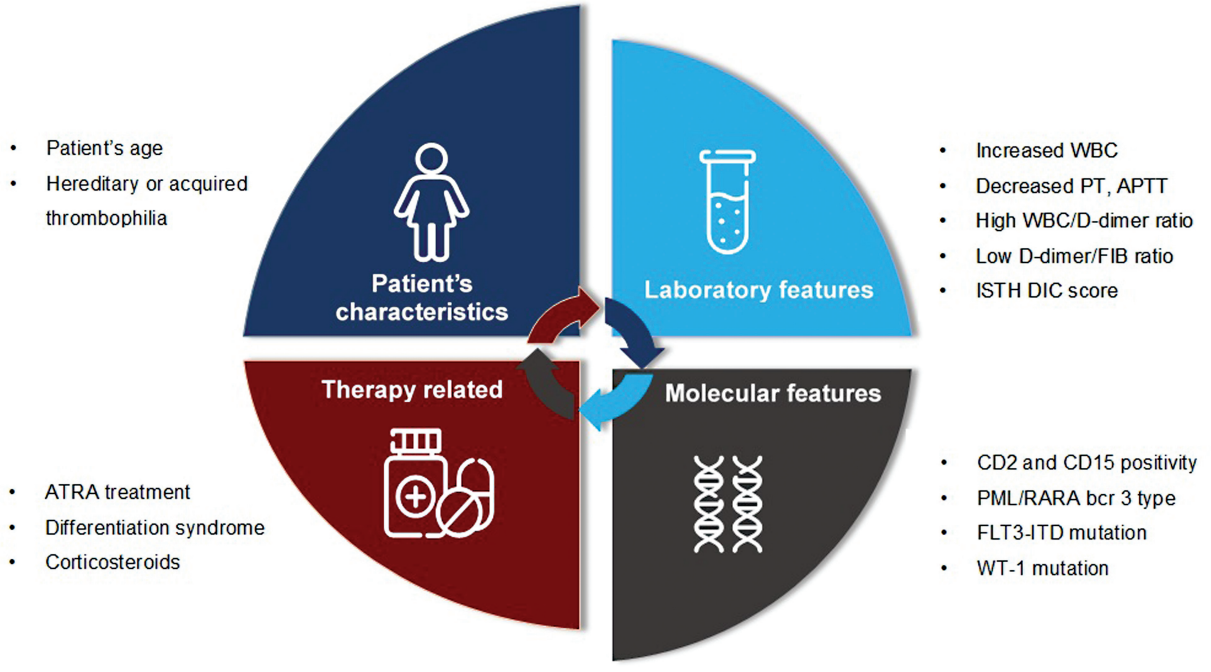


Fig. 1 Potential risk factors for thrombosis in acute promyelocytic leukemia.

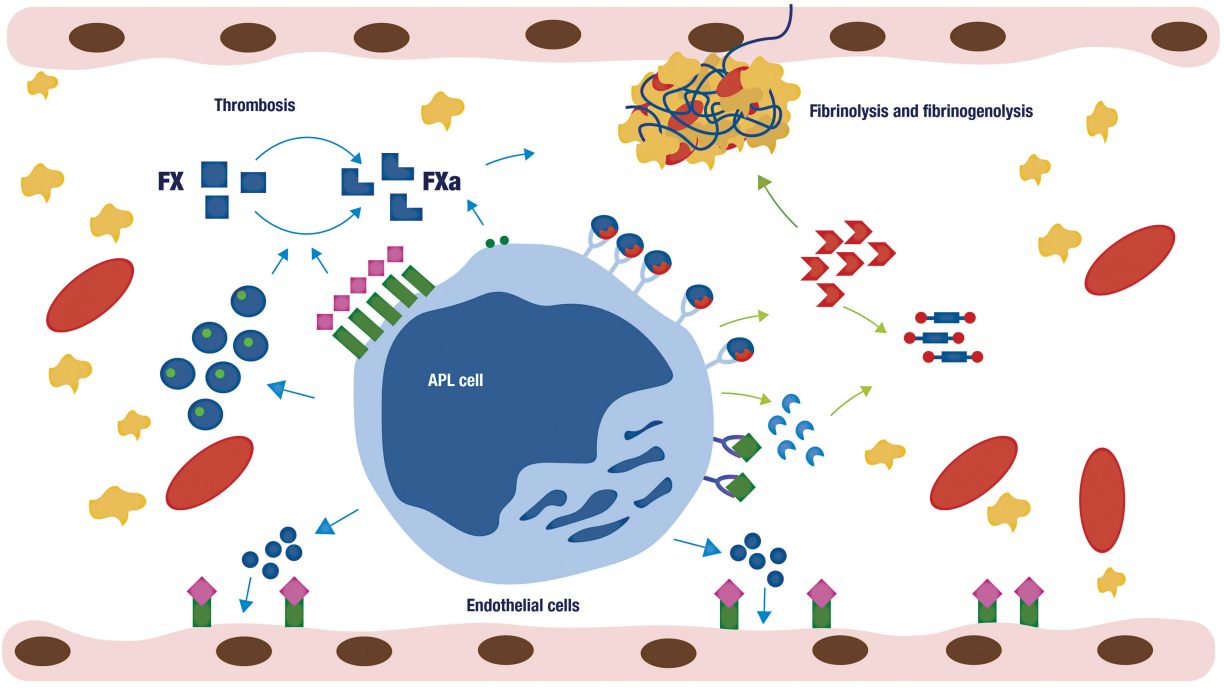
for VTE derived from previous history of VTE (3 points), lymphoblastic leukemia (2 points), and platelet count $> 50 \times 10^9$/L at the time of diagnosis (1 point).[35] Despite this RAM seeming to be a promising tool, unfortunately this score has not been externally validated to date, and also the score was developed for all types of acute leukemia with different VTE and DIC incidence, and different therapy types.

