Original Article

Acute lymphoblastic leukemia and Down syndrome

Presenting features and treatment outcome in the experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP)

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KEYWORDS

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ABSTRACT

BACKGROUND.

The presenting features and treatment outcome of 120 patients with Down syndrome (DS) and childhood acute lymphoblastic leukemia (ALL) were compared with 6237 non-DS patients treated in the same years.

METHODS.

We reviewed the database of 6 consecutive Italian Association of Pediatric Hematology and Oncology (AIEOP)-ALL trials conducted between 1982 and 2004. Features of DS patients were compared with those of non-DS patients.

RESULTS.

The 120 DS patients (1.9%) were more often girls ($P = .027$), aged ≥10 years ($P = .014$), and high risk according to National Cancer Institute (NCI) criteria ($P = .045$). The distribution of white blood cell count did not differ ($P = .32$). DS patients belonged less frequently to the current high-risk group ($P = .017$). In all but 1 case they demonstrated B-cell precursor (BCP) immunophenotype ($P \leq .001$). *TEL/AML1* molecular fusion transcript was found in only 1 of 44 (2.2%) tested patients. Induction death occurred more often in DS patients (4.2%, $P = .009$), but not failure to achieve remission. Leukemia relapse occurred in 31.6% of DS patients (vs 23.5%; $P = .003$), usually in the marrow. Remission death was more frequent in DS patients (4.2%, $P = .03$). Ten-year event-free survival and survival were significantly worse compared with non-DS patients ($P < 0.001$). DS patients diagnosed since 1995 had a better outcome ($P = .06$) than those diagnosed in previous years, but still had worse outcomes than non-DS patients ($P = .04$). Event-free survival of DS patients at NCI standard risk was lower than that of non-DS patients ($P = .006$).

CONCLUSIONS.

Presenting features of childhood ALL in DS differ from those in non-DS patients. They are almost invariably characterized by BCP phenotype, and are often *TEL/AML1* negative. Treatment results, although not as good as for non-DS patients, improved progressively, with modern therapy and support allowing 75% to survive. Cancer 2008. © 2008 American Cancer Society.

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ARTICLE TEXT

Children with Down syndrome (DS) are at increased risk to develop acute leukemia. The features of cancer in DS are different from those in non-DS subjects.[1][2] The relative risk of acute leukemia in the first 5 years has been estimated to be 56 times that of non-DS individuals,[1][2] with an equal frequency of acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL).[3]

Many reports have described the special features of leukemia in children with DS.[1][3-8] AML in DS children is characterized by unique features, so that its classification as a separate disease entity, "myeloid leukemia of Down syndrome," has been proposed.[9] The exact features of ALL in DS children have not yet been clarified. Most reports came from institutional series, with only a few studies performed in a population-based setting.[2][10-12]

Recent advances in the treatment of childhood ALL have raised the cure rate above 80%. Inferior treatment results in children with DS have been associated with incomplete disease control and a higher rate of infectious complications.[4-7][13][14]

In this study, we reviewed the presenting features and the treatment outcome of children with ALL and DS treated between 1982 and 2004. They were compared with those of the remaining patients with ALL enrolled in 6 contemporary Italian Association of Pediatric Hematology and Oncology (AIEOP)-ALL trials.

MATERIALS AND METHODS

Patients

From 1982 through 2004 patients with newly diagnosed ALL seen at the participating Italian institutions were enrolled in 6 consecutive studies: ALL-82,[15] ALL-87,[16] ALL-88,[17] ALL-91,[18] ALL-95[19] and AIEOP-BFM-ALL-2000.[20][21] Whereas the traditional cutoff age for eligibility had been younger than 15 years, starting with the most recent studies, AIEOP-ALL-95 and AIEOP-BFM-ALL-2000, the cutoff age was extended to younger than 18 years.

The diagnosis of ALL was made at the AIEOP reference laboratory, based on morphologic evaluation of bone marrow aspirates and negative staining for myeloperoxidase or Sudan Black. Complete immunophenotyping has been routinely evaluated since 1987. Treatment schedule was related to that of the current ALL trial (to which DS patients were, however, not eligible until the AIEOP-BFM-ALL 2000 study), as well as supportive therapy, which was delivered according to the individual policy of the treating center.

