A CUTE PROMYELOCYTIC leukemia (APL) is a distinct variety (French-American-British M3) of acute myelogenous leukemia (AML) distinguished by the presence of a balanced reciprocal translocation between chromosomes 15 and 17, by the achievement of complete remission (CR) without obligatory marrow aplasia, and by the association with a potentially life-threatening hemorrhagic diathesis. Although thromboembolic events such as arterial occlusions, pulmonary emboli, hepatic vein occlusion, and portal vein occlusion are very infrequently depicted in Fig 1.

The first and most generally recognized abnormality is the release of procoagulants from the APL cells resulting in DIC. Several types of procoagulant activity have been found in APL cells capable of activating factor X through both intrinsic and extrinsic pathways, including tissue factor-like activity. A unique procoagulant with cysteine proteinase activity distinct from tissue factor capable of directly activating factor X has been shown to be increased in APL compared with other AML subtypes.

In this report we examine the mechanisms of the bleeding diathesis in patients with APL, review the role of heparin and other strategies in the management of patients with APL, propose a therapeutic approach for patients with APL and coagulopathy, and suggest future directions for studies to address these issues.

MECHANISMS OF THE BLEEDING DIATHESIS IN APL

The pathogenesis of the bleeding diathesis in APL is not completely understood, although the pattern of abnormal laboratory findings is well recognized. The most consistently observed coagulation abnormalities include thrombocytopenia, prolongations of the prothrombin (PT), activated partial thromboplastin (PTT) and thrombin times (TT), increased levels of fibrin degradation products (FDPs), and hypofibrinogenemia. These findings are not diagnostic of any single coagulation disorder, but reflect a complex interaction of several pathophysiologic processes depicted in Fig 1.

The first and most generally recognized abnormality is the release of procoagulants from the APL cells resulting in DIC. Several types of procoagulant activity have been found in APL cells capable of activating factor X through both intrinsic and extrinsic pathways, including tissue factor-like activity. A unique procoagulant with cysteine proteinase activity distinct from tissue factor capable of directly activating factor X has been shown to be increased in APL compared with other AML subtypes. A recent report identified a correlation between tissue factor related antigen and the development of DIC. As a result, intravascular thrombin is generated as evidenced by the release of the activation peptide, prothrombin fragment 1 + 2 from the amino terminal end of prothrombin and of thrombin-antithrombin (TAT) complex. Thrombin in turn liberates fibrinopeptide A from fibrinogen. Although heparin has been advocated to block this coagulant activity, its action is not completely successful in reverting the elevated fragment 1 + 2 and TAT levels. This is believed to be due to heparin's inability to block the action of factor Xa, which is protected by its binding to platelets. A novel mechanism by which leukemic cells can activate the coagulation system has been proposed by Cozzolino et al, who reported that interleukin-1 (IL-1) secreted by leukemic cells may lead to DIC. These investigators studied 37 patients and found 14 patients with DIC (four with APL) whose leukemic cells secreted IL-1 spontaneously, 6 patients with DIC whose...
leukemic cell elaborated IL-1 only after induction by the stimulant phytohemagglutinin, and 17 patients without DIC whose leukemic cells did not release IL-1 spontaneously or after stimulation. Indeed, IL-1 may induce procoagulant activity in endothelial cells.

The second abnormality contributing to the hemostatic defect in APL is fibrinolysis. Excessive fibrinolytic activity was believed to be responsible by early observers. With the recognition of DIC, the excess fibrinolysis was felt to be a secondary response to DIC. Recently, it has been shown that tissue plasminogen activator (t-PA), and to a lesser degree other plasminogen activators such as the urokinase-type (u-PA), may also be released from endothelial cells. Tumor cells, including myeloid leukemia cells and lymphoid leukemia cells, especially the T-cell phenotype, contain both types of plasminogen activators in varying quantities. Leukemic promyelocytes have been shown to contain u-PA and t-PA in sufficient quantities to generate plasmin. The single-chain proenzyme form of urokinase (scu-PA) has little effect on plasminogen. Activation of plasminogen requires the conversion of scu-PA to the two-chain active form (tcu-PA). Stephens et al. found that cells from solid tumors produced almost exclusively scu-PA while all leukemic cell lines studied, including APL, produced tcu-PA. In one study in patients with DIC and secondary fibrinolysis, t-PA was generated where as u-PA was found both within the leukemic cells and in the plasma of patients with APL. Plasminogen activator inhibitor-1 (PAI-1) is the main naturally occurring inhibitor of t-PA and, recently, decreased PAI-1 activity has been described in patients with APL. Because thrombin formation may accompany the coagulopathy in APL, predominant fibrinolysis would be an appropriate term to describe the fibrinolysis encountered in those cases where fibrinolysis outweighs DIC.