In summary, the actual incidence of thromboembolism and predictors for this complication in APL are still unclear. Even more, the real impact of thromboembolism on overall survival is yet to be determined.

Mechanisms of Thrombosis in APL

Disseminated intravascular coagulation (DIC) has been historically described as one of the hallmarks of APL occurring in 84% of patients, but in contrast to microvascular thromboses and skin necrosis observed in DIC, clinical presentation of thrombosis with APL is distinctively different. Various reports emphasized the high rates of DVT, pulmonary embolism, myocardial or cerebral infarction, indicating that the pathophysiological mechanism of thrombosis in APL is more complex and diverse from that of DIC (►Fig. 2).[5,8–17]

Several pathophysiological mechanisms exist for the procoagulant state in APL. First, two procoagulant factors were found to be highly expressed on the surface of APL cells: tissue factor (TF) and cancer procoagulant (CP).[2,36] In contrast to other acute leukemia types, it has been shown that the levels of CP are much more elevated in the APL cells.[37] While CP activates directly factor X, TF by activating factor VII and then factor X promotes thrombin generation.[2,37] Furthermore, TF-bearing microparticles (MPs) can also activate coagulation cascade



	Red blood cells		Platelets
	TF-bearing microparticles		Tissue factor (TF)
	Cancer procoagulant (CP)		Factor VII
	Anexin II		Tissue plasminogen activator (tPA)
	Plasminogen		Fibrin
	Plasmin		Urokinase type plasiminogen activator (uPA)
	Preteases		Cytokines
	Urokinase type plasiminogen activator Receptor (uPAR)		

Fig. 2 Illustration of acute promyelocytic leukemia coagulopathy pathogenesis.

and increase propensity for thrombosis.[2] A novel study by Zhao et al proposed that TF-MPs levels, mainly derived from APL cells/partly differentiated cells, were markedly increased in APL patients compared with healthy controls.[38] A thromboinflammatory state is also present in APL with numerous proteases and cytokines (interleukin-1β [IL-1β], interleukin-6 [IL-6], and tumor necrosis factor α [TNF-α]) released by the APL cells converting endothelial cells to a large procoagulant field.[2] Orchestrated activity of TNF-α and IL-6 was shown to upregulate endothelial cells' expression of adhesion molecules, TF and its isoform, alternatively spliced human tissue factor (asHTF), all together promoting procoagulable state.[39,40] Furthermore, effects of cytokines on fibrinolytic system have been proposed. TNF-α and IL-1β can enhance the activity of plasminogen activator inhibitor 1 (PAI-1) and, at the same time, decrease the secretion of tissue plasminogen activator (tPA) leading to the reduction of fibrinolytic activity and promoting hypercoagulability.[37,41] TNF-α downregulates the transcription of thrombomodulin (TM) which in normal circumstances forms a complex with thrombin. The TM/thrombin complex further activates protein C and thrombin-activatable fibrinolysis inhibitor and also inhibits inflammation.[37,42] TNF-α-induced decrement in TM is responsible for decreased fibrinolytic activity.[37]