TEL/AML1 Fusion Gene Study

The presence of the *TEL/AML1* fusion transcript was retrospectively investigated by reverse transcriptase-polymerase chain reaction, as previously described.[22]

Study Design and Statistical Analysis

We retrospectively reviewed the AIEOP database for childhood ALL to identify all patients in whom DS was reported in association with newly diagnosed ALL. Survival and event-free survival (EFS) probabilities were calculated by the Kaplan-Meier method, with Greenwood standard error (SE). Comparisons between probabilities in different patient groups were performed using the log-rank test. In EFS analysis, time from diagnosis to induction failure, relapse, second malignant neoplasm, and death in remission or to date of last follow-up was considered. Death from any cause was the event in survival analysis. Pearson chi-square or Fisher exact test was used to evaluate association between characteristics and presence of DS. All *P* values were 2-sided. The SAS package (SAS Institute, Cary, NC) was used for analysis of the data.

RESULTS

During the study period, a total of 120 children with ALL had DS, and another 6237 without DS were consecutively enrolled in the 6 ALL trials. In this study, results are based on an overall median follow-up of 7.5 years.

Presenting Features

The main presenting features of ALL patients with and without DS are summarized in Table 1. Patients with DS were more often girls (*P* = .027) and more often >10 years old (*P* = .014); this last feature was responsible for a more frequent classification in the high-risk group by National Cancer Institute (NCI) criteria, based on age and white blood cell (WBC) count (*P* = .045). In patients with DS, the distribution of WBC count did not differ (*P* = .32) from that of non-DS patients,

and the proportion of cases with very high count (>100,000/mm^3) was slightly less. Significantly less often, DS patients belonged to the high-risk group, defined according to the stratification adopted in each AIEOP study (P = .017). Patients with DS and ALL had in all but 1 case a B-cell precursor immunophenotype ($P \leq .001$). The *TEL/AML1* molecular fusion transcript was found in only 1 (2.2%) patient of the 44 DS cases tested.

Table 1. Comparison of Presenting Features of 120 Patients With Acute Lymphoblastic Leukemia (ALL) and Down Syndrome Versus Remaining Patients Enrolled in 6 Consecutive Italian Association of Pediatric Hematology and Oncology (AIEOP)-ALL Studies

	Down syndrome		No Down syndrome		Total		
	No.	%	No.	%	No.	%	*P*
Total	120	1.9	6237	98.1	6357	-	
Sex							.027
Male	54	45.0	3440	55.1	3494	45.0	
Female	66	55.0	2797	44.9	2863	55.0	
Age, y							.014
<1	0	-	84	1.3	84	1.3	
1-5	65	54.2	3701	59.3	3766	59.2	
6-9	21	17.5	1351	21.7	1372	21.6	
10-17	34	28.3	1101	17.7	1135	17.9	
WBC count							.32
<20,000	77	64.2	3935	63.1	4012	63.1	
≥20,000 to <100,000	35	29.2	1629	26.1	1664	26.2	
≥100,000	8	6.6	672	10.8	680	10.7	
Not known	0	-	1	-	1	-	
NCI criteria							.045
Standard	70	58.3	4180	67.0	4250	66.9	
High	50	41.7	2057	33.0	2107	33.1	
Immunophenotype							<.001
Non-T	119	99.2	5492	88.1	5611	88.3	
T	1	0.8	736	11.8	737	11.5	
Not known	-	-	9	0.1	9	0.2	
Risk group							.017
SR	16	13.3	982	15.7	998	15.7	
IR	91	75.8	3992	64.0	4083	64.2	
HR	13	10.8	1263	20.3	1276	20.1	

WBC indicates white blood-cell count; NCI, National Cancer Institute; SR, standard risk; IR, intermediate risk; HR, high risk.

Treatment Outcome

To define the impact of DS in patients with ALL, their outcome was compared with that of the non- DS patients. Because all but 1 DS patient had B-lineage ALL, formal comparisons were restricted to B-lineage ALL.

