

HYPERCOAGULABILITY DURING INDUCTION THERAPY OF ACUTE LYMPHOBLASTIC LEUKEMIA IS OF SCARCE CLINICAL RELEVANCE

To the Editor:

Recently Sarris et al¹ and Solano et al² claimed a high incidence of disseminated intravascular coagulation (DIC) during the remission induction in adult patients with acute lymphoblastic leukemia (ALL) before any treatment with L-asparaginase. Sarris et al¹ found low fibrinogen levels (<160 mg/dL) in 31 of 45 patients (68%), with severe hypofibrinogenemia (<100 mg/dL) in 14 (31%). Venous thromboembolism or hemorrhagic complications occurred in 4 and 9 cases, respectively. Solano et al,² even in the absence of clinical complications, found hypofibrinogenemia (<100 mg/dL) in 13 of 34 patients (38%). Nevertheless, both series lack a thorough investigation of markers of hypercoagulability and fibrin split products were positive only in 10 of 79 total patients (12%), so that the assumption of DIC as main underlying cause of hypofibrinogenemia is questionable.

We studied prospectively 50 ALL consecutive adult patients treated according to the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) ALL 0288 trial: vincristine 2 mg/m² intravenously (IV) days 1, 8, 15, 22; daunorubicin 40 mg/m² IV days 1, 8, 15; prednisone 60 mg/m²/d from day 1 to day 14 and 40 mg/m²/d from day 15 to day 31; *Escherichia coli* L-asparaginase 6,000 U/m²/d subcutaneously (SC) from day 15 to day 21; cyclophosphamide, randomly assigned, at the daily dose of 800 mg/m² IV days 1 and 2. The effects of L-asparaginase on the hemostatic system (with or without supplementation of antithrombin III concentrate) have been reported elsewhere.^{3,4} In our studies the basal values before administration of L-asparaginase were obtained at the day 15 of the induction protocol; thus, we evaluated coagulation activation after 2 weeks of chemotherapy (without L-asparaginase), similarly to Sarris et al¹ and Solano et al.² We considered the following parameters: fibrinogen <160 mg/dL, a value <65% for antithrombin III activity, protein C activity, protein S total and free antigen, plasminogen activity, α -2-antiplasmin activity, fibrinopeptide A (FpA) >2.5 μ g/L (nv < 2.5), thrombin-antithrombin complexes (TAT) >4 μ g/L (nv 0.7 to 3.7), prothrombin fragment 1 + 2 (F1 + 2) >1.2 nmol/L (nv 0.44 to 1.1), D-dimer (D-D) >150 μ g/L (nv 33 to 124) (Table 1).

Hypofibrinogenemia (<160 mg/dL) (range 79 to 156, median value 126) was found in 12 patients (24%), with a concomitant increase in one or more signs of hypercoagulability in half of them (Table 1). Only two patients (4%) had fibrinogen <100 mg/dL. The other 38 patients had fibrinogen >160 mg/dL (range 160 to 560, median value

250), with an isolated alteration of at least one marker of hypercoagulability in 21 of them. However, an increase in two or more indices suggesting a prothrombotic state was found only in nine patients (two with hypofibrinogenemia) (18%) (Table 1).

Decreased levels of plasminogen or α -2-antiplasmin were found in 10 patients (20%), but in none of them was a concomitant hypofibrinogenemia present. No patient had decreased levels of antithrombin III, protein C, or protein S. No thrombotic episode or major hemorrhagic complication was recorded during the first 2 weeks of chemotherapy, before L-asparaginase was started.

Therefore, the blood coagulation activation during remission induction with vincristine + daunorubicin + prednisone \pm cyclophosphamide in our experience does not induce severe laboratory alterations and its meaning is questionable, being not related to the presence or the absence of hypofibrinogenemia. Moreover, only a minority of patients showed an alteration of at least two indices of hypercoagulability. Finally, in our patients no thrombosis or major hemorrhage occurred before L-asparaginase, in contrast with the data of Sarris et al.¹ We conclude that chemotherapy not including L-asparaginase in adult patients with ALL can induce a hypercoagulable state but not severe enough to lead to severe laboratory alterations or clinical manifestations in the majority of cases; a similar conclusion has been recently claimed also for patients with acute myelogenous leukemia (AML).⁵ We point out that the thrombotic risk in ALL patients seems mainly caused by the hypercoagulable state after the administration of L-asparaginase: in this series 2 patients (of the 25 not receiving antithrombin III concentrate) developed venous thrombosis after *E coli* L-asparaginase.³ Moreover, in a previous ret-

Table 1. Results Obtained in 50 ALL Adult Patients After 15 Days of Induction Chemotherapy (Without L-asparaginase)

FpA or TAT or F1 + 2 or D-D	FBG < 160 mg/dL	FBG > 160 mg/dL	Total
Increased parameters:			
One	4	14	18
Two or more	2	7	9
N FpA, TAT, F1 + 2, D-D	6	17	23
Total	12	38	50

Abbreviations: FBG, fibrinogen; N, normal.

rospective study on the GIMEMA ALL 0288 trial 10 of 238 patients (4.2%) developed thrombosis (fatal in five cases) during or shortly after L-asparaginase.⁶

V. DE STEFANO
L. GUGLIOTTA
M.G. MAZZUCCONI
G. LEONE

F. MANDELLI

*For the GIMEMA,
Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto
(Chairman: F. Mandelli)
Rome, Italy*

REFERENCES

1. Sarris AH, Kempin S, Berman E, Michaeli J, Little C, Andreeff M, Gee T, Straus D, Gansbacher B, Filippa D, Glaser B, Clarkson B: High incidence of disseminated intravascular coagulation during remission induction of adult patients with acute lymphoblastic leukemia. *Blood* 79:1305, 1992
2. Solano C, Lopez J, Gomez N, Fernandez-Ranada JM: Acute lymphoblastic leukemia: Hypofibrinogenemia with a low incidence of clinical complications is often found during induction therapy. *Blood* 80:1366, 1992
3. Leone G, Gugliotta L, Mazzuconi MG, De Stefano V, Mattioli Belmonte M, Dragoni F, Specchia G, Centra A, Gamba G, Camera A, Mandelli F: Evidence of a hypercoagulable state in patients with acute lymphoblastic leukemia treated with low dose E. Coli L-asparaginase: A GIMEMA study. *Thromb Haemost* 69:12, 1993
4. Gugliotta L, Mazzuconi MG, Leone G, Mattioli Belmonte M, De Stefano V, Defazio D, Annino L, Mandelli F: E. Coli L-asparaginase related haemostatic abnormalities in adult acute lymphoblastic leukaemia patients. Role of antithrombin concentrates. 24th Congress of the International Society of Haematology. *Br J Haematol* (Congress suppl), 1992, abstr 632
5. Velasco F, Torres A, Rojas R, Alvarez MA, Gomez P, Castillo D: Increase in the D-dimer levels during treatment in patients with acute myelogenous leukemia. *Haemostasis* 22:117, 1992
6. Gugliotta L, Mazzuconi MG, Leone G, Mattioli Belmonte M, Defazio D, Annino L, Tura S, Mandelli F, the GIMEMA Group: Incidence of thrombotic complications in adult patients with acute lymphoblastic leukaemia receiving L-asparaginase during induction therapy: A retrospective study. *Eur J Haematol* 49:63, 1992