Epsilon-Aminocaproic Acid in the Treatment of Patients with Acute Promyelocytic Leukemia and Acquired Alpha-2-Plasmin Inhibitor Deficiency

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Patients with acute promyelocytic leukemia often develop bleeding diatheses during treatment. In seven patients who had this disease, the plasma level of alpha-2-plasmin inhibitor was the best predictor of severity of coagulopathy and bleeding. Clinical bleeding occurred when alpha-2-plasmin inhibitor levels measured less than 30% of normal levels. Patients with acute promyelocytic leukemia who had acquired deficiencies of alpha-2-plasmin inhibitor were considered to have deficits similar to those in persons congenitally deficient in alpha-2-plasmin inhibitor, and were assumed to be at increased risk for bleeding. Treatment with the fibrinolytic inhibitor, epsilon-aminocaproic acid, along with heparin resulted in prompt cessation of bleeding, reversal of laboratory evidence of fibrinolysis, and a decreased need for blood product support. The only thrombotic complication—thrombosis around a central venous catheter—resolved when treatment with epsilon-aminocaproic acid was discontinued. Epsilon-aminocaproic acid is a safe and effective therapy for those patients with acute promyelocytic leukemia who develop coagulopathy associated with low levels of alpha-2-plasmin inhibitor.

Therapy for acute promyelocytic leukemia (acute nonlymphocytic leukemia M3 of the French-American-British classification (1)) presents special problems because of the coagulopathy that often accompanies the disease (2-4). The administration of heparin during induction chemotherapy allows patients to achieve remission with fewer bleeding complications (5-7). However, many patients with acute promyelocytic leukemia still develop major bleeding problems, and death from intracranial hemorrhage is not uncommon (8).

The defibrination that occurs in patients with acute promyelocytic leukemia is caused by activation of the fibrinolytic system as well as intravascular coagulation (9-13). The physiologic fibrinolytic response, initiated with the formation of fibrin (14), may be exacerbated in patients with acute promyelocytic leukemia by the release of proteases from leukemic promyelocytes at cell lysis. Leukemic promyelocytes contain plasminogen activators (15, 16) and enzymes, such as leukocyte elastase, that may inactivate inhibitors of fibrinolysis or degrade fibrinogen directly (17). Although the diagnosis of a primarily fibrinolytic state is difficult (18), recent evidence suggests that depletion of the fast-acting plasmin inhibitor of plasma (alpha-2-antiplasmin, or alpha-2-plasmin inhibitor) is a specific marker for systemic fibrinolysis (19, 20).

Persons who have congenital deficiencies in this inhibitor have severe, lifelong bleeding tendencies that are alleviated by treatment with the fibrinolytic inhibitor, tranexamic acid (21-25). Results of several studies have shown low levels of alpha-2-plasmin inhibitor in patients with acute promyelocytic leukemia (10, 11, 26-28). This inhibitor has an accelerated turnover in these patients (26) that resembles that found in patients treated with streptokinase (20). Because we were not satisfied with the clinical outcomes with standard heparin treatment, we began to monitor alpha-2-plasmin inhibitor levels in patients with acute promyelocytic leukemia. We used a low level of alpha-2-plasmin inhibitor as an indication for addition of the antifibrinolytic drug, epsilon-aminocaproic acid, to heparin in the regimen given to such patients. This strategy worked well, and we suggest a role for epsilon-aminocaproic acid in a properly chosen and monitored subgroup of patients receiving heparin for acute promyelocytic leukemia.

Methods and Protocols

We determined prothrombin times (normal range, 10.5 to 12.5 seconds) and activated partial thromboplastin times (normal range, 22 to 32 seconds) with commercial reagents on an automated instrument (MLA-700; Scientific Products, McGaw Park, Illinois). Fibrinogen concentrations were determined by a clotting time assay (American Dade, Miami, Florida), and fibrin/fibrinogen degradation products, by a latex bead immunosassay (Dade); normal ranges were 150 to 350 mg/dL (4 to 10 μmol/L) for fibrinogen and less than 8 μg/mL for fibrin/fibrinogen degradation products. Alpha-2-plasmin inhibitor levels were determined by measuring inhibition (by diluted plasma) of plasmin turnover of a fluorogenic substrate (Dade Protopath). The normal range was 79% to 118%, as obtained by standard plasma pool. The coefficient of variation of the assay was 5% for samples with values in the normal range and 8% for samples with values measuring less than 50% of normal activity. Concentrations of antithrombin III (normal range, 90% to 130% of standard) and plasminogen (normal range, 75% to 130% of standard) were determined using automated chromogenic substrate-based assays (ACA; E.I. DuPont de Nemours Co., Wilmington, Delaware). In some samples, levels of antithrombin III and plasminogen were determined by using a manual fluorogenic substrate-based technique (Dade Protopath).