Analysis of failures

Death in induction occurred in 4.2% of patients with DS, more frequently than in non-DS patients (P = .009) (Table 2). By the end of induction therapy, only 1 patient failed to achieve complete remission (0.8%), a proportion that was not significantly different from that of the remaining patients.

Table 2. Comparison of Treatment Outcome of 119 Patients With B-Cell Precursor Acute Lymphoblastic Leukemia (ALL) and Down Syndrome Versus Non-Down Syndrome Patients Enrolled in 6 Consecutive Italian Association of Pediatric Hematology and Oncology (AIEOP)-ALL Studies

	Down syndrome		No Down syndrome BCP ALL		No Down syndrome T-ALL	
	No.	%	No.	%	No.	%
Total	119*	-	5492	-	736	-
Death in induction	5	4.2	60	1.1	18	2.4
Resistant	1	0.8	67	1.2	20	2.7
Relapses	38	31.6	1293	23.5	261	35.5
Bone marrow	27	22.5	823	15.0	145	19.7
Central nervous system	5	4.2	176	3.2	46	6.3
Testis	1	0.8	87	1.6	10	1.4
Bone marrow+other	4	3.3	185	3.4	38	5.2
Other	1	0.8	20	0.3	21	2.8
Not known	0	-	2	-	1	0.1
Death in complete remission	5	4.2	87	1.6	35	4.8
Second malignant neoplasm	0	-	16	0.3	2	0.3
Continuous complete remission	70	59.2	3969	72.3	400	54.3

BCP indicates B-cell precursor.
*** Excludes 1 patient with T-immunophenotype, who was in complete clinical remission at 7 years from diagnosis.**

The most frequent adverse event was leukemia relapse, occurring in 31.6% of DS patients, compared with 23.5% of non-DS patients (P = .03). Most patients relapsed in the bone marrow, with isolated extramedullary relapses accounting for a total of 5.8%. This was not different from what was observed in the non-DS patients.

Death in complete remission occurred in 4.2% of patients with DS, and was significantly more frequent than the 1.6% observed in non-DS patients (P = .03). No second malignancies were reported in DS patients.

Analysis of EFS and survival

The probability of EFS (SE) at 10 years was 55.8% (4.9) in DS patients, compared with 69.7% (0.7) in non-DS patients (P < 0.001) (Fig. 1A). The overall survival was also lower in DS patients compared with non-DS patients (Fig. 1B) (P < .001).

Figure 1. Probabilities are shown of event-free survival (EFS) (A) and overall survival (B) for 119 patients with ALL and Down syndrome (DS) versus 5492 patients with B-cell precursor ALL enrolled in the 6 consecutive AIEOP-ALL studies.
[Normal View 30K | Magnified View 80K]

The 57 DS patients who were diagnosed within 1995 had an EFS of 48.3% (6.7), which was markedly lower than that of the 2708 patients diagnosed in the same era (P = .006); their overall survival was 49.0% (6.8) versus 75.0% (0.9) (P < .001).

For the 62 patients with DS diagnosed in 1995 or later, the EFS was higher than before 1995 (P = .06) but still lower than that of the non-DS patients (P = .04). The same pattern was observed for overall survival (Fig. 2).

Figure 2. Probabilities are shown of event-free survival (EFS) (A, B) and survival (C, D) for 119 patients with ALL and Down syndrome (DS), versus the remaining 5492 patients with B-cell precursor ALL enrolled in the 6 consecutive AIEOP-ALL studies, according to the treatment era (B, D: more recent era; cutoff, 1995).
[Normal View 53K | Magnified View 143K]

DS patients at NCI standard risk, ie, with age <10 years and WBC count <50.000/mm^3, had an EFS of 59.5% (6.3), lower than that of non-DS patients (P = .006). This difference was smaller in patients at NCI high risk (P = .28) (Fig. 3). This finding was reflected in the survival curves.

Figure 3. Probability of event-free survival (EFS) (A, B) and survival (C, D) for 119 patients with B-cell precursor ALL and Down syndrome, versus the remaining 5492 patients with B-cell precursor acute lymphoblastic leukemia (ALL) enrolled in the 6 consecutive AIEOP-ALL studies, according to National Cancer Institute criteria (A, C: standard risk: age <10 years and white blood cell count <50,000/mm^3).
[Normal View 51K | Magnified View 142K]

DISCUSSION

We describe a large cohort of patients with DS consecutively diagnosed and treated at AIEOP centers in Italy between 1982 and 2004. Comparison of their presenting features and treatment outcome with those of the non-DS children enrolled in the AIEOP studies in the same period revealed interesting differences.

