Bleeding in Acute Leukemia

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Bleeding is a major cause for morbidity and mortality in patients with acute leukemia. Life-threatening hemorrhage has been associated in a variety of settings, including hyperleukocytosis [1], monocytic differentiated acute myeloid leukemia (AML) [2–4], and in acute promyelocytic leukemia (APL) [5]. The bleeding diathesis in APL has been intensively investigated. The vitamin A derivative, all-trans retinoic acid (ATRA) induces terminal differentiation of leukemia promyelocytes which results in complete remission in the majority of patients with APL [6]. Furthermore, remission induction with ATRA has been accompanied by rapid resolution of the coagulopathy. The mechanism by which ATRA leads to reversal of the biochemical markers in clinical bleeding has not been completely elucidated. Historically, the bleeding diathesis in APL has been attributed to disseminated intravascular coagulation, thought to be caused by the release of tissue factor from leukemic cells. However, recent data suggests that the pathogenesis of the coagulopathy is more complicated [7, 8]. Peripheral blood and bone marrow cells have been obtained before and after treatment from 25 patients with previously untreated APL on Intergroup protocol 0129 which compared the efficacy of ATRA to conventional induction chemotherapy. Blood samples were collected on days 1, 8, 15, and 30 of either ATRA or chemotherapy treatment. A variety of markers of activation of coagulation and of fibrinolysis were studied. In addition,

the cellular expression of the genes for tissue factor and interleukin-1 β were examined. The mean plasma levels of fibrin D-Dimer, prothrombin fragment 1.2, antithrombin complex and fibrinopeptide A were markedly elevated prior to therapy and declined during the first 30 days of treatment with either ATRA or chemotherapy, but more rapidly so and to a greater extent in patients treated with ATRA. Therapy with ATRA was associated with a significant decrease in tissue factor gene expression during the first 30 days whereas the expression of the interleukin-1 β gene declined in some patients treated with chemotherapy but increased in some patients treated with ATRA. These data as well as those from other investigators indicate that treatment with either ATRA or chemotherapy rapidly improves the coagulopathy as reflected by a decline in the markers of clotting activation [9–11]. ATRA appears to induce such a reduction to a greater extent than is observed with chemotherapy. The majority of patients with APL can now be expected to be cured of their disease with a combination of ATRA and chemotherapy before induction, chemotherapy consolidation and maintenance therapy. Indeed, approximately 75–80% of patients enjoy prolonged disease-free survival [12]. However, the induction mortality rate, partly attributable to hemorrhage, remains approximately 10% in most studies. Therefore, further investigation of the coagulopathy and investigational strategies to reduce this risk, may contribute to the cure of all patients with APL.

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