Other proteolytic enzymes are also present, including elastases that interact with components of the fibrinolytic system by inactivating two known inhibitors of plasmin namely, α-1-plasmin inhibitor (α-PI) and C1 esterase inhibitor. α-PI is a fast-acting inhibitor and rapidly binds plasmin. Thus, a decrease in the plasma level of α-PI signifies the activation of the fibrinolytic system, although it does not distinguish between predominant and secondary fibrinolysis. This has been reported in patients with APL. Other markers of systemic fibrinolysis are the peptide products resulting from the plasmin-induced proteolysis of fibrinogen or fibrin. These include the various FDPs, activation peptides, and B6 1-42. Such increases in fibrinolysis may partially account for the bleeding diathesis among patients with APL. Avvisati et al. reported that only 2 of 12 patients with APL had low levels of protein C activity and corresponding low antigen levels, an observation shared by Bauer et al. further suggesting that a major cause for the coagulopathy is, at least in part, predominant fibrinolysis or proteolysis rather than DIC, because protein C levels are usually low in DIC.

Another mechanism that may contribute to excessive fibrinolysis has been reported by Sterrenberg et al. These investigators provide evidence that direct fibrinogen breakdown by leukocyte proteases, including both plasmin and elastase, accounts for the elevation in FDPs and the decrease in fibrinogen usually attributed to DIC. The digestion of fibrinogen by elastase proceeds in a similar fashion to that which occurs with plasm. Fibrinogen is first digested to an X fragment and then to a Y fragment and a D fragment. With plasmin-induced fragments X, Y, and D, there is initially an increase in the anticoagulant activity with the transition from fibrinogen to fragments X and Y followed by a decrease such that fragment D has little anticoagulant activity. In contrast, the early X-like fragment produced by elastase initially has strong anticoagulant activity that lessens as the late fragment is generated. Anticoagulant activity then increases again with formation of the D-like fragment (induced by elastase), which inhibits clotting more strongly than fragment D induced by plasmin. Factor XIIa cross-links fibrin monomers and the D domain is the site of cross-linking. Therefore, the lysis of fibrin results in the formation of D-dimer. In primary fibrinolysis there is no thrombin generation so that factor XIIa and D-dimer are not formed. Thus, the D-dimer measurement serves to distinguish between secondary fibrinolysis occurring in response to DIC and primary fibrinolysis unaccompanied by significant thrombin formation. D-dimer levels in APL have not been studied on a large scale.

Thrombin generated in DIC forms complexes with antithrombin III (AT-III) resulting in a decrease in the plasma AT-III level. However, AT-III levels in patients with APL are generally normal, which lends further support to the hypothesis that the bleeding abnormality is not simply DIC. Because both protein C and AT-III are synthesized in hepatic cells, their plasma levels in part reflect hepatic function. In DIC with hepatic dysfunction, these levels are often decreased, whereas in DIC without hepatic dysfunction these levels can be normal or only mildly decreased. Thus, normal AT-III levels do not exclude DIC in patients with APL.