Standard Treatment

Acute promyelocytic leukemia was diagnosed by bone marrow aspiration and biopsy according to the French-American-British criteria (1). We inserted a central venous catheter in six patients and a double-lumen Raff catheter in one patient. Combination chemotherapy consisted of daunorubicin, 60 mg/m2 body surface area given intravenously on days 1 through 3; cytarabine, 200 mg/m2, given daily by continuous intravenous infusion or intravenous bolus on days 1 through 5; and 6-thioguanine, 100 mg/m2, given orally every 12 hours on days 1
Levels of 20% of normal, which is the lowest level the assay can measure. Three of the four patients with nadir levels less than 30% of normal had significant bleeding. No patient had bleeding with an alpha-2-plasmin inhibitor level of greater than 30% of normal. Antithrombin III levels changed very little during induction chemotherapy and remained normal throughout treatment, except for isolated low values in two patients.

**CLINICAL OUTCOME**

Three patients had low alpha-2-plasmin inhibitor levels and significant bleeding (gross hematuria, oozing from venipuncture sites, mucosal bleeding, or intracranial bleeding). One of these patients received orally administered epsilon-aminocaproic acid and died of intracranial bleeding 48 hours after the start of induction chemotherapy. At autopsy, two large intracranial chloromas were found. Two other patients, whose clinical courses are charted in Figure 2, received continuous intravenous infusions of epsilon-aminocaproic acid; bleeding stopped within 24 hours of the initiation of this treatment. An additional two patients were treated with epsilon-aminocaproic acid when their plasma alpha-2-plasmin inhibitor activity levels were found to measure below 40% of normal; neither of these patients had any bleeding. Two patients had no bleeding, and additional measurements of alpha-2-plasmin inhibitor levels showed them to be consistently greater than 40% of normal. Epsilon-aminocaproic acid was not given to these patients and no bleeding complications occurred. In all four patients treated with intravenous epsilon-aminocaproic acid, fibrinogen levels began to increase and titers of fibrin/fibrinogen degradation products began to decrease within 24 hours of initiation of the treatment. Plasminogen and alpha-2-plasmin inhibitor levels, however, remained low for 3 to 10 days more. No patient developed bacteremia during the administration of this treatment. One patient had sympot-
matic subclavian vein thrombosis at the site of a Raaf catheter that resolved quickly when epsilon-aminocaproic acid therapy was stopped and heparin therapy was continued. No other evidence of thrombosis was seen in the patients receiving epsilon-aminocaproic acid. The patient who died had no evidence of thrombosis at autopsy. Five patients, including four who had received epsilon-aminocaproic acid treatment, achieved complete remission after one or two cycles of chemotherapy, one patient died during induction chemotherapy as described, and one patient had persistent leukemia.

Discussion

Bleeding in patients with acute promyelocytic leukemia remains a vexing problem despite the routine use of heparin infusions. Results of this study and others (9-13, 15, 26) suggest that a major cause of consumptive coagulopathy in patients with acute promyelocytic leukemia is activation of the fibrinolytic system, which results in rapid dissolution of clots before permanent hemostasis can be achieved. Every patient in this series had depletion of alpha-2-plasmin inhibitor at some point during the course of his or her disease. Levels of alpha-2-plasmin inhibitor of less than 30% of normal were associated with depletion of fibrinogen and generation of high titers of fibrin/fibrinogen degradation products. Three of four patients with alpha-2-plasmin inhibitor levels of less than 30% of normal had clinically apparent bleeding, whereas none of the three patients with alpha-2-plasmin inhibitor levels of greater than 30% had symptoms of bleeding.

