Early Death in Patients With Acute Promyelocytic Leukemia


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Abstract
With the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide, acute promyelocytic leukemia (APL) has become a highly curable malignancy. Approximately 90% of patients achieve complete remission with induction, which generally includes ATRA and an anthracycline-based chemotherapy. Early death, either before treatment is initiated or during induction, has emerged as one of the most critical issues involved in the current care of patients with APL. The main cause of early death in APL is bleeding, often intracranial. It has become increasingly clear that induction therapy should be initiated in patients at the earliest time possible, even before confirmation of the diagnosis of APL has been made. In this roundtable, several experts discuss important insights into the high rate of early death observed in APL. In addition to the importance of rapid diagnosis, the pathophysiology of the coagulopathy associated with APL will be discussed, as will factors that may be predictive of early death and potential interventions to prevent this important limitation to the cure of many, if not most, patients.
The Pathophysiology of Coagulopathy in APL

Hau C. Kwaan, MD, PhD

At the time of presentation, the majority of APL patients have a significant degree of coagulopathy. This is why this malignancy should be considered a medical emergency. Before the introduction of differentiation therapies, including ATRA and ATO, bleeding occurred in more than half of patients. Currently, coagulopathy is still responsible for more than 60% of early deaths in APL. Among the presenting bleeding complications in APL, intracranial hemorrhage is the most common (65–80%), followed by gastrointestinal hemorrhage and diffuse intra-alveolar hemorrhage in the lung.\(^1\)\(^-\)\(^3\) Adding to the complexity is the presence of thrombosis in up to one-quarter of patients. Approximately one-third of these thrombotic complications occur after induction treatment.

**Typical Coagulation Profile in APL**

Most patients with APL have varying degrees of abnormalities in their coagulation profiles. Overall, almost all patients present with signs of disseminated intravascular coagulation (DIC) and exhibit increased prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time (Figure 1). Both fibrinogen and platelet counts are decreased, along with an increase in fibrin degradation products (measured as D-dimer).\(^4\)\(^-\)\(^6\)

In addition to coagulopathy, abnormalities in the fibrinolytic system are also present, as evidenced by increased levels of tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), the uPA receptor, and the fibrinolytic receptor annexin A2.\(^6\)\(^-\)\(^8\) However, the picture is confounded by a simultaneous increase in the expression of plasminogen activator inhibitor (PAI)-1 and PAI-2, both of which are antifibrinolytic.\(^5\) Thus, the resultant picture represents a balance between the profibrinolytic and antifibrinolytic factors, and this varies from one patient to the other.

As the result of these hemostatic abnormalities, bleeding is the dominant clinical feature. Several risk factors for bleeding have been identified. These include a high white blood cell count (WBC), thrombocytopenia, low fibrinogen levels, and the presence of infection.

**Pathogenesis of Thrombosis**

In APL, bleeding and thrombosis are triggered by a number of events, including thrombocytopenia, increased tissue factor expression in the promyelocyte, abnormalities in fibrinolytic factors, apoptosis (induced by chemotherapy), comorbidities such as infection, and treatment with ATRA.\(^9\)\(^-\)\(^12\) APL promyelocytes typically display a high expression of tissue factor. In vitro, the extent of this upregulation varies across different APL cell lines, with up to a 300-fold increased expression in the NB4 cell line.\(^11\) Such increased expression of tissue factor is further escalated by inflammatory cytokines, such as tumor necrosis factor alpha (TNF\(\alpha\)) and interleukin (IL)-1b, and tumor-derived cytokines, such as IL-6. Tissue
factor is the primary factor that triggers the coagulation activation cascade. Normally encrypted and dormant on the surface of the intact cell, tissue factor is activated by phospholipids. During apoptosis, the phospholipids present in the cell membrane are exteriorized, enabling them to activate the dormant tissue factor. In addition, another activating process is by lipid peroxidation. Both apoptosis and lipid peroxidation occur during chemotherapy. Thus, the highest risk for coagulopathy occurs during treatment with chemotherapy, especially anthracyclines.

Other components that play a role in the pathogenesis of thrombosis include cancer procoagulant and fibrinolytic inhibitors (such as PAI-1 and PAI-2). Recent studies of microparticles in the plasma of APL patients revealed that high levels of activated tissue factor are present in those microparticles derived from myeloid cells. The tissue factor level returns to normal on CR of the disease. These findings support the concept of the hyper-coagulability of this disorder.

A number of risk factors for thrombosis in APL have also been defined. One factor is an elevated median WBC (>17,000). APL featuring the molecular characteristics of the bcr3 isomorph (expressing CD2, CD15, and the internal tandem duplication [ITD] in the Fms-like tyrosine kinase [FLT3] gene) is associated with a higher risk of thrombosis. There is a high risk of portal vein thrombosis, especially in the microgranular variant of APL that expresses CD2. Other factors include the differentiation syndrome (previously referred to as the retinoic acid syndrome), the use of chemotherapy, and thrombophilia (either hereditary or acquired).

Management

With treatment using ATRA and/or ATO, coagulopathy often resolves within 4–6 days after initiation of therapy. However, during this time, the patient may experience extensive and life-threatening bleeding. Unfortunately, this coagulopathy is not well controlled with heparin, as was shown in a retrospective study that compared heparin with antifibrinolytic agents in the pre-ATRA era. Even when antifibrinolytic agents are given prophylactically, they have not been shown to prevent intracranial hemorrhage. Thus, ATRA should be initiated at the earliest point possible, particularly in patients at high risk for bleeding.

Discussion

Martin S. Tallman, MD There is a movement in the field to combine ATRA with ATO as initial therapy for APL patients. Is there reason to believe that this combination will result in a faster resolution of the coagulopathy?

Hau C. Kwaan, MD, PhD To my knowledge, there is no evidence for an improved or more rapid resolution with the combination of these 2 agents. In addition, ATO induces apoptosis, which itself is a trigger for bleeding.

Martin S. Tallman, MD Are there any new agents that may warrant investigation as a combination therapy with ATRA in order to induce a faster resolution of coagulopathy?

Hau C. Kwaan, MD, PhD Agents that inhibit the coagulation pathway, such as those that block the action of tissue factor, may be effective in this setting. However, as of yet, none have been developed in clinical trials. Recombinant activated factor VII has been investigated to a limited extent, but because of its high cost and short half-life, it would be hard to administer over 4 days. In a randomized trial, heparin was shown to not improve survival.

Steven D. Gore, MD Heparin did not work in a randomized trial, but it works in individual patients if administered correctly. We still use heparin for patients with coagulopathy, and their fibrinogen goes right up.

Martin S. Tallman, MD Is there a risk of promoting thrombosis when too much cryoprecipitate is administered?

Hau C. Kwaan, MD, PhD No, I do not believe there is a significant risk, because we can safely adjust the dose of cryofibrinogen to normalize the plasma fibrinogen level.

References