

Five patients relapsed at different points (from 8 to 27 months) of CR. In three of them (n. 4, 8 and 9) consistent PCR-positivity was observed during 10, 20 and 15 months before relapse. One patient (n. 11) was not studied during the 4 months before relapse. Thus, no patient relapsed after durable PCR-negativity.

We believe that durable PCR-negativity for the *AML1-ETO* transcript in CR is a good prognostic sign. Perhaps patients with durable PCR-negativity do not need frequent quantitative testing but conversion from durable PCR-negativity to positivity in at least two assays needs to be checked by quantitative assay.

Combination qualitative and quantitative RT-PCR might be reasonable for monitoring MRD in the t(8;21) AML. To confirm this conclusion and our suggestion for frequent monitoring a larger series of patient must be studied. Studies of PB, as an alternative to BM, for frequent testing is of current interest. This strategy also needs further investigation.

Elena W. Fleischman,\* Julia A. Baturina,\* Olga I. Sokova,\* Aleksander V. Popa,\* Inna S. Kosorukova,\* Janet D. Rowley\*

\*Russian Cancer Research Center, Moscow; °Department of Medicine, University of Chicago, IL, USA

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Correspondence: Elena W. Fleischman, MD, Russian Cancer Research Center, Moscow, Russia. E-mail: elefle@rol.ru

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### T-immunophenotype is associated with an increased prevalence of thrombosis in children with acute lymphoblastic leukemia. A retrospective study

We retrospectively evaluated the prevalence of symptomatic thrombotic events in a group of 2,318 children with acute lymphoblastic leukemia (ALL) and found that it was 0.95%. The prevalence of thrombotic events in the patients with T-ALL was significantly greater than in the patients with non-T-ALL.

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Thrombosis is a frequent complication in children with acute lymphoblastic leukemia (ALL). The reported incidence ranges from 2.4% to 11.5%.<sup>1-3</sup> The etiopathogenesis of this complication is thought to be multifactorial: a pro-thrombotic effect of leukemic cells, genetic predisposition, central venous catheters, septic complications and use of drugs such as steroids and L-asparaginase (L-Asp) have all been implicated.<sup>1-4</sup> Previously we reported a greater amount of thrombin generation, especially in children with T-ALL.<sup>5</sup>

The aim of this study was to evaluate the prevalence of symptomatic thrombotic events in a cohort of ALL children treated according to the AIEOP (*Associazione Italiana di Ematologia ed Oncologia Pediatrica*) ALL '91 and '95 studies, including L-Asp combined with prednisone during induction therapy,<sup>5</sup> and to examine the role of the T-ALL immunophenotype in this phenomenon.

Symptomatic thrombotic events were retrospectively evaluated by means of a questionnaire sent to each of the 43 AIEOP centers. Data were collected about the number, type and time of occurrence of the thrombotic events, the biological and immunologic features of each case, as well as the patients' clinical characteristics. Twenty-seven centers out of 43 (63%) answered and returned their questionnaires. Data were expressed as percentage, mean and median values and analyzed by Fisher's exact test and the Mann Whitney U test.

Out of a total of 2,318 ALL cases considered, 22 symptomatic thrombotic events (0.95%), confirmed by appropriate imaging methods, were reported in 22 patients (13 males and 9 females, mean age 8 years, range 3-16 years). The thrombotic events were: 11 cerebral venous thromboses, 10 deep venous thromboses (1 of the superior vena cava, 3 of the subclavian vein, 4 of the femoral vein, 2 of the popliteal vein) and one case of pulmonary thromboembolism. The main characteristics of the study population are reported in Table 1. In all cases family history for thrombosis was negative. Seventeen thrombotic events (77%) were reported during induction, 4 during re-induction and 1 during consolidation. The immunophenotype subgroups were T-ALL (n=6), common (n=13), pre-B (n=2), and pre-B (n=1). The prevalence of thrombotic events in the T-ALL patients was significantly higher than in the non-T-ALL patients [6/269 (2.23%) vs 16/2049 (0.78%);  $p < 0.05$ ]. Five thromboses in the T-ALL patients occurred during induction and 1 during consolidation. The prevalence of thrombotic events during the induction phase in T-ALL patients was still higher than in the non-T-ALL patients [5/269 (1.86%) vs 12/2049 (0.58%);  $p < 0.05$ ]. Moreover, T-ALL patients had a higher number of white blood cells at the onset of the disease than did non-T-ALL subjects (median values: 26,100/mm<sup>3</sup> and 6,330/mm<sup>3</sup>, respectively;  $p < 0.05$ ).

