

## IRRELEVANT HEMOSTATIC TOXICITY OF ERWINASE AT INTERMEDIATE DOSE IN ADULT PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA: PRELIMINARY DATA

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### ABSTRACT

The hemostatic toxicity of low dose L-asparaginase by *Erwinia Carotovora* (Erwinase) has been reported to be negligible in adult patients with acute lymphoblastic leukemia (ALL), conversely no consistent data have been obtained when Erwinase is administered at intermediate dose. We report the preliminary clinical and laboratory hemostatic data of 10 adult patients with ALL treated during the induction phase with intermediate dose of Erwinase (20.000 IU/m<sup>2</sup>/s.c. every other day, for a total of six administrations). No thrombotic or hemorrhagic events have been registered and the mean values of PT, aPTT, fibrinogen, antithrombin and D-dimer did not change during the treatment. Only one patient showed a decrease of antithrombin (48 % on day VIII) requiring transitory withdrawal from Erwinase therapy. These data suggest that also intermediate doses of Erwinase have irrelevant hemostatic toxicity in adult patients with ALL.

Key words: L-asparaginase, leukemia, antithrombin

Both low and high dose of L-asparaginase (L-Ase) by *Erwinia Carotovora* (Erwinase) have been shown weakly toxic for the hemostatic system of children with acute lymphoblastic leukemia (ALL).<sup>1-3</sup>

In adult patients Erwinase, administered at low dose, (6000 IU/m<sup>2</sup>/day x7 days), induces minor changes of the hemostatic system, yet to a lower degree than that induced by E. Coli L-Ase.<sup>4</sup> Recently a pilot study has demonstrated that Erwinase administered at intermediate dose (10000IU/m<sup>2</sup>/day x 7 days) had resulted in the impairment of the hemostatic system similar to E. Coli L-Ase.<sup>5</sup>

In this paper we prospectively studied 10 adult patients with ALL, treated according to the L-20 modified regimen, in order to investigate the effect on the hemostatic system of intermediate dose of Erwinase (20000 IU/m<sup>2</sup> on alternate days x6 administrations).

### Materials and Methods

#### Patients

Ten patients, 5 males and 5 females, 31 years mean age at diagnosis (range 16-49), affected by ALL, were enrolled into the study at the Hematology Institute "L. e A. Seràgnoli" in Bologna from June 1992 to December 1993.

At diagnosis the mean values  $\pm$  1SD of the following parameters were: hemoglobin 10.2 $\pm$ 2.6 g/dL; white blood cells 37.8 $\pm$ 49.6 $\times$ 10<sup>6</sup>/L (median value 11.7 $\times$ 10<sup>6</sup>/L); platelets 92 $\pm$ 78 $\times$ 10<sup>9</sup>/L; albumin 4.3 $\pm$ 0.5g/L; prothrombin ratio 1.04 $\pm$ 0.08; activated partial thromboplastin time 0.94 $\pm$ 0.14; fibrinogen 324 $\pm$ 169 mg/dL; antithrombin III 83 $\pm$ 2%; D-dimer 134 $\pm$ 28 ng/mL.

#### Therapy

In the induction phase, the modified L-20

protocol is scheduled as follows: vincristin 2 mg/m<sup>2</sup>/day on days 1, 8, 15, 22, 29; cyclophosphamide 1000 mg/m<sup>2</sup> on day 4 and 600 mg/m<sup>2</sup> on day 34; prednisone 60 mg/m<sup>2</sup>/die from day 1 to day 30; doxorubicin 20 mg/m<sup>2</sup>/day on days 16, 17, 18 and 30 mg/m<sup>2</sup>/day on day 34; L-asparaginase (Erwinase) 20000 IU/m<sup>2</sup>/48 hours on days 5, 7, 9, 11, 13, 15.

The transfusional support consisted of packed red cells when hemoglobin was less than 8g/dl, platelet concentrates when platelet count was less than 20×10<sup>9</sup>/L and fresh frozen plasma when antithrombin was <50% and/or fibrinogen value below 50 mg/dL.

### Samples

Venous blood samples were collected in 3.8% sodium citrate (9 vol:1 vol) immediately before the administration of the first L-Asp dose (day I) and on days IV, VIII, XI, XV, XIX.

### Laboratory tests

Platelet counts, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were determined by standard methods. Fibrinogen was measured by immunodiffusion (M-Partigen, Behringwerke AG, Marburg, G).

Antithrombin activity was measured spectrophotometrically using a commercially available kit (Kabi, Stockholm, Sweden). Plasma D-dimer was measured by a commercial enzyme-linked immunoassay (Dimertest EIA kit, Agen Biomedica, Acacia Ridge, Australia).

### Statistical analysis

Statistical analysis was performed using a statistical software package (SOLO) distributed by BMDP Statistical Software Inc, Los Angeles, USA. For each parameter the variance within the group of patients was calculated. Comparisons among the groups of patients and controls were evaluated by the Student's T-test.

### Results

All patients received the six administrations of Erwinase as scheduled. Only one patient had a temporary interruption (10 days) of therapy after the third Erwinase infusion as a consequence of decreased antithrombin (48%) and fibrinogen (106 mg/dL) plasma levels. No patients had thrombotic complications throughout the period of observation.

In Table 1 are reported the mean values±1SD

Table 1. Laboratory parameters in 10 adult ALL patients receiving Erwinase. PT ratio = prothrombin time ratio; aPTT ratio = activated partial thromboplastin time ratio; FBG = fibrinogen; ATIII = antithrombin; D-D = D-dimer; ALB = albumin; PLT = platelets. Normal range is reported with each parameter.

