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Predicting APL lethal bleeding in the ATRA era

Anna Falanga HOSPITAL PAPA GIOVANNI XXIII

In this issue of Blood, Mantha and colleagues advance our understanding of risk factors for early hemorrhagic death (HD) in patients with acute promyelocytic leukemia (APL) in the all-trans retinoic acid (ATRA) era. Analysis of HD risk factors in a large series of ATRA-treated patients convincingly shows that high white blood cell (WBC) count is an independent predictor of early HD. The results help to construct a profile of patients at high-risk for bleeding.

Patients with APL typically present with a life-threatening hemorrhagic diathesis, which is the main cause of early death. Lethal bleeding most frequently occurs in the brain or lung. Thrombotic manifestations can coexist with hemorrhage. Before the ATRA era, early HD occurred in up to 20% of new patients with APL. Presently, the standard of induction treatment with ATRA- and arsenic trioxide (ATO)-based regimens results in a complete remission rate $\geq 90\%$ with resolution of the coagulopathy. Unfortunately, the rate of early HD remains 3% to 10%. Most HDs occur within the first 2 to 3 weeks, and HD represents one of the main impediments to the cure of APL.

The coagulopathy of APL is complex and multifactorial. Laboratory coagulation abnormalities are consistent with the diagnosis of disseminated intravascular coagulation with excess hyperfibrinolysis. Despite the enormous improvements in the understanding of the biology of APL and the development of effective treatments, there is no specific strategy to defeat the associated coagulopathy. An imbalance between procoagulant, anticoagulant, and fibrinolytic forces occurs in the patient’s hemostatic system, triggered by circulating APL cells interacting with the different compartments of hemostasis (see figure). The cellular differentiation induced by ATRA results in the loss of procoagulant and fibrinolytic properties in APL cells, with a parallel improvement of the hypercoagulable state. Similar effects, although less well characterized, are observed with ATO. Certainly, ATRA and ATO ameliorate the bleeding syndrome. Indeed, experts recommend that ATRA be started as soon as the diagnosis of APL is suspected.

A retrospective analysis showed that delays in starting ATRA lead to increased early HDs. Unfortunately, it takes 1 to 3 weeks for ATRA treatment to resolve the APL coagulopathy; therefore, additional measures to prevent bleeding are often required. These include aggressive supportive therapy with platelet concentrates, cryoprecipitate, or fibrinogen, and, although they are still controversial, treatments with anticoagulants or antifibrinolytics. None of these measures have been evaluated for efficacy and safety in prospective randomized trials. There are no data-driven algorithms available to guide blood product support for the coagulopathy. Similarly, no trial data exist to demonstrate the utility of new anticoagulants, i.e., direct factor Xa or thrombin inhibitors, with a relatively safer profile, or low-molecular-weight heparins (LMWHs). Given this background, one obstacle that prevents the start of prospective trials to decrease early HD is the difficulty of identifying patients who are at greatest risk of fatal bleeding. Published reports have provided conflicting results on which patient characteristics are predictors of early HD. These studies are also limited by small sample size. Thus, it has been impossible to identify a high-risk patient profile. Some of the risk factors for hemorrhage that have been suggested include age $\geq 60$ years, high WBC count, high peripheral blast cell count, low fibrinogen levels ($<10 \, \text{g/L}$), poor performance status, elevated creatinine, elevated lactate dehydrogenase, prolonged prothrombin time and partial thromboplastin time, and low platelet counts.

To address this issue, Mantha and colleagues examined the data on most of the identified risk factors in patients enrolled in 5 major clinical trials of APL that included ATRA in the induction regimen. The authors considered the risk factors at baseline in 995 evaluable patients, the largest cohort examined so far, and estimated the potential predictive value on the occurrence of fatal bleeding within 30 days of treatment. There were 37 HD cases, for an estimated cumulative incidence of 3.7%. The results show a significant association of early HD with WBC $\geq 20 \times 10^9$/L and poor Eastern Cooperative Oncology Group performance status. At multivariate analysis, a high total WBC count $\geq 20 \times 10^9$/L emerged as an independent predictor of early HD. Interestingly, the performance status approached statistical significance, suggesting that this parameter may be a good candidate to consider in future studies of HD.

A limitation of this study is that the results were obtained by retrospective data collection from 5 different trials, which may have influenced the results. For instance, differences in the type and intensity of supportive therapy...
Induction of prothrombotic vascular endothelium. The APL cell and hemostasis: APL cells express procoagulant factors (ie, tissue factor, cancer procoagulant, procoagulant microparticles), fibrinolytic proteins (ie, plasminogen activators [u-PA, t-PA] and inhibitors [PAI-1 and their receptors [u-PA, annexin II]), and nonspecific proteases (ie, elastase), which activate coagulation and fibrinolysis. In addition, these cells possess an increased capacity to adhere to the vascular endothelium, and secrete inflammatory cytokines (ie, interleukin-1β [IL-1β] and tumor necrosis factor α [TNF-α]), which downstream stimulate the expression of prothrombotic properties of endothelial cells, leukocytes, and platelets. All of these events are reflected in the peripheral blood by alterations in the levels of circulating biomarkers of hypercoagulation, hyperfibrinolysis, proteolysis, and inflammation. u-PAR, urokinase-type plasminogen activator receptor; VEGF, vascular endothelial growth factor. Professional illustration by Somersault18:24.

may have altered the results of coagulation parameters, which did not show significant associations with early HD. Furthermore, the analysis of data from clinical trials, which involve patient selection, may not be generalizable to the entire APL population. Despite these limitations, this is the largest data set of patients and clinical outcomes in APL that is available at this time. The clear-cut primary end point of early HD in this study guarantees the standardization and quality of data.

In conclusion, there is a need to identify reliable risk factors of early HD in APL. The study by Mantha and colleagues identifies high WBC count as an independent predictor of HD, and supports the inclusion of performance status in future risk profiles.

Future studies should identify whether circulating plasma biomarkers of hypercoagulation and/or hyperfibrinolysis (see figure) or global rapid coagulation assays (ie, thrombin generation, or thromboelastography) can add value to the predictive model of early HD. Finally, the evaluation of efficacy and safety of new oral anticoagulants and LMWHs in reducing HD risk should be considered.

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REFERENCES


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Comment on Gayle et al, page 1768

Toward autophagy-targeted therapy in lymphoma

Lapo Alinari THE OHIO STATE UNIVERSITY

In this issue of Blood, Gayle et al provide evidence that apilimod, a potent and selective phosphatidylinositol-3-phosphate 5 kinase (PIKfyve) inhibitor, induces significant cytotoxicity at clinically achievable concentrations in preclinical models of B-cell non-Hodgkin lymphoma (NHL) via inhibition of the autophagy flux and perturbation of lysosome homeostasis.1
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