**ROLE OF HEPARIN IN THE MANAGEMENT OF PATIENTS WITH APL**

Because the coagulopathy associated with APL has most often been attributed to DIC, heparin therapy has become widely accepted. Although there have been no prospective, randomized, and controlled studies to establish the benefits of heparin therapy in this setting, a number of publications have addressed this issue (Table 1). The interpretation of
these results requires caution. The majority of studies involve small numbers of patients, are retrospective, and are not controlled. Two investigators, Drapkin and Cordonnier, independently suggest that irrespective of the initial coagulation studies, prophylactic heparin is useful during remission induction. In the first of these studies, the investigators compare nine patients administered prophylactic heparin, of whom two died of intracerebral hemorrhage, to eight patients not treated with prophylactic heparin, of whom five died of intracerebral bleeding. However, the groups are not comparable. The median age of heparinized patients was 54 years (v 46 years). The duration of heparin varied from 5 to 14 days as did the dose from 10 to 20 U kg/h. The amount of platelet and blood transfusions is not detailed. Patients were generally treated prior to 1975, before modern supportive care and chemotherapy was recognized. In Cordonnier’s study, blood product supportive care was standardized with respect to platelet transfusions and heparin administration. The CR rate was lower than currently reported and the death rate during induction was high (27 of 57 or 47%). In this study, 61% of patients older than 30 years died, most often of intracerebral hemorrhage. Patients were given massive platelet transfusions to maintain a platelet count of at least 60,000/μL. This degree of intensive platelet support itself may have accounted for the apparent improved outcome with heparin. Both Cunningham et al and Kantarjian et al observed that heparin is particularly valuable for patients at high risk for fatal hemorrhage, although these data are also retrospective. In Kantarjian et al’s study, heparin was administered as prophylaxis to some patients and as therapy to others when clinical bleeding was present. In addition, fresh frozen plasma was given and platelets were transfused to maintain a platelet count above 50,000/μL. These investigators identified four independent risk factors for hemorrhagic deaths in patients with APL. They were anemia, thrombocytopenia, absolute myeloblast and promyelocyte count, and age greater than 50 years. The incidence of hemorrhagic death in patients with no more than two risk factors was 5%, whereas the incidence in those who had more than two was 58%. In the population at low risk for hemorrhagic death, prophylactic heparin did not appear to be efficacious (5% v 61%) whereas among the high risk patients there was a trend toward a decreased incidence of hemorrhagic deaths (67% v 45%). In Cunningham et al’s study, heparin was discontinued if there were signs of significant hemorrhage or headache and platelet counts were maintained at above 20,000/μL. The incidence of early fatal hemorrhage in this report of 14% is lower than in all other reports, perhaps attributable to the small numbers of patients at high risk for hemorrhage as identified by Kantarjian et al. Collins et al recommended the prophylactic use of heparin if abnormal pretreatment coagulation studies are present. In this limited study of only seven patients, fresh frozen plasma and cryoprecipitate were administered in addition to heparin. These patients were age 50 years or older and the oldest patient was 54 years. In addition, only two patients had an absolute blast and promyelocyte count ≥1,000/μL—both high risk factors for hemorrhage as identified by Kantarjian et al.

Goldberg et al in another retrospective analysis, reported that the coagulopathy associated with APL can be managed with intensive blood product support alone with-

