High Incidence of Disseminated Intravascular Coagulation During Remission Induction of Adult Patients With Acute Lymphoblastic Leukemia


We determined the incidence and complications of disseminated intravascular coagulation (DIC) at presentation and during remission induction of previously untreated adults with acute lymphoblastic leukemia (ALL) or de novo Philadelphia chromosome-positive ALL (PCALL) seen at Memorial Hospital between January 1, 1978 and December 31, 1989. DIC was diagnosed in the presence of (1) low fibrinogen (≤ 160 mg/dL), (2) prolonged prothrombin time (PT) and falling fibrinogen, or (3) prolonged PT and positive fibrin split products (FSP). L-Asparaginase was not used during remission induction. Among adequately screened patients with ALL, DIC was detected in 7 of 58 (12%) before initiation of chemotherapy and in 35 of 45 (78%) during remission induction. DIC was not simply the result of infection because clinical and laboratory signs of infection were absent in 16 patients, whereas only 2 of the 22 febrile patients with DIC had positive cultures. Among the 38 patients with DIC at presentation or during remission induction, serious complications were seen in 13 in temporal association with DIC (pulmonary embolus in one, sagittal sinus thrombosis in three, and serious hemorrhage in nine) and were major factors in the deaths of three patients. Among the 10 patients with thorough screening but no evidence of DIC there was only one hemorrhage during the same time interval. In patients with PCALL, DIC was detected in 9% at presentation and in 80% during remission induction. We conclude that DIC is rare at presentation but common during remission induction of adult ALL and PCALL and may be associated with significant thrombotic and hemorrhagic complications. We suggest daily screening for DIC during the first 14 days of remission induction. The treatment of DIC in ALL and PCALL should be a subject of future clinical studies.

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DISEMINATED intravascular coagulation (DIC) is an important cause of bleeding and thrombosis in various benign and malignant diseases. The association of fibrinogenopenia with fatal hemorrhage in acute leukemia was first reported in 1935, 20 years before the recognition of DIC as a clinical entity. Subsequently, DIC was reported in 30% of all patients with an acute leukemia. The contribution of DIC to the early fatalities of acute promyelocytic leukemia (APL) led to the introduction of prophylactic heparin to induction regimens with subsequent decrease in early deaths and increase in complete remission rates. Others have achieved similar results with intensive use of fresh frozen plasma (FFP) and platelets, but without using heparin.

In 1975 Al-Mondhiry reported four cases of DIC without clinical complications during prednisone and vincristine induction of adult ALL patients at Memorial Hospital. Subsequently, DIC was detected in 4 of 11 cases of adult acute lymphoblastic leukemia (ALL), in 3 of 11 cases of adult T-cell lymphoma/leukemia, and in 1 of 17 pediatric ALL patients. Additional cases of DIC in ALL, adult T-cell lymphoma/leukemia, and leukemia Burkitt’s lymphoma have been published. Fatal hemorrhages have been reported in 6% of adult ALL patients during remission induction without mention of DIC, but we and others have not reported DIC or hemorrhages.

The low frequency of early hemorrhagic deaths in ALL has sustained the impression that DIC is neither a laboratory nor a clinical problem in adult ALL. This report demonstrates that although rare at presentation, DIC is very common during remission induction of adult ALL and is often associated with significant morbidity and mortality.

MATERIALS AND METHODS

Patient population, remission induction. All adult (age ≥ 18) untreated patients with ALL and Philadelphia chromosome-positive ALL (PCALL) seen for remission induction at Memorial Hospital between January 1, 1978 and December 31, 1989 were eligible for this study. There were 158 patients with ALL, but clinical records were incomplete in five patients, leaving 153 patients for analysis. Cytogenetic analysis was performed in 84 (abnormal in 20, but without Philadelphia chromosome), was unsuccessful in 29 (no mitoses), and was not obtained in 40 patients. There were 30 PCALL patients with karyotypes containing at least one Philadelphia chromosome but without a recognized chronic phase either before the diagnosis of ALL or after the induction of complete remission. The L-10, L-10M, L-17, L-17M, and L-20 protocols were used for the diagnosis and treatment of patients without L-asparaginase during the induction period.

The first day of induction is designated day 1.

Data collection. Records of all patients were reviewed for evidence of hemorrhage, thromboembolic disease, sepsis, acute or chronic hepatitis, heparin or coumadin administration, infection, antibiotic treatment, and laboratory hemostatic abnormalities. Autopsy reports were reviewed for pathologic evidence of thromboembolic disease, and all available autopsy slides were reviewed for microscopic evidence of DIC. Platelet counts were measured by an automated particle counter and were verified using phase-contrast microscopy with a hemocytometer. Prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) were assayed by standard methods. Fibrinogen (F) was measured as thrombin-coagulable protein, and fibrin split products (FSP) were measured by the Burroughs Wellcome Thrombo-Wellcotest.

