Open issues on bleeding and thrombosis in acute promyelocytic leukemia

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**ABSTRACT**

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia characterized by a specific genetic alteration, affecting the retinoic acid receptor-alpha (RAR-alpha), and leading to the accumulation of the promyelocytic blasts in the bone marrow and blood which is frequently associated with a life-threatening consumptive coagulopathy. The body of biological information on APL establishes this leukemia as a unique entity that has to be promptly recognized to counteract the coagulopathy, especially in light of its striking response to treatment with all-trans retinoic acid. In fact, the current standard for induction therapy results in extremely high antileukemic efficacy, achieving 90 to 95% complete remission rate. However, while primary leukemia resistance has virtually disappeared as a cause of remission induction failure, death due to hemorrhage remains the major problem during the early treatment phase. As a part of the clotting activation commonly present in APL, thrombosis is a less recognized and probably underestimated life-threatening manifestation in patients with this disease. In addition to reviewing the available data on the incidence, outcome and prognostic factors of bleeding and thrombosis in APL, we discuss the current consensus and controversies on the most appropriate management of these complications.

**Introduction**

Since the advent of all-trans retinoic acid (ATRA) and, more recently, arsenic trioxide (ATO) into the therapy of acute promyelocytic leukemia (APL), significant improvements in patient outcomes have been achieved, and this disease has become the most curable subtype of acute myeloid leukemia. Several treatment strategies using these agents, usually in combination with chemotherapy, but also without or with minimal use of cytotoxic agents, have provided excellent therapeutic results. In fact, the current standard for induction therapy results in extremely high antileukemic efficacy, achieving 90 to 95% complete remission (CR) rate. It should be noted, however, that while primary leukemia resistance to therapy has virtually disappeared as a cause of induction failure, death during induction from hemorrhage has remained the major problem during the early treatment phase, followed by infection, and differentiation syndrome (DS)[1]. As a part of the clotting activation commonly present in APL, thrombosis is a less recognized and probably underestimated life-threatening manifestation in patients with this disease. However, although the incidence of thrombotic events in large cohorts of patients with APL has been rarely reported[2,3], they seem to be more common than previously appreciated in this disease.

In the present article, in addition to reviewing the available data on the incidence, outcome and prognostic factors of life-threatening bleeding and thrombosis in APL, we aim to discuss the current consensus and controversies on their most appropriate management.

**Bleeding in APL**

APL is characterized by easy bruising and bleeding due to thrombocytopenia and coagulopathy. The pathophysiology of this coagulopathy is complex. The most compelling pathogenic mechanism is most likely the molecular properties of the leukemic cell itself, which releases a variety of mediators that can activate blood coagulation through at least three mechanisms: disseminated intravascular coagulation, fibrinolysis, and direct proteolysis of several proteins[4]. This process is further complicated by the concomitant thrombocytopenia and the rapid cell releasing of tumor products induced by chemotherapy.

Lethal or life threatening hemorrhages, mainly intracerebral and pulmonary, are relatively common complications occurring while the characteristic coagulopathy of APL is active. These complications are not only the most frequent cause of death early during induction therapy but can also occur before the diagnosis of APL has been made and therapy started.

Data about the proportion of patients developing life threatening hemorrhages before starting induction therapy are extremely scarce in the literature. In general, major series have not provided details about patients considered not eligible for treatment because of poor clinical condition that in many cases is due to life-threatening hemorrhages. The US Intergroup[5] and the PETHEMA group[6]...
have reported around 5% of patients considered not eligible for induction therapy due to very poor clinical condition, mostly due to lethal or life threatening hemorrhages before starting therapy. This is the case of the latter study[1], in which more than half of 42 patients considered not eligible for the treatment among 792 patients registered in two subsequent PETHEMA trials (LPA96 and LPA99) had a lethal bleeding (intracranial, 15; pulmonary, 4).