<table>
<thead>
<tr>
<th>Author</th>
<th>Years of Study</th>
<th>No. of Patients</th>
<th>Criteria for Heparin Administration</th>
<th>Control</th>
<th>Route, Dose and Schedule of Heparin</th>
<th>Blood Product Support</th>
<th>CR Rate</th>
<th>Hemorrhagic Deaths During Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drapkin et al</td>
<td>1974-76</td>
<td>17</td>
<td>As prophylaxis</td>
<td>Yes</td>
<td>ci 5-20 U/kg/h</td>
<td>0 0 +</td>
<td>7/9</td>
<td>2/8</td>
</tr>
<tr>
<td>Ruggero et al</td>
<td>1972-76</td>
<td>13</td>
<td></td>
<td>No</td>
<td></td>
<td>0 0 +</td>
<td>7/13</td>
<td>4/13</td>
</tr>
<tr>
<td>Daly et al</td>
<td>1973-79</td>
<td>15</td>
<td>As therapy, for clinical bleeding and laboratory evidence of DIC</td>
<td>Yes</td>
<td>50 U/kg loading dose IV at 150-200 U/kg/24 h</td>
<td>0 0 +</td>
<td>8/10</td>
<td>3/5</td>
</tr>
<tr>
<td>Cordonnier et al</td>
<td>1972-82</td>
<td>57</td>
<td>As prophylaxis</td>
<td>No</td>
<td>ci 1-3 mg/kg/d</td>
<td>0 0 +</td>
<td>30/57</td>
<td>6/57</td>
</tr>
<tr>
<td>Cunningham et al</td>
<td>1974-84</td>
<td>57</td>
<td>As prophylaxis</td>
<td>No</td>
<td>ci 7.5-15 U/kg/h</td>
<td>+ 0 +</td>
<td>41/57</td>
<td>8/57</td>
</tr>
<tr>
<td>Kantarjian et al</td>
<td>1973-84</td>
<td>60</td>
<td>As prophylaxis in 24 pts, as therapy in 7 pts for clinical bleeding</td>
<td>Yes</td>
<td>ci 5-10 U/kg/h</td>
<td>+ 0 +</td>
<td>1/32</td>
<td>19/28</td>
</tr>
<tr>
<td>Goldberg et al</td>
<td>1974-85</td>
<td>25</td>
<td></td>
<td>No</td>
<td></td>
<td>+ 0 +</td>
<td>19/25</td>
<td>4/25</td>
</tr>
<tr>
<td>Hoyle et al</td>
<td>1976-86</td>
<td>115</td>
<td>As prophylaxis</td>
<td>Yes</td>
<td>5,000 U subcut Bid, 2,400-24,000 U IV daily</td>
<td>+ 0 +</td>
<td>30/35</td>
<td>30/80</td>
</tr>
<tr>
<td>Kingsley et al</td>
<td>1980-86</td>
<td>11</td>
<td>As prophylaxis</td>
<td>No</td>
<td>5,000 U loading dose IV</td>
<td>0 + +</td>
<td>6/11</td>
<td>3/11</td>
</tr>
<tr>
<td>Rodughiero et al</td>
<td>1984-87</td>
<td>282</td>
<td>As prophylaxis</td>
<td>Yes</td>
<td>2,500 U-37,500 U daily, or subcut</td>
<td>+ + +</td>
<td>58/94</td>
<td>66/107</td>
</tr>
</tbody>
</table>

Includes those with at least an anthracycline and cytosine arabinoside as induction chemotherapy.

Abbreviations: ci, continuous infusion; 0, not given; +, given; pts, patients; Pts, platelets; IV, intravenous; Cryo, cryoprecipitate; Bid, twice daily; subcut, subcutaneously.
out the routine use of heparin. Fresh frozen plasma was administered to maintain the fibrinogen level at 150 mg/dL or to correct the prothrombin time to less than 3 seconds beyond control. In this study, 85% of patients had evidence of DIC, yet only four patients (17%) had elevation of the PTT. Bernard et al reported an improved remission rate (78%) with heparin together with more liberal use of platelet transfusions in addition to daunorubicin compared with daunorubicin alone (45%). However, the criteria for DIC was not detailed. In the majority of cases, DIC was suggested by the presence of FDPs and soluble complexes that result from the action of thrombin on fibrinogen. Yet, these studies were not performed in all patients. Hoyle et al retrospectively studied 115 patients treated at multiple institutions and observed a higher remission rate (86%) among those receiving heparin compared with that among patients not receiving heparin (49%) (P = .002). This difference was attributed to a reduction in the number of hemorrhagic deaths, especially those due to intracranial hemorrhage in the heparin-treated group. However, many patients also received platelet transfusions, fresh frozen plasma, and cryoprecipitate both as prophylaxis and as therapy. Doses of heparin varied widely from 5,000 U twice a day subcutaneously to between 2,400 and 24,000 U intravenously administered daily. This study has the advantage of having a control group, although it is not prospective. The investigators report more than one third of the patients (46 of 114) had no DIC at diagnosis and, additionally, one half of patients (63 of 112) had no DIC during treatment. However, the precise criteria for defining DIC were not provided and these data were derived from questionnaires given to physicians participating in a multicenter registry. In the largest study published, Rodeghiero et al retrospectively analyzed 268 consecutive patients, 94 of whom received heparin, 67 received an antifibrinolytic agent, and 107 were given only supportive care. These investigators were not able to demonstrate a significant benefit with heparin with respect to the incidence of early hemorrhagic deaths, CR rate, or overall survival. This study is subject to many of the same limitations as the previous studies. However, for the first time, a substantial number of patients administered an antifibrinolytic agent was reported.

