Acute lymphoblastic leukemia in children with Down syndrome: Comparative analysis versus patients without Down syndrome

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ABSTRACT

Introduction. Children with Down syndrome (DS) more commonly have acute lymphoblastic leukemia (ALL) and a lower survival rate than those without Down syndrome (WDS). We analyzed the clinical, demographic, and biological characteristics and treatment response of children with DS-ALL versus those WDS-ALL. Patients and methods: Patients with ALL between January 1990 and November 2016. The demographic and biologic characteristics and treatment response were compared using the χ² and Wilcoxon rank-sum tests. The overall survival and event-free interval (EFI) were analyzed using the Kaplan-Meier and log-rank tests.

Results. 1795 patients were included; 54 had DS. Patients with DS-ALL were older (p= 0.0189). All had B-cell precursor immunophenotype and a lower incidence of recurrent abnormalities (p < 0.0001). They showed a better response rate to prednisone (p= 0.09) and a higher mortality in induction and complete remission (p < 0.0001). All deaths of patients with DS-ALL were treatment-related. The event-free survival (EFS) was 47% (± 8%) versus 73% (± 1%) (p= 0.006) and the EFI was 54% (± 9%) versus 75% (± 1%) (p= 0.0297) among patients with DS-ALL versus those WDS-ALL, respectively. The rate of relapse was similar in both groups (p= 0.6894). The EFI of patients with DS-ALL was lower in the group aged 6-9 years: 39% (± 19%) (p= 0.7885).

Conclusions. A lower survival was observed among children aged 6-9 years with DS-ALL. Although these children showed a better early response, their EFS and EFI were lower due to treatment-related mortality.

Key words: acute lymphoblastic leukemia, children, Down syndrome, prognosis.

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INTRODUCTION

Patients with Down syndrome (DS) have a 10-to-35-times higher risk for developing acute leukemias.1,2 Although these patients have been adequately characterized for having a better prognosis among those with acute myeloid leukemia, patients with DS and acute lymphoblastic leukemia (DS-ALL) have a lower survival rate than those without DS and ALL (WDS-ALL).

Patients with DS-ALL account for 3% of all ALL cases.3-5 Although no significant differences have been described in terms of demographic or baseline clinical characteristics,4,5 the diagnosis of children with DS younger than 1 year is unusual.4,6 Children with DS-ALL almost exclusively have B-cell precursor immunophenotype; T-cell and mature B-cell immunophenotypes are uncommon.5,7 A normal G-banding karyotype has been observed in 40% of these patients versus 10-20% of those WDS-ALL.4,8 No association has been established between the lower survival rate and recurrent cytogenetic abnormalities of prognostic value.3,5,7,10 Recently, the IKZF1 gene deletion, present in 30% of
patients with DS-ALL, has been associated with a lower survival.3,11-14

No significant differences have been reported in the early treatment response and the distribution by risk group.5,15 However, patients with DS-ALL have a higher mortality rate15 with an overall survival (OS) and an event-free survival (EFS) that are 10-20% lower than in patients WDS. The worst prognosis has been attributed to a higher treatment-related morbidity and mortality (TRMM)3,8 and a higher relapse rate.8 No second malignancies have been described in patients with DS-ALL.4,15

Not knowing the characteristics of prognostic value of these patients and searching for a balance between a lower TRMM and an increased relapse rate pose serious difficulties to adequately establish treatment intensity.

For the purpose of presenting other tools that will help to understand this subgroup of patients, the objective of this study was to analyze the clinical, demographic, and biological characteristics and the treatment response of patients with DS-ALL versus those WDS-ALL.

**POPULATION AND METHODS**

This was a retrospective, observational study. The study initially included all patients diagnosed with ALL, younger than 19 years, and admitted to Hospital de Pediatría SAMIC “Prof. Dr. Juan P. Garrahan” between January 1990 and November 2016. All patients were enrolled into four consecutive treatment protocols: ALL-90, ALL-96, Acute Lymphoblastic Leukemia Intercontinental (ALLIC) 2002, and ALLIC 2009.16,17 The treatment was adapted to the risk group based on the criteria for each study. In all cases, diagnosis was made by light microscopy, flow cytometry, G-banding, and reverse transcription polymerase chain reaction (RT-PCR) in accordance with the methods previously described for such determinations.18-21

No exclusion criteria were applied to analyze the clinical and demographic characteristics. For the analysis of biological characteristics, children younger than 1 year were excluded. For the rest of the study analyses, children who did not meet the following criteria were considered eligible for assessment: age younger than 1 year, receiving a previous treatment, and lost-to-follow-up.

The outcome measures assessed for the analysis of clinical and demographic characteristics were baseline leukocyte count, extramedullary involvement at the time of diagnosis, and distribution by age and sex. For the analysis of biological characteristics, immunophenotype, cytogenetics, and recurrent genetic abnormalities were used. In addition, early treatment response (response to prednisone by Day 8, morphologic remission in the bone marrow by Day 15), stratification by risk group (high, standard or low risk of lack of treatment response according to the criteria implemented in the treatment protocols),16,17 EFS, event-free interval (EFI), OS, and mortality causes, including TRMM, were analyzed.