In spite of an early aggressive supportive care given to all patients in the aforementioned PETHEMA study[1], hemorrhage was the single most common cause of death (5%) during induction therapy, followed by infection (2.3%) and DS (1.4%) in patients with APL receiving ATRA and idarubicin (AIDA regimen). Hemorrhagic deaths were almost exclusively due to intracranial (65%) and pulmonary hemorrhages (32%), with only one case of fatal gastrointestinal bleeding registered in this study. It should be noted that 2 out of 24 patients with intracranial bleeding developed the hemorrhage over an extensive cerebral thrombosis. Typically, the majority of lethal hemorrhages occurred early during induction (Fig. 1). The median interval time from treatment start to intracranial and pulmonary hemorrhage occurrence was 6 days (range, 1–21) and 9 days (range, 1–23), respectively. A majority of patients (69%) who died from cerebral or pulmonary hemorrhage had a fulminant course, with death occurring within 24 hours from the onset of bleeding.

Regarding the predictive factors of fatal hemorrhage, few data are available in the literature. Increased peripheral blast count at presentation has been identified as a factor with independent value to predict an increased risk of death due to hemorrhage in two independent studies carried out by the PETHEMA[1] and GIMEMA[6] groups. In the former study, abnormal creatinine level and presence of biological signs of coagulopathy were also identified in multivariate analysis as independent prognostic factors of lethal bleeding. The acknowledgment of prognostic factors may be useful to identify very high-risk patients as potential target population to explore experimental or novel approaches to minimize the risk of death due to hemorrhage.

Once the patient is in CR, the risk for both thrombosis and hemorrhage seems similar to that observed in other subtypes of AML. Regarding the risk of severe bleeding, it should not be minimized, especially during the consolidation courses containing intensive chemotherapy, in which severe thrombocytopenia is usually observed. In fact, 2 out of 14 deaths occurring during consolidation courses in the PETHEMA protocols were due to intracranial hemorrhage in the context of severe thrombocytopenia.

**Thrombosis in APL**

Recent studies suggest that thrombosis is more common than previously appreciated in individuals with all types of adult acute leukemias[7,8], including APL. While the use of ATRA has produced a high rate of CR with rapid resolution of the coagulopathy[9], the exacerbation of the procoagulant state of APL that can be observed with the development of DS[9–12], may lead not only to an increased risk of hemorrhage but also to a higher incidence of thrombosis. However, only two studies [2,13] have been reported addressing this issue in large cohorts of patients treated with ATRA but the available data are contradictory. While the study carried out in a single institution (La Sapienza University, Rome)[2] was not able to demonstrate any association between thrombosis and DS, a recent study of the PETHEMA group[13] did find this association of DS and activated procoagulation in terms of thrombotic events in spite of analyzing a considerably larger cohort of patients also treated with AIDA.

The incidence of thrombotic events during induction therapy in the aforementioned Italian study[2] and in a recent report of the PETHEMA group[3] both using the same AIDA regimen, was very similar. 5.6% (7 out of 124 patients) in the former and 4.5% (33 out of 734 patients) in the latter study. It should also be noted that among 26 patients who died before initiation of chemotherapy in the former study, 6 (23%) presented with severe thrombotic complications: 3 cerebral stroke, 2 pulmonary embolism and 1 acute myocardial infarction. The thrombotic events observed in 33 patients who were treated with AIDA were 18 deep venous thromboses, 3 pulmonary embolisms, 7 cerebral strokes, 3 acute myocardial infarctions and 2 others) (Fig. 2).

Regarding the clinico-biological characteristics associated with thrombosis, the Italian study[2] found that patients who developed this complication had a statistically higher WBC count, a higher prevalence of the short PML/RARalpha isoform (bcr3), and FLT3-ITD.
as well as CD2 and CD15 expression. Most of these findings were not confirmed in a larger PETHEMA study [3] as shown in Table 1. It should be noted that in the PETHEMA study a higher WBC count was also identified as predictive of thrombosis in univariate analysis, but it was removed from the final set of variables selected in multivariate analysis, probably due to its association with M3 variant subtype. Another interesting finding in this study was that two additional variables emerged as independent prognostic factors of thrombosis: a low level of fibrinogen and the previously mentioned morphological subtype. Both were associated with a higher risk of thrombosis before and during induction therapy. In addition, a historical comparison of the LPA99 trial, in which tranexamic acid prophylaxis was systematically used, with the LPA96 trial, without tranexamic acid prophylaxis, showed that this prophylactic measure did not impact on decreasing hemorrhagic mortality, but that there was a trend toward a higher incidence of thrombosis. Therefore, the benefit of this, and probably other antifibrinolytic therapy, to attenuate the thrombohemorrhagic risk remains questionable and certainly not recommended outside the context of clinical trials.