In light of these wide variations involving the criteria for initiating heparin therapy, the dose, route, and schedule of heparin administration, and the concurrent use of blood product support, it is difficult to attribute the improved survival in any one series to heparin alone. Furthermore, in those patients with severe hemostatic abnormalities, the dose of heparin and its effects were difficult to monitor by conventional clotting assays. As a result, the dose cannot be adjusted according to the severity of the putative DIC in each individual patient. Thus, other approaches to control the coagulopathy have been proposed.

**MANAGEMENT STRATEGIES IN TREATING THE HEMOSTATIC DISORDER OF APL**

Since increased fibrinolytic and other protease activities have recently been implicated in the pathogenesis of the coagulopathy, newer therapeutic regimens including antifibrinolytic agents such as epsilon-aminocaproic acid and tranexamic acid, or protease inhibitors such as aprotinin, have been explored. Some investigators have recommended heparin for all patients, while others have suggested its use only for patients at high risk of bleeding. Still others have recommended heparin together with blood products such as fibrinogen for persistent bleeding and severe hypofibrinogenemia. Epsilon-aminocaproic acid may be beneficial without the use of heparin as well as in combination with heparin, especially for patients with low levels of α2-PI. Other antifibrinolytic agents have been studied, including tranexamic acid which, in a double-blind placebo-controlled study of 12 patients, decreased the number of hemorrhagic episodes as well as platelet and red blood cell transfusion requirements. These agents act by occupying lysine-binding sites on the plasminogen molecule involved in the binding to fibrin. This study involved a very small number of patients and fibrinogen levels (range) at the study entry were higher in the group of patients receiving tranexamic acid and the FDPs were lower (both median and range), suggesting the possibility of a less severe coagulopathy in the tranexamic acid-treated patients. However, it is of interest that there were no thrombotic events, indicating that tranexamic acid may be administered safely to these patients.

An important contribution to the literature was made by Rodeghiero et al, who reported in their retrospective analysis of 268 consecutive patients with APL collected from multiple institutions a substantial number of patients treated with an antifibrinolytic agent. Ninety-four patients (35%) received heparin, 67 (25%) were treated with antifibrinolytic agents (tranexamic acid, epsilon-aminocaproic acid, or aprotinin), and 107 (40%) received supportive care alone. There were no significant differences in the incidence of early hemorrhagic deaths, CR rates, or duration of survival between the three groups. Three different antifibrinolytic agents were used (tranexamic acid, epsilon-aminocaproic acid, and aprotinin) and in widely varying doses and schedules. For example, the dose of tranexamic acid varied from 1.5 to 14 g/d and the dose of aprotinin varied from 800,000 to 2,000,000 U/d. Despite its limitations, this study does suggest that antifibrinolytic agents can be administered safely in this setting with no thrombotic complications and without the potential protective benefit of heparin.

