Thrombosis Research 164 (2018) S82–S88

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Mechanisms and management of coagulopathy in acute promyelocytic leukemia

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ARTICLE INFO

Keywords:
APL
Early hemorrhagic deaths
Tissue factor
Annexin II
ETosis

ABSTRACT

Acute promyelocytic leukemia (APL) is a subtype of leukemia which is associated with unique and distinctive coagulopathy. In the absence of treatment it is rapidly fatal and even after initiation of therapy the major cause of early mortality is related to hemorrhagic complications. The coagulopathy can be exacerbated with the start of treatment. In the absence of early hemorrhage related deaths the probability of cure exceeds 90% in low and intermediate risk patients and 80% even in high risk patients, highlighting the importance of understanding the pathophysiology of this complication and instituting prompt and appropriate management strategies. The coagulopathy in APL is complex and results from a combination of thrombocytopenia, disseminated intravascular coagulation and hyperfibronlysis. Recently the effect of all-trans retinioc acid (ATRA) induced ETosis on exacerbating coagulopathy in the first few days after starting therapy with this agent raises the potential for potentially novel strategies to reduce the risk of hemorrhage. Currently management is mainly related to rapid initiation of therapy with ATRA along with appropriate and adequate replacement of blood products to correct the coagulopathy. There is limited role for the use of low dose anti-coagulants and anti-fibrinolytic agents in the initial management of this disease. There is limited data on the use of rFVIIa or the use of global tests of hemostasis in the management of this condition.

1. Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) with distinct molecular and clinical features and characterized by the presence of a reciprocal translocation involving a portion of the retinoic acid receptor alpha gene (RARα) on chromosome 17 and a variable portion of a partner gene, which in 95% of cases is the PML gene on chromosome 15 and hence most often denoted as t(15;17)(q22;q21) [1]. However, APL is biologically, clinically, prognostically and therapeutically distinctively different from other sub-types of AML. Early advances in treatment of APL with conventional anthracycline based chemotherapy were associated with high treatment related mortality (TRM), usually secondary to hemorrhagic complications and remained the most challenging subset of AML to manage. Significant and rapid advances in the management of APL over the last few decades have transformed it from a leukemia with the worst to that with the best prognosis [2]. Currently, it is reasonable to expect > 90% remission rates with long term survival exceeding 80%, even in high risk APL [2]. Remarkably, most of these improvements in clinical outcome have happened without intensification of conventional chemotherapy but with the use of combination of non-myelotoxic differentiating agents such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). This in turn was facilitated and paralleled by the detailed understanding of the cellular and molecular pathogenesis of this leukemia and as a result APL has become a model of bench to bedside and back scientific progress.

A distinctive and unique pattern of coagulopathy seen in APL remains the major cause of early mortality in newly diagnosed patients in spite of recent advances in the management of this condition. This is especially true in the real world, outside the context of clinical trials, where early mortality approaches figures of 17%–30%, the majority of which is related to the coagulopathy seen in this condition [3,4]. Even in the setting of clinical trials the risk of early mortality varies between 5 and 10% [5] though these figures are favorably skewed due to a significant selection bias based on fitness to receive therapy and ability of patient to remain stable in spite of time required to start therapy on clinical trial protocols which may often require establishment of molecular diagnosis generated in a central laboratory. Even with these limitations, it is increasingly clear from these studies that early hemorrhagic deaths (EHD) cannot be attributed only to delays in diagnosis and initiation of therapy [6,7]. EHD are loosely defined as deaths occurring within the first 10–14 days of diagnosis and starting therapy

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https://doi.org/10.1016/j.thromres.2018.01.041
Received 18 January 2018; Accepted 24 January 2018

[8]. Conventional chemotherapy agents such as anthracylines have been known to exacerbate the coagulopathy in APL while differentiating agents such as ATRA and ATO improve it [9]. The improved clinical outcomes and ease of management has for a large part been due to the significant reduction hemorrhagic related complications after the introduction of ATRA and ATO in the management of APL. ATRA and ATO are not only effective in clearing the leukemia but even more significantly have the ability to rapidly correct the hemostatic defects that occur in APL and reduce the EHD that is relatively common in this condition. However, significant challenges still remain with EHD in newly diagnosed APL, especially outside the setting of clinical trials. New insights into the pathogenesis of the hemostatic defects and novel therapeutic strategies have the potential to further reduce EHD. Challenges also remain in the management of high risk APL and a small subset of relapsed APL with regards to disease recurrence. This review will focus on recent advances in our understanding and management of coagulopathy of APL.

2. Clinical features

The sine qua non of APL is the distinctive clinical and laboratory features of coagulopathy at diagnosis [5,8,10,11]. In one study, which is representative of most clinicians experience with this condition, it was noted that close to 76% of patients with APL have some clinical features suggestive bleeding in the early part of diagnosis and treatment of this condition [12].