	Days						F value	P value
	I	IV	VIII	XI	XV	XIX		
PT ratio (0.90-1.10)	1.08±0.08	1.08±0.08	1.09±0.08	1.09±0.06	1.06±0.08	1.03±0.08	0.72	N.S.
aPTT ratio (0.79-1.15)	0.88±0.02	0.89±0.14	0.89±0.14	0.89±0.13	0.85±0.09	0.86±0.12	0.19	N.S.
FBG mg/dL (200-400)	187±85	174±72	143±55	136±48	168±81	251±175	1.72	N.S.
ATIII % (80-120)	100±12	93±13	89±18	88±15	92±14	99±18	1.00	N.S.
D-D ng/mL (31-195)	160±35	180±74	155±84	143±75	168±55	150±63	0.82	N.S.
PLT 10 <sup>9</sup> /L (150-400)	101±80	167±89	142±82	143±87	145±80	136±66	0.64	N.S.
ALB g/L	3.9±0.1	4.0±0.2	4.0±0.3	4.0±0.8	3.8±0.2	3.9±0.5	0.83	N.S.

of the hemostatic parameters and plasma albumin of the 10 studied patients. The values were not significantly different from normal values before Erwinase therapy. Furthermore, no significant changes of the same parameters have been observed during Erwinase treatment compared to basal values. However, it should be stressed that fibrinogen ranged from 100 to 130 mg/dL in 5 out of 10 patients between days VIII and XI of Erwinase treatment. As shown in Figure 1 antithrombin was always higher than 80% at baseline and subsequently over 70% in all patients but one: in this patient a plasma level of 48% was in fact detected on day VIII and consequently interruption of Erwinase administration and infusion of fresh frozen plasma were done.

### Discussion

This study shows that Erwinase treatment at intermediate dose has little hemostatic toxicity in adult patients with ALL treated according to the modified L-20 protocol during the induction of complete remission phase. In fact, only 1 out of 10 patients had a significant reduction of antithrombin level together with low fibrinogen levels on day VIII. In this case it was felt safer to stop drug administration and to infuse fresh

frozen plasma. After a quick antithrombin level normalization, the Erwinase treatment started again 10 days later without further complications.

In a recent study of Castaman and Rodeghiero a daily administration of Erwinase at a lower total dose than that used in our study (70.000 IU/m<sup>2</sup> vs 120.000 IU/m<sup>2</sup>) resulted in a high hemostatic toxicity inducing a deep venous thrombosis in one patient and a significant reduction of the antithrombin and fibrinogen plasma levels.<sup>5</sup> To explain this discrepant data we hypothesize that Erwinase if administered at intervals higher than 24 hours results less toxic for the hemostatic system.

Noteworthy the recent experience of the Italian Cooperative Group AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) in children with ALL has shown that Erwinase administered weekly at high dose (25.000 IU/m<sup>2</sup>) had no significant hemostatic toxicity.

In a previous series of adult ALL patients, treated according to the modified L-20 protocol, we observed a relevant impairment of the hemostatic laboratory parameters, with particular reduction of the natural anticoagulant inhibitors<sup>6,7</sup> when we used E. Coli L-Ase at the same dose and the same intervals as scheduled

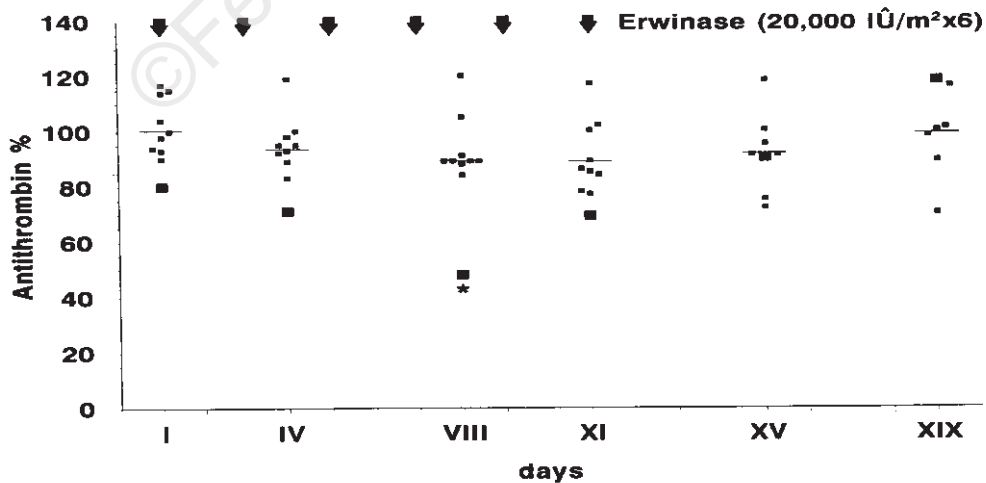


Figure 1. Antithrombin plasma levels in adult ALL patients receiving Erwinase. The bigger square represents a patient who stopped Erwinase infusion on day VIII (\*) and received plasma infusion.

in the present study (20000 IU/m<sup>2</sup> on alternate days for a total of six administrations). Thus, although our present results can not be compared with those obtained in a historical series of patients, it could be hypothesized that L-Ase by *Erwinia* induces lower hemostatic toxicity respect to *E. Coli* L-Ase, mainly with regard to the reduction of antithrombin levels. Moreover, the results of a recent study in adult ALL patients using low dose Erwinase (GIMEMA trial 0288) support this hypothesis.<sup>4</sup>

Analysis of larger group of patients within a controlled randomized trial will be useful to evaluate the hemostatic toxicity of Erwinase and to optimize dose and interval infusion in ALL patients.<sup>8</sup>

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