Sakuragawa et al studied the proteolytic activity of the lysate of APL cells and found both procoagulant activity as well as fibrinolytic activity. They reported the inhibition of procoagulant activity by the protease inhibitor, aprotinin (Trasylol; Novo Nordisk Pharmaceuticals, Inc, Princeton, NJ), and heparin as well as the inhibition of fibrinolytic activity by aprotinin and soybean trypsin inhibitor. Wijermans et al recommended the combined use of heparin, tranexamic acid, and fresh frozen plasma because they observed both procoagulant activity as well as fibrinolytic activity in the human promyelocytic cell line HL-60. Leone et al reported effective control of hemorrhage with large doses of glucocorticoids, in addition to aprotinin, to stabilize lysosomes thereby preventing enzyme release. Other investigators are exploring the alternative approach of...
All-trans retinoic acid, a vitamin A derivative, has recently been reported to promote terminal differentiation of leukemic promyeloblasts, resulting in a bone marrow and cytogenetic CR rate of 64% to 96%86 with rapid correction of the coagulopathy.86 With this novel approach, the earliest indication of response was normalization of the coagulation abnormalities. Other investigators have made similar observations (Table 2). No patient died of hemorrhage in these initial reports. There was a high relapse rate in these two studies (8 of 23 or 35% and 9 of 14 or 63%) when the all-trans retinoic acid was discontinued. In a subsequent report from the French investigators, 31 previously untreated patients with APL were given all-trans retinoic acid.85 Nineteen patients achieved CR; however, 12 died during induction after 3 to 20 days from central nervous system (CNS) bleeding (two patients, including one who had CNS bleeding at diagnosis), thrombosis (three patients of myocardial infarction, three patients of multiple strokes), intrapulmonary bleeding (three patients), and multiorgan failure (one patient). In 10 of these 12 patients abrupt leukocytosis developed (32,000 to 150,000/μL). Five of these 10 patients had leukocytosis at diagnosis (12,000 to 60,000/μL), whereas the remaining five were leukopenic (<4,000/μL). The investigators believe the thrombotic deaths were due to leukostasis and concluded that chemotherapy should be added to all-trans retinoic acid if the white blood cell count rises greater than 5,000 to 6,000/μL by day 5 or greater than 10,000/μL by day 10 of treatment to avoid bleeding and thrombosis. Only three additional patients in the published series have died due to hemorrhage or thrombosis. One 67-year-old woman died of a myocardial infarction and two patients with bleeding at diagnosis (hematuria in one and soft tissue in the other) died of intracerebral hemorrhage within 1 week of treatment with all-trans retinoic acid. Toxocities frequently observed include skin and mucosal dryness and elevations in both the serum cholesterol and triglyceride levels. Pseudotumor cerebri has been reported. As experience with all-trans retinoic acid has accumulated, a cardiorespiratory distress syndrome has been observed which includes fever, episodic hypotension, hypoxemia, pulmonary infiltrates, pleural or pericardial effusions, and congestive heart failure with impaired myocardial contractility.88 This syndrome has occurred both with and without the development of leukocytosis and postmortem examinations in several instances have shown pulmonary parenchymal infiltration with mature leukocytes. This syndrome appears to be particularly responsive to small doses of corticosteroids (dexamethasone 10 mg twice daily for 3 days). Wijermans et al89 found that cell differentiation in a myeloid direction induced by retinoic acid resulted in diminished procoagulant activity, without altering fibrinolytic activity. Monocytic differentiation induced by 1, 25 dihydroxy vitamin D3 led to resolution of proteolytic activity of the cell lysate that retained procoagulant activity. The validity of any of these approaches remains to be confirmed by prospective clinical trials. The optimal therapeutic strategy for the prevention and control of bleeding has not been established, in part because the mechanisms responsible for hemorrhage are not completely understood.

**PROPOSED APPROACH TO THE PATIENT WITH APL**

The hemostatic disorder associated with APL is complex. Predominant fibrinolysis appears to play a central role in some patients. The best treatment can only be determined by carefully designed prospective clinical trials randomizing patients at the time of diagnosis. If a patient is not participating in a clinical trial, we propose a management strategy based on clinical experience and the reported literature. All patients with fibrinogen levels less than 100 mg/dL with or without active bleeding are given cryoprecipitate to maintain the fibrinogen above this level without the routine use of prophylactic heparin. Platelets are transfused to maintain the platelet count above 20,000/μL in patients not actively bleeding and above 50,000/μL in patients actively bleeding. Fresh frozen plasma is administered to patients actively bleeding with prolonged PT and PTT, but not to patients without active bleeding. If there are persistently elevated or increasing FDPs or if the fibrinogen is difficult to maintain above 100 mg/dL, suggesting the coagulopathy is ongoing, heparin is administered at 500 U/h. The choice of this fixed initial dose is empiric due to the difficulty in using the PTT test for monitoring.