Effects of ATRA on coagulopathy are complex and not fully clarified. It is observed that ATRA reduces the TF and annexin II surface expression and also downregulates TF production. Furthermore, ATRA also diminishes fibrinolytic activity by increasing levels of PAI-1, while by increasing levels of TM on endothelial cell surface it reduces thromboinflammatory state and indirectly reduces the plasmin generation.[2,37,43] Despite increased synthesis of cytokines, ATRA counteracts on their prothrombotic effects on endothelial cells and promotes expression of tissue plasmin activator (t-PA) in minor concentration of PAI-1 by endothelial cells, promoting fibrinolysis and anticoagulation. It has been shown that ATRA has no influence on nonspecific proteases synthetized by APL cells.[43] Recent data on animal model observed that therapeutic dose of ATRA can also inhibit platelet aggregation and clot retraction.[44] Even though observed mechanisms of ATRA are favoring anticoagulant rather than procoagulant activity, it is observed that around 60% of all thromboses in APL occur during ATRA treatment, but results from large trials are lacking.[45] Also, studies have shown that patients experiencing DS during ATRA are more prone to thrombosis.[11] On the other hand, results from De Stefano et al point out that the incidence of thrombosis at the time of diagnosis of APL remains similar or even slightly decreased during induction with ATRA (9.6 vs. 8.4%).[9] Novel insight on ATRA mechanism of action on APL cells by inducing ETosis, cell death pathway, in which released chromatin or even cell free DNA interact with procoagulants and activate coagulation, could potentially give as an answer why patients are prone to thrombosis despite treatment.[46–48]

It still remains unclear if thrombotic complications during treatment with ATRA are consequences of impaired balance of procoagulant versus anticoagulants or is reported more commonly due to the prolonged survival of ATRA treated patients in the current era.

Management of Thrombosis in APL

Supportive management of APL has not changed in decades. Current guidelines suggest routine coagulation parameters (PT, APTT, fibrinogen, D-dimer) and platelet count monitoring at least daily and more frequently if required.[23] Routine conventional coagulation tests were not designed to identify a hypercoagulable state with numerous studies providing evidence that PT and APTT are not able to indicate when the patient may be in a hypercoagulable state.[49,50] Mao et al observed no difference in PT and APTT in patients without malignance but with confirmed DVT in comparison with healthy controls.[50] These authors showed that only increased fibrinogen and a hypercoagulable pattern on thromboelastography were evident in the DVT group of patients.[51] Despite thromboelastography being shown to be reliable in indicating hypercoagulability and VTE in several studies, its routine use is still not proposed by guidelines.[51–55] On the other hand, D-dimer measurement is suggested in VTE diagnostic algorithms, although elevated values in the context of APL may lose its significance due to low D-dimer specificity.[55]

Patients with acute leukemia generally are underrepresented in clinical trials addressing prophylactic use of anticoagulants in malignancies due to thrombocytopenia, the presence of DIC, and increased bleeding risk, especially in those with APL; so, the results of prospective trials are lacking. The use of anticoagulants in APL patients before and during induction therapy is still questionable and the current consensus states there is no place for its routine use.[23] In cases of confirmed thrombosis, heparin (unfractionated heparin or low-molecular-weight heparin) could be used, but the dose should be adjusted to platelet count and confirmation of the overall benefit outweighing the hemorrhagic risk should be documented.[48]

The use of recombinant thrombomodulin (rTM) is a common practice in APL treatment in Japan, and it is thought that rTM can moderate hypercoagulability.[53] The rationale for the use of rTM in this setting is to compensate an APL-induced decrease in endogenous TM which normally makes the complex thrombin–rTM, and activates protein C inhibiting thrombin formation.[42,56] Furthermore, rTM possesses anti-inflammatory effects which could be helpful in the setting of APL thromboinflammation-induced hypercoagulability.[42,56] However, novel results comparing APL patients anticoagulated with rTM and those without anticoagulants showed no improvement in in-hospital mortality and thrombotic events occurrence.[56] Due to rTM questionable effectiveness, its use is currently not proposed by guidelines.[23]

Conclusion

Prevention and treatment of thrombotic complications in APL remains an open field. Further studies, better understanding of pathophysiological mechanisms, and development of models with ability to identify the exact patient with increased thrombotic risk could lead us to create a more personalized guideline policy and help us reduce this

underrecognized but life-threatening complication. Currently, the only thing that we can do is to be more aware and not to forget that even in patient with hemorrhage, thrombotic complication can occur.

Authors' Contribution

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

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Conflict of Interest

The authors declare that they have conflicts of interest.

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