From The Lymphoma-Leukemia Service, and the Pathology Service, Memorial Hospital, New York, NY.
Definition and treatment of DIC. The diagnosis of DIC was accepted when any of the following combinations of laboratory results were present in the absence of liver disease: (1) low fibrinogen (≤160 mg/dL) irrespective of the PT, aPTT, TT, and FSP. (2) Prolonged PT and rapidly decreasing fibrinogen. (3) Prolonged PT and positive FSP. These criteria are similar to those previously reported. In our series, fibrinogen levels in patients with DIC were comparable to those observed in patients with sepsis or septic shock (13). In addition, fibrinogen levels were normal in 10 patients who were febrile, but without a documented septic condition. In a group of 22 patients with DIC, fibrinogen levels were normal in 8 patients and increased in 3 patients. The median duration of DIC was 6.5 days (range 1 to 43), and in most cases it was detected during the first 2 weeks of remission induction (Fig 2).

Clinical complications were associated with DIC in 13 of 38 patients. Sagittal sinus thrombosis occurred in three patients: it was fatal in one (patient 33), and caused persistent seizures and hemiparesis in the other two patients (patients 9 and 15). One pulmonary embolus was associated with untreated DIC and fatal sepsis (patient 13). Serious hemorrhages were seen in nine patients. One clinically diagnosed pulmonary hemorrhage was confirmed at postmortem (patient 19). One central nervous system (CNS) hemorrhage was associated with untreated DIC, fibrinogen of 153 mg/dL, and a platelet count of 218,000/µL (patient 12); and another with partially treated DIC, fibrinogen of 142 mg/dL, and a platelet count of 193,000/µL (patient 21). One patient with a platelet count of 145,000/µL had recurrent epistaxis that was controlled with heparin and FFP (patient 5). A generalized hemorrhage with complete defibrination required heparin and FFP for control (patient 16). Gastrointestinal hemorrhage was seen in three cases (patients 7, 24, and 35, respectively). Profuse bleeding with platelet count varying between 85,000 and 105,000/µL led to the discovery of DIC in patient 25. DIC was partly responsible for 3 of 13 deaths occurring during remission induction (patients 13, 19, and 33).

We saw only one hemorrhage (menorrhagia, with platelet count of 14,000 to 28,000/µL) among the 10 screened patients without DIC. There were no sagittal sinus thromboses or CNS hemorrhages. Among the 108 patients without adequate screening there were three thromboses (one sagittal sinus thrombosis, two deep vein thromboses), two CNS hemorrhages (with platelet count of 33,000 and 180,000), and a pulmonary hemorrhage. In all cases the PT was prolonged, in a manner consistent with DIC, but incomplete hemostatic screening precluded the determination of the presence or absence of DIC in these patients.

DIC was managed with FFP in 4 of 38 patients, with heparin in 3 of 38 patients, and with a combination of FFP and heparin in 14 of 38 patients. A subarachnoid hemorrhage that occurred during the sixth day of heparinization resolved without neurologic deficits (patient 14).

De novo PCALL. Of the 30 patients with de novo PCALL, 11 were adequately screened at presentation and DIC was discovered in one (9%, patient 39). During remission induction 10 patients were adequately screened, and eight cases of DIC were discovered (80%, patients 40 through 47). Two patients had a normal platelet count at the time of diagnosis of DIC, but in one the platelet count fell below normal to a nadir of 123,000/µL on day 7 (patient 45). In the other (patient 44) the platelet count decreased from 395,000/µL at presentation to 230,000/µL on day 7 and increased to 450,000/µL at remission. In both of these cases the changes of the platelet count paralleled the
DIC IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

Anticoagulation was stopped in the remaining three patients, one of whom developed DIC during remission induction without any evidence of DIC. All five were anticoagulated before referral to Memorial Hospital and two remained heparinized during remission induction without any evidence of DIC. Anticoagulation was stopped in the remaining three patients, one of whom developed DIC during induction. The remaining two patients were not screened and did not suffer any additional thrombotic or hemorrhagic complications.

Table 1. DIC at Presentation and During Remission Induction of Adult ALL and PCALL

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<th>Patient No.</th>
<th>PT</th>
<th>APTT</th>
<th>TT</th>
<th>FSP</th>
<th>F</th>
<th>Platelets</th>
<th>Day</th>
<th>H</th>
<th>FFP</th>
<th>Nadir</th>
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<td>-</td>
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DISCUSSION