Because at present, we do not know what role DIC may play, we believe that it is prudent to use heparin if blood product replacement is not effective. The dose of heparin is adjusted according to the response of clinical bleeding as well as the fibrinogen and FDP levels. The platelet count is less valuable as an indication for heparin therapy because it not only may reflect consumption, but also marrow hypoplasia resulting from chemotherapy. If heparin is started, platelets are transfused to maintain the platelet count above 50,000/μL. In the presence of continued active bleeding while on heparin, we suggest the addition of an inhibitor of fibrinolysis such as tranexamic acid or epsilon-aminocaproic acid.

Several measurements are helpful in monitoring treatment progress. Platelet counts and fibrinogen levels are measured at short intervals after transfusion of platelets and cryoprecipitate, respectively, to determine whether a significant increment has been achieved. Subsequent levels are measured at 4- to 6-hour intervals to determine the platelet and fibrinogen half-lives. A 1-hour posttransfusion increment in the platelet count will help exclude alloimmunization, which is a frequent complication. Tests not helpful in monitoring include the PT, PTT, thrombin time, and prothrombin paracoagulation test. The D-dimer and the FDPs may be of some value. Because the D-dimer is formed by plasmin degradation of cross-linked fibrin, it is not seen in primary fibrinolysis where the substrate for plasmin degradation is fibrinogen and there is no thrombin formation; however, it will not distinguish predominant fibrinolysis from DIC.

A better understanding of this and other hemorrhagic diatheses will result from prospective controlled clinical
<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Dose</th>
<th>CR Rate</th>
<th>Median Time to CR in days</th>
<th>Toxicities</th>
<th>Coagulopathy/ No. of Patients</th>
<th>Blood Product Support</th>
<th>Response of Coagulopathy</th>
<th>Early Death Hemorrhage or Thrombosis/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al⁹⁵</td>
<td>24</td>
<td>45-100 mg/m²/d</td>
<td>23+/24 (96%)</td>
<td>53 (20-119)</td>
<td>Dryness of lips and skin, occasional headache, digestive symptoms</td>
<td>3/21†</td>
<td>†</td>
<td>Response within 7 d</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13/22</td>
<td>0/0/+/+3</td>
<td>Fibrinogen normalized between days 2-19 (median 8), FDPs disappeared between days 3-14 (median 4); first sign of clinical response</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/11</td>
<td>+/0/+0</td>
<td>Disappearance of coagulopathy was generally first sign of clinical response; rise in fibrinogen</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Castaigne et al⁹⁷</td>
<td>22</td>
<td>45 mg/m²/d</td>
<td>14/22 (64%)</td>
<td>34 (30-90)</td>
<td>Skin and mucosal dryness, hypertriglyceridemia, increase in hepatic transaminases, hyperleukocytosis, bone pain</td>
<td>0/0/+/+3</td>
<td>Fibrinogen normalized between days 2-19 (median 8), FDPs disappeared between days 3-14 (median 4); first sign of clinical response</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/21†</td>
<td></td>
<td></td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Warrell et al⁹⁸</td>
<td>11</td>
<td>45 mg/m²/d</td>
<td>9/11 (82%)</td>
<td>41 (24-53)</td>
<td>Leukocytosis, headache, nasal congestion; hypertriglyceridemia pseudomotor cerebri; skin rash</td>
<td>6/11</td>
<td>+/0/+0</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Wiernik et al⁹⁹</td>
<td>15</td>
<td>46 mg/m²/d</td>
<td>Normalization of blood counts; resolution of constitutional symptoms and splenectomy maturation in bone marrow</td>
<td>Normalization of blood counts, resolution of constitutional symptoms and splenomegaly; maturation in bone marrow</td>
<td>t</td>
<td>t</td>
<td>N/A</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Group</td>
<td>Dose Range</td>
<td>Response Rate (%)</td>
<td>Death Due to MI (%)</td>
<td>Course of Bone Pain, Dryness, Hyperleukocytosis</td>
<td>Death Due to Other Causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>------------</td>
<td>-------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lo Coco et al</td>
<td>Untreated</td>
<td>45-50 mg/m²/d</td>
<td>1 (80%)</td>
<td>1/1 (100%)</td>
<td>Bone pain, dryness, hyperleukocytosis (1 patient)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenaux et al</td>
<td>3 in 1st relapse</td>
<td>45 mg/m²/d</td>
<td>19/31 (62%)</td>
<td>12 induction deaths</td>
<td>Hyperleukocytosis</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creagh et al</td>
<td>Refractory</td>
<td>45 mg/m²/d</td>
<td>1/1 (100%)</td>
<td>0</td>
<td>Mild skin dryness; modest increase in cholesterol and triglycerides but within normal limits</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al</td>
<td>47 untreated</td>
<td>60-80 mg/d</td>
<td>47/50 (94%)</td>
<td>39 (25-70)</td>
<td>Dryness of mouth and lips hyperkeratosis; cutaneous infection</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: N/A, not applicable; +, given; 0, not given; FFP, fresh frozen plasma; Plts, platelets; Cryo, cryoprecipitate.