Levels of antithrombin III, which is consumed when thrombin and several other proteolytic clotting factors are generated (30), were normal in our patients—a finding that has been reported previously in patients with acute promyelocytic leukemia (10, 31). No evidence therefore existed for large-scale activation of procoagulant enzymes. Many patients reported to have had clinical and laboratory evidence of fibrinolysis, including those with acute promyelocytic leukemia and patients with low levels of alpha-2-plasmin inhibitor, have been treated effectively with antifibrinolytic agents (10, 32-35). In each patient in the present series, with the exception of one patient with intracranial leukemic masses who had received a low dosage of oral epsilon-aminocaproic acid, clinical and laboratory evidence of coagulopathy showed improvement within 24 hours after epsilon-aminocaproic acid treatment had begun. Depletion of alpha-2-plasmin inhibitor could be caused by the release of high levels of plasminogen activators from leukemic promyelocytes, which would lead to the subsequent generation of plasmin (15), or the release of leukocyte elastase, leading to the subsequent inactivation of alpha-2-plasmin inhibitor (17). Regardless of the mechanism of depletion, however, a low plasma level of alpha-2-plasmin inhibitor in a patient with acute promyelocytic leukemia appears to be a risk factor for bleeding and justifies treatment with an antifibrinolytic drug. Observations based on patients congenitally deficient in alpha-2-plasmin inhibitor provide an additional rationale for this approach. Such patients have severe, lifelong bleeding tendencies that respond well to antifibrinolytic therapy (21-25).

Because alpha-2-plasmin inhibitor deficiency appears to correlate with clinical bleeding in patients with acute promyelocytic leukemia, serial alpha-2-plasmin inhibitor measurements can be used both to decide when antifibrinolytic therapy should be initiated and to monitor the

![Figure 2. Clinical courses of two patients (panels A and B) treated with epsilon-aminocaproic acid. Bleeding was associated with alpha-2-plasmin inhibitor levels of less than 30% of normal in both patients. Days on which daunorubicin (dauno), cytarabine (Ara C), 6-thioguanine (6TG), low-dose cytarabine (i.D. Ara C), epsilon-aminocaproic acid (EACA), and heparin were given are indicated by bars at top of figure; arrows indicate days on which cryoprecipitate and fresh frozen plasma were given. Plasma concentrations of antithrombin III (AT III), alpha-2-plasmin inhibitor (α2 PI) and plasminogen (Pg) are indicated by crosses, triangles, and closed circles, respectively, and are given as percentage of normal. Plasma fibrinogen (Fg) concentrations (open circles) are given in mg/dl. Note that in panel B, the second course of chemotherapy was not accompanied by a drop in alpha-2-plasmin inhibitor titer; the patient had no bleeding, and epsilon-aminocaproic acid was not given.](image)
effects of therapy. At present, treatment with epsilon-aminocaproic acid is given to any patient with acute promyelocytic leukemia in whom the alpha-2-plasmin inhibitor level has fallen to below 40% of normal. Because continuous infusion of epsilon-aminocaproic acid results in more constant blood levels than does intermittent, oral, or intravenous administration (32), patients weighing 70 kg are given intravenous bolus injections of 3 g, followed by continuous infusions of 1 g/h. All patients continue to receive heparin infusions and are given cryoprecipitate and fresh frozen plasma as necessary to keep the fibrinogen levels at more than 100 mg/dL (2.7 μmol/L) and the prothrombin times at less than 15 seconds.

The use of epsilon-aminocaproic acid in the treatment of consumptive coagulopathies has been discouraged because of the possibility that interference with secondary fibrinolysis associated with disseminated intravascular coagulation could lead to widespread thrombosis (18, 36). A patient at another institution who had acute promyelocytic leukemia and fibrinolysis received epsilon-aminocaproic acid without heparin and developed bilateral renal cortical thrombosis and intracerebral hemorrhage. Our patients all were given heparin simultaneously with epsilon-aminocaproic acid to minimize the likelihood of the development of thrombosis. We would have discontinued epsilon-aminocaproic acid treatment if clinical evidence of sepsis had developed; however, sepsis did not occur in any patient. The patient who died while receiving epsilon-aminocaproic acid had no evidence of thrombosis at autopsy. One patient developed symptomatic thrombosis around a central venous catheter while receiving heparin and epsilon-aminocaproic acid, which resolved quickly on heparin therapy (500 U/h with no attempt to prolong the activated partial thromboplastin time) after discontinuation of epsilon-aminocaproic acid therapy. Because such catheter-related thrombosis occurs often in patients with leukemia—occurring in 4% to 37% of patients, depending on the series (37, 38)—its cause cannot be attributed solely to epsilon-aminocaproic acid therapy. The other patients who received heparin and epsilon-aminocaproic acid also had catheters, but did not develop signs or symptoms of thrombosis.

Based on the results of our study, we believe that the use of epsilon-aminocaproic acid in patients receiving heparin for acute promyelocytic leukemia, who have excessive fibrinolysis and decreased alpha-2-plasmin inhibitor levels, is a safe and effective treatment for the coagulopathy associated with the disease. The addition of an antifibrinolytic drug such as epsilon-aminocaproic acid to the heparin regimen usually given to these patients should result in fewer hemorrhagic complications than would occur if heparin alone were used.

References