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Early Death in Patients With Acute Promyelocytic Leukemia

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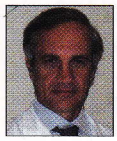

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Abstract

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.

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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.[6] 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.

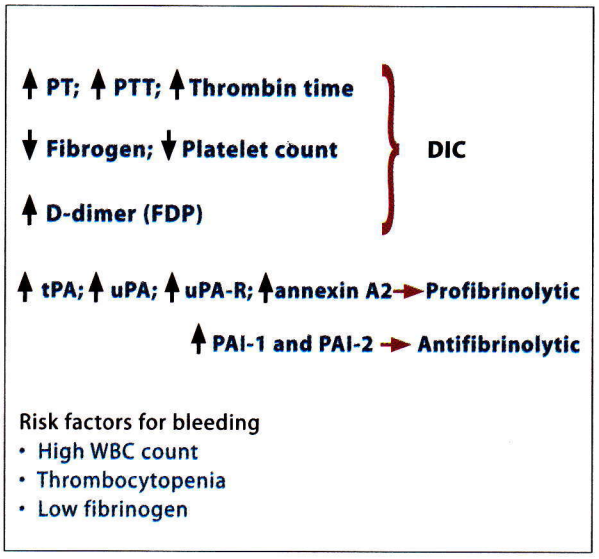

Figure 1. Coagulation profile in acute promyelocytic leukemia.

DIC=disseminated intravascular coagulation; FDP=fibrin degradation products; PAI=plasminogen activator inhibitor; PT=prothrombin time; PTT=partial thromboplastin time; tPA=tissue plasminogen activator; uPA=urokinase-type plasminogen activator; uPA-R=urokinase plasminogen activator receptor; WBC=white blood count.

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 (TNFα) 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.[12] The tissue factor level returns to normal on CR of the disease. These findings support the concept of the hypercoagulability 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 isoform (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.[13] There is a high risk of portal vein thrombosis, especially in the microgranular variant of APL that expresses CD2.[14,15] 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.[5,6,16] 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.[17] Even when antifibrinolytic agents are given prophylactically, they have not been shown to prevent intracranial hemorrhage.[18] 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

1. de la Serna J, Montesinos P, Vellenga E, et al. Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. *Blood.* 2008;111:3395-3402.
2. Di Bona E, Avvisati G, Castaman G, et al. Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in acute promyelocytic leukaemia. *Br J Haematol.* 2000;108:689-695.
3. Kwaan HC, Huyck T. Thromboembolic and bleeding complications in acute leukemia. *Expert Rev Hematol.* 2010;3:719-730.
4. Dombret H, Scrobohaci ML, Ghorra P, et al. Coagulation disorders associated with acute promyelocytic leukemia: corrective effect of all-trans retinoic acid treatment. *Leukemia.* 1993;7:2-9.
5. Watanabe R, Murata M, Takayama N, et al. Long-term follow-up of hemostatic molecular markers during remission induction therapy with all-trans retinoic acid for acute promyelocytic leukemia. Keio Hematology-Oncology Cooperative Study Group (KHOCS). *Thromb Haemost.* 1997;77:641-645.
6. Tallman MS, Lefebvre P, Baine RM, et al. Effects of all-trans retinoic acid or chemotherapy on the molecular regulation of systemic blood coagulation and fibrinolysis in patients with acute promyelocytic leukemia. *J Thromb Haemost.* 2004;2:1341-1350.
7. Bennett B, Booth NA, Croll A, Dawson AA. The bleeding disorder in acute promyelocytic leukaemia: fibrinolysis due to u-PA rather than defibrination. *Br J Haematol.* 1989;71:511-517.
8. Menell JS, Cesarman GM, Jacovina AT, McLaughlin MA, Lev EA, Hajjar KA. Annexin II and bleeding in acute promyelocytic leukemia. *N Engl J Med.* 1999;340:994-1004.

9. Polliack A. Acute promyelocytic leukemia with disseminated intravascular coagulation. *Am J Clin Pathol.* 1971;56:155-161.
10. Dally N, Hoffman R, Haddad N, Sarig G, Rowe JM, Brenner B. Predictive factors of bleeding and thrombosis during induction therapy in acute promyelocytic leukemia—a single center experience in 34 patients. *Thromb Res.* 2005;116: 109-114.
11. Falanga A, Marchetti M, Giovanelli S, Barbui T. All-trans-retinoic acid counteracts endothelial cell procoagulant activity induced by a human promyelocytic leukemia-derived cell line (NB4). *Blood.* 1996;87:613-617.
12. Kwaan HC, Rego EM. Role of microparticles in the hemostatic dysfunction in acute promyelocytic leukemia. *Semin Thromb Hemost.* 2010;36:917-924.
13. Breccia M, Avvisati G, Latagliata R, et al. Occurrence of thrombotic events in acute promyelocytic leukemia correlates with consistent immunophenotypic and molecular features. *Leukemia.* 2007;21:79-83.
14. Arthur DC, Bloomfield CD. Partial deletion of the long arm of chromosome 16 and bone marrow eosinophilia in acute nonlymphocytic leukemia: a new association. *Blood.* 1983;61:994-998.
15. Vahdat L, Maslak P, Miller WH Jr, et al. Early mortality and the retinoic acid syndrome in acute promyelocytic leukemia: impact of leukocytosis, low-dose chemotherapy, PMN/RAR-alpha isoform, and CD13 expression in patients treated with all-trans retinoic acid. *Blood.* 1994;84:3843-3849.
16. Falanga A, Iacoviello L, Evangelista V, et al. Loss of blast cell procoagulant activity and improvement of hemostatic variables in patients with acute promyelocytic leukemia administered all-trans-retinoic acid. *Blood.* 1995;86: 1072-1081.
17. Rodeghiero F, Avvisati G, Castaman G, Barbui T, Mandelli F. Early deaths and anti-hemorrhagic treatments in acute promyelocytic leukemia. A GIMEMA retrospective study in 268 consecutive patients. *Blood.* 1990;75:2112-2117.
18. Sanz MA, Martin G, Gonzalez M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. *Blood.* 2004;103: 1237-1243.