Mucosal bleeding from gums and epistaxis along with easy bruisability, petechaie and purpura are fairly common at presentation. Patients can also occasionally present with large purpura and hematomas. However, the most dreaded complication is intracranial hemorrhage (ICH), which is the major cause of EHD in this condition. Another distinctive feature is the occurrence of ICH and other major bleeds at platelet levels and prothrombin and activated partial thromboplastin times (PT, APTT) where one would not expect such significant bleeding in another clinical setting, such as sepsis related disseminated intravascular coagulation (DIC). Additionally, it is not uncommon for the coagulopathy to worsen with the initiation of treatment especially conventional chemotherapy agents such as anthracyclines. With the introduction of ATRA and subsequently ATO there has been a reduction in early deaths after initiation of therapy. Table 1 summarizes the early deaths after starting treatment and the proportion of those that were due to hemorrhage (EHD) in a series of clinical trials. As illustrated in Table 1 one can see that there has been a steady reduction in early deaths from 12 to 26% in the pre-ATRA era to < 10% in the post ATRA era and even < 5% in recent studies, however one will notice that the proportion of early deaths secondary to hemorrhage (EHD) among these early deaths has remained remarkably the same, as stated earlier this is significantly higher when data outside clinical trials are included. This data highlights the importance of accurate diagnosis, appropriate management and need for further studies to reduce EHD in a leukemia which is highly curable provided we can avoid this complication in the first two weeks of starting treatment.

While bleeding related complications in APL gets the most attention when one discusses the clinical features of APL it is also important to understand that it is not uncommon for patients to present with complications thrombosis which can involve arteries and veins, the microvasculature as well as large vessels. It has been estimated that thrombosis can occur in about 10% of cases with APL [5,13,14]. From the reported studies, usually limited by small numbers, it was noted that the frequency of thrombosis was the highest in APL compared to all other forms of leukemia and that while introduction of ATRA appeared to reduce the risk of bleeding related complications it had not reduced the risk of thrombosis. Finally, from post mortem studies it has been recognized in close to 25% of patients with APL who died had evidence of thrombosis which was frequently not recognized ante-mortem [15]. While the presence of thrombosis and bleeding is very much akin to what one would expect and see in a case of disseminated intra-vascular coagulation (DIC), the thrombosis in APL is distinctly different in that microvasculature thrombosis resulting in multi-organ failure and skin necrosis rarely occurs in this condition. There are numerous reports of thrombosis leading to fatal cerebrovascular events, pulmonary embolism (PE), myocardial infractions, renal vein thrombosis and limb and digital gangrene.

The high degree of variability in the clinical presentation of coagulopathy in APL points the complex pathophysiology that causes it and the even more complex interplay with additional factors such as the type of treatment and supportive care provided in the management of APL.

3. Laboratory parameters

Patients with APL frequently present with pancytopenia and platelet counts are often very low at presentation ($< 10 \times 10^9$/Lt). Additionally there is evidence that in acute myeloid leukemia there are qualitative platelet defects which are not routinely evaluated [16]. Conventional coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) are frequently, but not invariably prolonged. It is not unusual to have normal values and at times a shorter than control value for APTT is seen. Serum fibrinogen levels are usually low and the D-dimer and fibrin degradation products (FDP) are usually elevated [5]. In contrast to DIC secondary to sepsis and malignancy, in APL the levels of protein C, protein S and antithrombin III are usually not reduced [5,17]. However, none of these parameters either alone or in combination have a pattern that can be considered diagnostic in APL [5] nor are the degrees of their abnormality predictive of the risk of ED or EHD. There is limited data on the role of global hemostasis tests such as whole blood viscoelastic assays in APL. Preliminary data from our center suggests the potential utility of thromboelastometry done with a ROTEM analyzer [18]. Our data suggests that the parameter of maximum clot firmness (MCF) generated by ROTEM with a value < 30 mm was significantly associated with an increased risk of death and was a better predictor of the hemostatic defect in APL. We also noted the significant discordance between the ROTEM values and conventional coagulation assays as illustrated in Fig. 1 and the potential for ROTEM based assays to more accurately reflect the hemostatic defect and guide replacement therapy. The utility of these assays however remain to be validated in larger studies and are also limited by the considerable challenges with standardizing these assays for reliable inter-laboratory comparison.

Parameters at diagnosis that have been associated with an increased risk of hemorrhage include a high WBC count at presentation [19,20], low fibrinogen level [19], poor performance status [19] and an elevated serum creatinine [20]. Parameters at diagnosis associated with an increased risk of thrombosis include an elevated white cell count, bcr3 isoform, CD2 immunophenotype and presence of a FLT3-ITD mutation [21]. Table 2 summarizes the common laboratory coagulation parameters APL and compares them with that seen in DIC and hyperfibrinolysis.

4. Pathophysiology of coagulopathy in APL and impact of therapeutic agents on it

There are multiple factors that contribute to the coagulopathy in APL. While the coagulopathy in APL does resemble DIC seen secondary to septicaemia there are many additional abnormalities in APL that make it distinctly different. As with many other leukemia's there is often thrombocytopenia due to decreased marrow production of platelets secondary to leukemic cell infiltration of the bone marrow. Over and above the quantitative defect there is evidence to suggest that there is an additional qualitative platelet dysfunction [16]. There is an increase in thrombin generation primarily driven by the increase in two pro-coagulants, namely tissue factor (TF) and cancer procoagulant (CP)