Some of the presenting features of ALL in subjects with DS differ from those of their non-DS counterparts. This is well illustrated by imbalance in sex (with lack of the usual prevalence of male sex), age (lack of infants younger than 1 year), and immunophenotype (T-lineage exceptionally rare). Furthermore, *TEL/AML1* accounts for about 20% of childhood ALL in most series worldwide.[23][24] In our series, a subgroup of 44 patients diagnosed since 1995 could be investigated for this chromosomal aberration, and only 1 case was positive. This might also be related to an age selection, given the propensity of DS patients to develop ALL at an older age, whereas *TEL/AML1* is usually more frequent in younger patients. In their recent review of 215 DS-ALLs, Forestier et al observed that a significant proportion of DS-ALL patients had typical B-cell precursor ALL abnormalities, including high hyperdiploidy (11%) and t(12;21) (10%).[25]

Altogether, these findings clearly support the concept, recently reviewed by Hasle,[1] that leukemia in DS results in most cases from a different pathway than in non-DS subjects. In only a minority of DS patients, leukemia may occur as a "random" event and thus behave as in non-DS subjects.

In a recent review of this issue, Izraeli et al[26] pointed out that B-cell precursor childhood ALL is usually associated with 1 of 2 genetic abnormalities: a structural chromosomal anomaly - fusing the *AML1 (RUNX1)* gene on chromosome 21 with the *TEL (ETV6)* gene on chromosome 12, or hyperdiploidy. These 2 genetic aberrations are mutually exclusive, suggesting that each activates an oncogenic pathway that leads to B-cell precursor leukemia. If constitutional trisomy 21 has a direct leukemogenic effect similar to the role of the acquired extra copies of chromosome 21 in hyperdiploid ALL, then we would expect a lower prevalence of *TEL/AML1* or hyperdiploid genotypes in the ALL of Down syndrome. Our findings seem to support this hypothesis.

Treatment results of acute leukemia in DS subjects are apparently more favorable in AML, but not in ALL.[4-7][10][14] The unfavorable outcome could be attributed to the biology of the disease, to the DS host characteristics, or to the treatment applied. Pui et al noted in 1993 that children with DS and ALL had a low frequency of adverse clinicobiologic features at diagnosis; however, these findings did not translate into a better outcome, apparently because of treatment-related toxicity.[14]

Although the proportion of deaths during induction or remission in our series was significantly higher than that observed in the non-DS control subjects, this difference apparently did not account for the disadvantage in outcome, resulting also from inferior leukemia control. We treated this large series of DS patients with different regimens, according to the current trial. Yet, 70% of them received an intensive, BFM-based chemotherapy.[21] Leukemia relapse occurred mainly in the bone marrow; the likely explanation for this is the reduced treatment intensity induced by inherent risk of infection in these constitutively immune-compromised patients. This is in keeping with the finding of the BFM group reporting that among 61 DS patients from trials ALL-BFM 81, 83, 86, and 90, EFS was comparable to that of the non-DS group once they received treatment with no major modifications.[6]

Can children with DS have access to a cure rate comparable to that of non-DS patients, provided they are able to receive intensive antileukemic treatment with no major modifications? If so, the challenge for leukemia specialists is to be able to devise supportive therapies that allow such nonreduced treatment intensity. We tried to answer this question indirectly by testing the "learning effect" of the AIEOP group in treatment of ALL in DS. In their report, Zeller et al for the Nordic group failed to observe such progressive improvement.[12] In our study, we observed a clear increase in EFS and survival in patients treated after 1995. This reflects not only the overall improvement in this field, but possibly the tendency to treat more intensively, in keeping with our decision to make these patient eligible for the most recent ALL-2000 study. Nonetheless, the persisting gap suggests that patients with DS and ALL retain a lower probability of cure by the current treatment approach.

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