We undertook this study to establish the incidence and clinical significance of DIC during remission induction of adult ALL and PCALL. DIC may be defined as a syndrome arising from the systemic action of thrombin, whose effects on the coagulation system are used for diagnosis. Our criteria for the diagnosis of DIC are comparable to those of a recent series of patients with APL and depend heavily on changes in fibrinogen, and could not be accounted by leukemic progression or the administration of the cyclophosphamide on day 5. Major thromboses (three deep vein, one arterial, one pulmonary embolus) were the presenting sign of PCALL in five patients, but inadequate hemostatic investigation did not allow determination of the presence or absence of DIC. All five were anticoagulated before referral to Memorial Hospital and two remained heparinized during remission induction without any evidence of DIC. Anticoagulation was stopped in the remaining three patients, one of whom developed DIC during induction. The remaining two patients were not screened and did not suffer any additional thrombotic or hemorrhagic complications.
Table 2. Characteristics of Adult ALL Patients (median values)

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<td>26.6</td>
<td>28.6</td>
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<td>Bone marrow blasts (%)</td>
<td>84</td>
<td>86</td>
<td>86</td>
<td>86</td>
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<td>Serum albumin (g/dL)</td>
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<td>4.2</td>
<td>4.2</td>
<td>3.7</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
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<td>0.6</td>
<td>0.6</td>
<td>0.5</td>
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<tr>
<td>Alkaline phosphatase</td>
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<td>120</td>
<td>120</td>
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<td>LDH</td>
<td>571</td>
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low or decreasing fibrinogen levels and FSP. Because initial fibrinogen levels are elevated at presentation of patients with ALL our criteria probably underestimate the incidence of DIC. Others have demonstrated that the coagulopathy of ALL, defined by similar criteria, is often due to thrombin activation but only rarely to isolated primary fibrinogenolysis. Recently, an assay for prothrombin activation fragment 1.2 was used to prove that thrombin activation is universal during remission induction of pediatric ALL. L-asparaginase administration induces hemo-
static abnormalities mimicking DIC but we did not use L-asparaginase during remission induction. Low platelet count is not an absolute requirement for the diagnosis of DIC, and it is normal in as many as 11% of all patients with DIC (3% of acute and 50% of chronic). The frequency of normal platelet count in the DIC of ALL is well within this reported range.

We reached two conclusions with this study. First, DIC is rare at presentation but is very common during remission induction of adult patients with ALL and PCALL. The high incidence of DIC during remission induction cannot be attributed to a different patient population in 1988 and 1989. Screening for DIC during 1978 to 1987 was often initiated as a result of clinical complications, high LDH, or high white blood cell counts, but we have included this population in our series because it demonstrates that untreated DIC in ALL may be associated with serious morbidity and occasional mortality. Our current protocols for adult ALL require prospective screening for all patients and have confirmed the high incidence of DIC. Induction or exacerbation of DIC by chemotherapy has been published in case reports of ALL and may occur via the release of procoagulants present in lymphoblasts. Methods of detection, a less aggressive induction regimen, or both may account for the reported low incidence or for the absence of DIC during remission induction of ALL.

Second, we show that the diagnosis of DIC in a patient with ALL was not always benign: it was associated with serious thrombotic and hemorrhagic complications in 13 of 38 (34%) of the patients and was a major factor in 3 of 13 deaths during remission induction. In contrast, among the 10 screened patients without evidence of DIC there were no sagittal sinus thromboses or CNS hemorrhages, while one patient had mild menorrhagia with a very low platelet count. We cannot estimate the incidence of complications of untreated DIC from our retrospective study of variously treated patients. The difference in the clinical consequences of DIC in ALL and APL is due to the different severity of DIC in these disorders. Most patients with APL present with fulminant DIC (low fibrinogen and low platelets), which is further exacerbated by remission induction chemotherapy and, if untreated, often results in fatal hemorrhage. However, at presentation of ALL initial platelet counts are occasionally normal or high, initial fibrinogen

Fig 1. Patterns of hemostatic abnormalities during remission induction in adult ALL patients. (A) Patient 4; (B) patient 27; (C) patient 23; and (D) patient 5.

Fig 2. Cumulative occurrence of all DIC cases during remission induction of adult ALL patients. All cases of DIC occurring before day 1 of induction were plotted on day 1.
levels are normal or high and DIC rare, but it develops gradually during remission induction. The subacute nature with the observed frequency of normal platelet count at its initial diagnosis. The subacute nature with the observed frequency of normal platelet count at its initial diagnosis. We could not determine the optimal treatment of DIC in ALL. However, it should be kept in mind that with the exception of APL there are no studies in acute leukemia defining the point at which treatment of DIC should begin. Patients with congenital hypofibrinogenemia (but with otherwise normal coagulation systems) tolerate fibrinogen levels of 50 to 100 mg/dL without bleeding complications. Patients with abruptio placentae and DIC require fibrinogen levels >150 mg/dL for prevention of surgical bleeding.41 We have not been able to define a level of fibrinogen above which complications do not occur, and therefore we could not identify prospectively which patients can be safely observed. Many of our patients were safely treated with heparin and FFP, but either heparin or FFP alone were also effective. Future studies of DIC in adult ALL should address prospectively which patients can be observed and whether heparin should be administered to all or to some patients.

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