To the Editor:

Sarris et al have recently published results of a high incidence of disseminated intravascular coagulation (DIC) among acute lymphoblastic leukemia (ALL) adults during induction chemotherapy. The investigators conclude that DIC is common early after starting treatment and suggest daily monitorization for DIC in the first 14 days after beginning therapy.

We have observed transient severe hypofibrinogenemia ( < 100 mg/dL) in: (1) 1 of 34 ALL patients (2.9%) at diagnosis, and (2) 13 of 34 (38%) ALL patients in the first 14 days after starting chemotherapy. Preliminary results have been published elsewhere. All but three patients were 14 years old or over. L-asparaginase was not administered before hypofibrinogenemia development. Patients were treated with ALL protocols that include vincristine and prednisone ± daunorubicin in the first days of therapy.

To the Editor:

ACUTE LYMPHOBLASTIC LEUKEMIA: HYPOFIBRINOGENEMIA WITH A LOW INCIDENCE OF CLINICAL COMPLICATIONS IS OFTEN FOUND DURING INDUCTION REMISSION THERAPY

We have observed transient severe hypofibrinogenemia ( < 100 mg/dL) in: (1) 1 of 34 ALL patients (2.9%) at diagnosis, and (2) 13 of 34 (38%) ALL patients in the first 14 days after starting chemotherapy. Preliminary results have been published elsewhere.2 All but three patients were 14 years old or over. L-asparaginase was not administered before hypofibrinogenemia development. Patients were treated with ALL protocols that include vincristine and prednisone ± daunorubicin in the first days of therapy.
Hypofibrinogenemia developed between 8 and 20 days after beginning treatment and lasted between 1 and 18 days. Fibrinogen nadir ranged between 28 and 100 mg/dL (median: 74 mg/dL). During this nadir, fibrin split products (FSP) were positive in 5 of 13 patients and D-dimer (D-D) was positive in the two patients in which the test was performed. Factor dosification, antithrombin III, euglobulin lysis test, and ethanol test remained in the normal range in all patients.

These results are similar to those published by Sarris et al; in their series, 39% of patients had a fibrinogen nadir less than 100 mg/dL. Mechanisms of hypofibrinogenemia in this setting are unknown, but DIC and/or fibrinogen metabolism by other noncoagulative pathways are the two most plausible explanations. Hypofibrinogenemia caused by hyperfibrinolysis is not supported by data from the literature and the normal euglobulin lysis tests found in our patients. Moreover, the D-D positivity in the only two patients in whom the test was performed favors the DIC hypothesis, as it has been suggested in other reports.

Proportion of high-risk patients and time to complete remission were not different between those patients who were hypofibrinogenemic and those who were not (84% v 95% and 18.8 days v 20.7 days, respectively). Patients with abnormal liver biochemistry were observed as often among patients who developed hypofibrinogenemia as among those who did not (50% v 53%). Sepsis also is not a probable explanation for hypofibrinogenemia because, although several hypofibrinogenemic patients were febrile, no microbiologic blood cultures were positive in these patients.

Sarris et al also observed a high incidence of serious thrombotic and hemorrhagic complications among ALL patients who developed DIC. Yet, in our series no serious thrombotic or hemorrhagic events were seen. A low incidence of clinical manifestations of DIC in acute leukemia has been published. Moreover, a high incidence of DIC-associated thrombosis or hemorrhage in the specific setting of ALL induction remission has not been reported.

In summary, we have observed a high incidence of hypofibrinogenemia in ALL patients during remission induction therapy. We have not found the high morbidity-related hypofibrinogenemia reported by Sarris et al and, in our experience, hypofibrinogenemia in these patients seems to have little clinical significance. Yet, our study is retrospective and number of patients is small, so conclusions about clinical impact of hypofibrinogenemia during ALL induction remission must be drawn with caution.

REFERENCES


RESPONSE

We were pleased to read the letter of Solano et al confirming that disseminated intravascular coagulation (DIC) is rare at presentation (2.9% v 8% in our study, ref 2), but is more common during remission induction of adult acute lymphoblastic leukemia (ALL) (38% v 78% in our study). Several factors may account for the different frequencies of DIC observed in the two studies. Solano et al reported severe hypofibrinogenemia (<100 mg/dL). We reported DIC whose diagnosis was made in the presence of low fibrinogen (<160 mg/dL) or in the presence of normal fibrinogen (≥160 mg/dL) in 4/7 patients at presentation and in 7/38 patients during remission induction. Severe hypofibrinogenemia (<100 mg/dL) was equally common in both series at presentation (2.8% v 5%) or during remission induction (38% v 31%). The clinical significance of DIC was doubted by Solano et al because no hemorrhagic or thrombotic complications were seen in 13 patients with hypofibrinogenemia. However, it is unclear if these patients received heparin, fresh frozen plasma, or cryoprecipitate. Obviously, if the coagulopathy was treated it is not surprising that complications were not seen and, as they admit, only limited conclusions that can be based on 13 patients. In addition, the clinical severity of chemotherapy-induced DIC may depend on the patient population and the intensity of the remission induction regimen. We have shown that the DIC of ALL is not always benign and that it may be associated with serious complications. Neither we nor Solano et al can state the incidence of complications of untreated DIC of ALL. In fact this is only known for acute promyelocytic leukemia (APL). Our retrospective cohort of patients with DIC includes patients who were selectively screened between 1978 and 1987 because of high LDH, elevated white blood cell count, or thrombohemorrhagic complications (Table 2, ref 2). This selection bias partly accounts for the high incidence of complications and does not reflect their incidence in the course of untreated DIC during remission induction of ALL. However, as we have stated, the DIC of ALL is subacute and not as severe as the DIC of APL. Therefore, prophylactic treatment for DIC in ALL is not necessary as it is in APL, and can be started at the time DIC is diagnosed. Even then, 21 of 47 of our patients with DIC were observed without any treatment (Table 2, ref 2). However, at present we cannot identify prospectively the patients with DIC that...
can be observed without treatment and without risk of complications. Future studies are needed to define prospectively the patients who need treatment and to determine if the treatment should be fresh frozen plasma, heparin, or both.

ANDREAS H. SARRIS  
MD Anderson Cancer Center  
Section of Lymphoma  
Houston, TX  
SANFORD KEMPIN  
The Desert Hospital  
Comprehensive Cancer Center  
Palm Springs, CA  

REFERENCES  