Management of thrombohemorrhagic syndromes

In spite of a lack of evidence of the benefit of any specific measure or strategy to prevent the relatively common occurrence of early life-threatening hemorrhagic and/or thrombotic events in APL patients, it is reasonable to recommend that supportive measures to counteract the coagulopathy should be instituted immediately when the diagnosis of APL is considered, even before it is confirmed [14]. These supportive measures consist of generous transfusions of fresh frozen plasma, fibrinogen and/or cryoprecipitate and platelets to maintain the fibrinogen concentration and platelet count above 100–150 mg/dL and 30–50 × 10^9/L, respectively, which should be monitored at least once a day (more frequently if required). Such replacement therapy should continue during induction therapy until disappearance of all clinical and laboratory signs of coagulopathy [14]. Despite a need-adapted transfusion policy under strict monitoring of the coagulopathy, patients presenting some factors (reviewed above in the article) have a higher risk of developing a fatal hemorrhage. Further investigation to explore experimental or novel approaches in these patients is warranted. Although, the benefit of heparin therapy in the treatment of the complex coagulopathy complicating APL has never been ruled out in a prospective randomized trial, no benefit for the prevention of early hemorrhagic deaths was demonstrated in a retrospective analysis of the GIEMEMA group [15]. Although today the use of heparin, once a mainstay of induction therapy in APL, has been completely abandoned, some investigators have suggested that a randomized clinical trial using either low-molecular-weight heparin or fondaparinux would seem appropriate in an effort to reduce the thrombohemorrhagic death rate in APL [16,17]. Falanga and Rickles [16] also consider it reasonable to test the hypothesis that the antiadhesive properties of low-molecular-weight heparins, which have been observed to reduce the interaction of tumor cells with the endothelium in vitro, might prevent some of the manifestations of the DS in patients with APL. This is of particular interest once the association between severe DS and thrombosis has been demonstrated in a large study of the PETHEMA group [13]. As for heparin, the benefit of tranexamic acid or other anticoagulant or antifibrinolytic therapy to attenuate the thrombohemorrhagic risk remains questionable and these agents should not be used routinely outside the context of clinical trials.

The role of factor VIIa or prothrombin complex concentrates for treating life-threatening hemorrhages in APL remains uncertain. Although theoretically these agents may enhance the thrombotic risk, there are anecdotal case reports in whom the use of recombinant factor VIIa was effective for life-threatening hemorrhage in patients with APL [18,19]. However, the level of evidence of its effectiveness is weak. Therefore, the use of procoagulant agents in this context should be restricted to clinical trials.

Other measures to reduce the risk of hemorrhagic complications in APL have been recommended [14] such as avoiding central venous catheterization, lumbar puncture, and other invasive procedures (e.g., bronchoscopy) before and during induction therapy, while coagulopathy is still active.

Conclusion and future directions

Hemorrhage is the predominant manifestation of the complex coagulopathy commonly observed in patients with APL remaining the major cause of death before and during induction therapy. As a part of the clotting activation, thrombosis is a probably underestimated life-threatening manifestation of this disease. A better knowledge of prognostic factors and pathogenetic mechanisms of these two faces of coagulopathy, bleeding and thrombosis, is crucial to improve the management and outcome of these life-threatening complications in APL. Attempts to attenuate the thrombohemorrhagic risk using heparin, tranexamic acid, or other anticoagulant or antifibrinolytic therapy have been disappointing. The potential role of newer anticoagulant and procoagulant agents should be established in well designed clinical trials.

Competing interests: None of the authors have any conflict of interest to declare in relation to this paper.

References


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