Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia in children with associated genetic conditions other than Down's syndrome. The AIEOP experience

We retrospectively reviewed the databases of seven studies on acute lymphoblastic leukemia (ALL) by the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) to identify patients with associated genetic disease, other than Down's syndrome. Forty-two patients were reported to have associated genetic conditions that included β-thalassemia (n=10), ataxia-telangiectasia (n=5), neurofibromatosis (n=3), Sotos syndrome (n=2) and other individual conditions. Patients with ataxia-telangiectasia, all with T-cell ALL, had a higher frequency of adverse events.

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Constitutional molecular defects may play a role in oncogenesis, and 7.2% of patients with cancer have a confirmed (3.9%) or suspected (3.3%) syndrome.[1] Some genetic abnormalities make children prone to develop acute lymphoblastic leukemia (ALL), and it is are that the presenting features and treatment outcome are influenced by the underlying condition.[1,2]

Over 20 years the Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP) enrolled 6,695 patients into seven studies: ALL-79, ALL-82, ALL-87, ALL-88, ALL-91, ALL-95, (age ≥15 years), AIEOP-BFM-ALL-2000 (≥18 years).[3] We extracted from the database all cases in which an associated genetic disease, other than Down's syndrome, had been reported. Additional information on these patients was obtained from their physicians.

Forty-two patients (0.62%) were reported to have an associated genetic condition. The incidence was higher in studies 95 and 2000, (24/2,739; 0.88%) in which this information was specifically requested, than before (18/3,932; 0.46%) (p=0.27). In the same studies, Down's syndrome was reported in 127 patients, of whom 55 were enrolled in the 95 and 2000 studies. Associated conditions were: β-thalassemia major (n=10);[4] ataxia-telangiectasia (AT, n=5); G6PDH deficiency (n=4); neurofibromatosis (n=4); Sotos syndrome (n=2); deficiency of coagulation factor VIII (n=2), V, X, or XII; cystic fibrosis;[5] Bloom, Noonan, Prader-Willy, Duane, and West syndromes, familial deafness, myelomeningocele + renal agenesia; polycystic kidney, spinal amyotrophy; X-linked agammaglobulinema; common variable immune deficiency; other unspecified condition: one case each. These patients' gender, age, immunophenotype, leukocyte count, and central nervous system (CNS) disease were not significantly different from those of the remaining patients with ALL. Response to steroid prephase was good in 31/33. By the end of induction therapy one patient had died, two were resistant, and two were not evaluable because of treatment modification. Of the 37 who achieved complete remission, ten had an adverse event: one remission death, one major toxicity, and eight (21.6%) relapses.

In this study we addressed the issue of an association between ALL and a genetic disorder other than Down's syndrome. Since this was not prospectively screened in an epidemiological study, the 0.62% incidence cannot be taken as a reliable estimate; the level of response may have been variable, as suggested by the 0.88% incidence in the most recent studies in which a specific query was introduced in the registration form. As expected, many different conditions were observed in association with ALL. The largest group consisted of patients with β-thalassemia, not unexpectedly given the 1-2% prevalence of heterozygotes in Italy. In this series, patients with β-thalassemia could be treated according to current ALL-directed regimens; application of such regimens did not induce unexpected toxicities, and the patients' treatment outcome was comparable to that of the general ALL population. Thus no special indication appears necessary for the treatment of such patients who may enter current ALL trials.

Table 1. Details on presenting features, treatment feasibility and outcome in five patients with ataxia-telangiectasia and T-cell acute lymphoblastic leukemia.

	Gender/ Age (yrs)	WBC/ mm³	Risk group Study	Response to steroid	CR after induction	Present status
1	F/6.3	7,000	SR-7901	good	Yes	Dead of infection in CR, month +6
2	F/11.4	5,600	HR-7903	good	Yes	Dead in CR1 at 14 months
3	M/4.1	46,800	HR-7903	good	Yes	Relapse 34 months, lost to follow-up
4	F/16.2	23,580	IR-9502	good	Yes	CR1, 8+ years
5	F/5.9	120,770	IR-9502	good	No	Off study

SR: standard risk, IR: intermediate risk, HR: high risk. CR: complete remission.

We found five patients with AT, characterized by cerebellar ataxia, telangiectases, and immune defects. In a prospective study of 161 AT families and 1,599 adult blood relatives, cancer rates were significantly higher among the subgroup of 294 blood relatives heterozygous for the AT gene than in their spouses. Estimated odds ratios for risk of cancer among heterozygotes versus non-carriers were 3.8 in men and 3.5 in women (5.1 for breast cancer).[6] A high prevalence of genomic ATM alterations was reported in childhood ALL,[7,8] loss of heterozygosity and protein deficiency in adult ALL.[9] A minimum frequency of a single AT gene in the USA white population was estimated to be 0.0017. In England, the birth frequency of AT was 1:300,000.

All of our five AT patients had T-lineage ALL, usually observed in 12% of patients, reflecting non-random mechanisms of leukemogenesis. AT carriers, defined by truncating mutations, were 12.9 times more frequent in 39 cases of childhood T-cell ALL than in normal population (p=0.004). The three missense variants were 4.9-fold more prevalent than in the normal population (p=0.03).[10] Thus, the association between missense alterations in the ATM gene and T-cell ALL appears non-random.

Remarkably, four of our five patients with AT had an adverse event (Table 1): one with hyperleukocytosis, despite an initial prednisone-good response, failed to achieve complete remission; two responders died of infection on therapy, another relapsed soon after comple-

tion of treatment, and only one patient remains in long-lasting complete remission. Thus, although made in a very limited number of patient, the finding that most children with AT in this series had an adverse outcome may suggest that the intensity of post-induction consolidation therapy should be reduced in these patients.

In conclusion, although this is not an epidemiological study, we found that patients with genetic conditions other than Down's syndrome, which sometimes go unrecognized before leukemia, are included in childhood ALL studies. ALL occurring in patients with AT is preferentially of T-lineage and may require specific treatment modification. Specific treatment modifications were not required in the patients with the remaining conditions. A co-operative, inter-group study might represent the ideal setting for identifying a sufficient number of such patients to draw conclusions on their characteristics and to tailor treatment for individual subgroups.

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