*The 24th patient required low-dose cytosine arabinoside to achieve CR.
†Not studied in three patients.
‡Not detailed.
§Chronic myelogenous leukemia-promyelocytic blast crisis.
‖Six patients required daunorubicin during induction with the all-trans retinoic acid starting between 4-20 days to control hyperleukocytosis.
||Myocardial infarction on day +20 of treatment.
#CNS bleeding in 2 patients (1 had same at diagnosis), myocardial infarction in 3 patients; multiple strokes in 3 patients; intrapulmonary bleeding in 3 patients, all between day 3-20 of treatment.
***Multivisceral failure.
††Clinical bleeding (24 severe); 16 laboratory evidence of DIC (19 definite; 6 equivocal).
‡‡Intracerebral hemorrhage in 2 patients within 7 days (both had bleeding at diagnosis); hematuria in 1 and soft tissue in the other.
trials randomizing patients at diagnosis to one of several regimens. These may include the use of aggressive blood product support (platelets, fresh frozen plasma, and cryoprecipitate) with and without heparin or antifibrinolytic agents (tranexamic acid, epsilon-aminocaproic acid, or aprotinin) or all-trans retinoic acid. Because APL is uncommon, these studies will likely require the collaboration of national cooperative oncology groups to accrue a sufficient number of patients. An international study initiated by the Eastern Cooperative Oncology Group randomizing patients to either all-trans retinoic acid or conventional chemotherapy as induction therapy in patients with previously untreated APL will soon be underway. Patients achieving a CR will receive consolidation chemotherapy and will then be randomized to maintenance therapy with all-trans retinoic acid or observation. The introduction of all-trans retinoic acid to the anthemorrhagic regimen in this kind of trial will provide a unique opportunity to study changes in abnormal coagulation parameters with both conventional chemotherapy and this putative differentiating agent.

Important information will have to be derived from additional studies of the markers of activation of coagulation and of fibrinolysis. These studies should include activation peptides, enzyme-inhibitor complexes, and degradation products. They serve as markers of the various biochemical steps shown in Table 3. Although the clinical utility of these tests are as yet unproven, careful evaluation of the results will likely lead to a better understanding of the pathophysiology of the coagulopathy associated with APL. Furthermore, they will also serve to monitor the clinical progress and effectiveness of therapy. The currently used routine coagulation tests such the PT, PTT, TT, and paracoagulation tests have not been useful in clarifying the mechanism of the coagulopathy. The information gained may have broader implications for coagulopathies encountered in other malignant diseases.

ACKNOWLEDGMENT

The authors thank Drs David Green, Sharon Murphy, and Peter Wiernik for their critical review of the manuscript as well as Marla Murray for her secretarial skill in manuscript preparation.

REFERENCES

18. Gralnick HR, Bagley J, Abrell E: Heparin treatment for the


88. R. Warrell: Personal communication

89. ECOG 2491: Phase III Randomized Trial at All-Trans Retinoic Acid Versus Cytosine Arabinoside and Daunorubicin as Induction Therapy for Patients with Previously Untreated Acute Promyelocytic Leukemia, 1992


From www.bloodjournal.org by guest on October 23, 2017. For personal use only.


From www.bloodjournal.org by guest on October 23, 2017. For personal use only.
Reassessing the hemostatic disorder associated with acute promyelocytic leukemia [see comments]

MS Tallman and HC Kwaan