*E. Coli* L-Asp was used in 9/22 cases (Crasnitin® in 7 cases and Medac® in 2 cases), *Erwinia* L-Asp was used in 10/22 cases and for 3/22 cases the L-Asp source was not reported. Ten of the 22 events were reported in subjects with a central venous line (CVL). However, the influence of these two latter risk factors (L-Asp and CVL) was not evaluated because no information was obtained on their presence in the group of

**Table 1. Main characteristics of the study population.**

	Subjects with symptomatic thrombosis	Subjects without symptomatic thrombosis
No. (% of total)	22 (0.95)	2296
Age (y, mean)	8	n.e.
Sex	13 M 9 F	n.e.
Family history	Negative	n.e.
T-ALL (% of total T-ALL)	6 (2.23)	263
Non-T-ALL (% of total non-T-ALL)	16 (0.78)	2033
Presence of CVL	10	n.e.
*Factor V Leiden	1	n.e.
*Prothrombin mutation	1	n.e.
*MTHFR mutation	5	n.e.

\*Data from only 14 cases out of 22. n.e.: not evaluated

patients without thrombosis. In the light of recent reports,<sup>6</sup> tests for genetic prothrombotic polymorphisms were performed in 14 of the 22 cases. Fifty percent of the investigated cases (7 out of 14) had thrombophilic risk factors, as reported by others:<sup>2</sup> one patient was heterozygous for factor V G1691A mutation (7%), one patient had the heterozygous prothrombin G20210A variant (7%), while 5 exhibited the TT 677 MTHFR genotype (36%). These prevalence rates were not different from those that have been previously reported in a control group of healthy Italian subjects,<sup>5</sup> except for the MTHFR genotype which was more frequent and whose prothrombotic role is still debated.<sup>7</sup> None of the patients with thrombosis had concomitant liver or renal insufficiency, sepsis or shock.

Our results show that the prevalence of thrombotic events is higher in children with T-ALL than in children with other ALL immunophenotypes. Previously we found that the T- cell subtype of ALL might represent an additional risk factor for thrombosis because of the greater amount of thrombin observed to be generated in these cases.<sup>5</sup> This activated blood coagulation may involve the action of T lymphoblast cells and other mononuclear cells producing cytokines, such as tumor necrosis factor- $\alpha$ , interferon  $\gamma$ , and interleukin-1.<sup>8-10</sup> In conclusion, our data suggest that children with T-ALL may have an increased risk of thrombotic complications. Additional prospective clinical and biological studies are currently in progress to establish the specific mechanisms underlying this phenomenon.

Paola Giordano, Nicola Santoro, Giovanni Carlo Del Vecchio, Carmelo Rizzari,\* Giuseppe Masera,\* Domenico De Mattia

Dipartimento di Biomedicina dell'Età Evolutiva, University of Bari, Italy; \*Clinica Pediatrica, University of Milano-Bicocca, Monza, Italy

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**Correspondence:** Domenico De Mattia, MD, Dipartimento di Biomedicina dell'Età Evolutiva, University of Bari, Policlinico, P.zza G. Cesare 11, 70124 Bari, Italy. Phone: international +39.80.5592276. Fax: international +39.80.5592290. E-mail: demattia@biotaev.uniba.it

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