**RESULTS**

In the reported period, 1795 patients diagnosed with ALL and younger than 19 years were admitted; of these, 54 (3%) had DS. The entire population was used to compare the clinical and demographic characteristics. Since no patient with DS was younger than 1 year versus 109 patients WDS-ALL, the infant population was excluded from the analysis of biological characteristics. A patient with DS-ALL was excluded because he had received previous treatment. For the analysis of the other outcome measures, 53 patients with DS-ALL and 1491 patients WDS-ALL were included.

The analysis of clinical and demographic characteristics only showed statistically significant differences in the distribution by age group (p= 0.0189) (Table 1, Figure 1), with an older median age among patients with DS-ALL due to the absence of children younger than 1 year. Also, no significant differences were observed in the initial extramedullary involvement (assessed with the initial involvement of the central nervous system by lumbar tap).
The comparison of immunophenotypic and cytogenetic characteristics showed a significant difference (p < 0.0001) (Figure 2). Among patients with DS-ALL, no recurrent genetic abnormalities were detected in association with a poor prognosis, such as hypodiploidy, translocation t(9;22), and rearrangements on chromosome 11q23. The ones associated with an adequate prognosis, such as hyperdiploidy and translocation t(12;21), were detected in a lower proportion (11% of patients with DS-ALL versus 30% of those WDS-ALL).

The acquired trisomy 21 in leukemia cells (+21) was detected in 14.6% of patients WDS who had B-cell precursor ALL and in 49% of those WDS-ALL who had hyperdiploidy.

The following was observed in relation to the stratification of patients by prognostic risk group: a high risk of 7.4% versus 20.9%; an intermediate risk of 70.3% versus 54.6%; a standard risk of 22.3% versus 24.5%; DS-ALL versus WDS-ALL, respectively (p= 0.036), which confirmed the lower percentage of patients with DS-ALL in the high risk group. In relation to the parameters of early treatment response, patients with DS-ALL showed a better early response in the first week of prednisone monotherapy: 98% for patients with DS-ALL versus 90% for those WDS-ALL (p= 0.09). The assessment of bone marrow on Day 15 after starting induction showed that 68% of patients with DS-ALL had less than 5% of blast cells by light microscopy (CR criteria by light microscopy) versus 64% of those WDS-ALL (p= 0.15).

The assessment at the end of induction on Day 33 showed a significantly lower rate of patients with DS-ALL who achieved CR (p < 0.0001) in association with the increased number of deaths in induction (13% in patients with DS-ALL versus

| Table 1. Distribution of clinical and demographic characteristics of acute lymphoblastic leukemia among patients with Down syndrome (n= 54) versus patients without Down syndrome (n= 1741) |
|-----------------|------------------|-----------------|
| **Age**         | **DS-ALL (n= 54)** | **WDS-ALL (n= 1741)** | **P value** |
| Range           | 1 y. and 4 m.o.-14 y. and 7 m.o. | 0 y. and 0 m.o.-16 y. and 11 m.o. |  |
| Median          | 5 y. and 9 m.o. | 5 y. and 7 m.o. |  |
| < 1 year old    | n= 0 (0%) | n= 109 (6.3%) | p= 0.0189 |
| 1-6 years old   | n= 29 (53.7%) | n= 819 (47.0%) |  |
| > 6 years old   | n= 25 (46.3%) | n= 809 (46.6%) |  |
| **Sex**         | **DS-ALL (n= 54)** | **WDS-ALL (n= 1741)** | **P value** |
| Female          | n= 23 (42.6%) | n= 759 (43.6%) |  |
| Male            | n= 31 (57.4%) | n= 980 (56.4%) | p= 0.88 |
| **Leukocyte count** | **DS-ALL (n= 54)** | **WDS-ALL (n= 1741)** | **P value** |
| < 20 000/mm³    | n= 35 (64.8%) | n= 1013 (58.1%) |  |
| > 20 000/mm³    | n= 19 (35.2%) | n= 725 (41.9%) | p= 0.10 |

**Figure 1.** Distribution of acute lymphoblastic leukemia by age range among patients with Down syndrome (n= 54) versus patients without Down syndrome (n= 1741)

Acute lymphoblastic leukemia in patients with Down syndrome (DS-ALL); acute lymphoblastic leukemia in patients without Down syndrome (WDS-ALL).
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1.5% in those WDS-ALL (Table 2). Following CR, 13% of patients with DS-ALL died versus 3.9% of those WDS-ALL (p = 0.0074). One hundred percent of deaths among patients with DS-ALL were caused by an infection, whereas in the case of those WDS-ALL, the most common causes of death also included acute tumor lysis syndrome and hemorrhage.

The rate of relapse was similar in both groups: 20.4% in patients with DS-ALL versus 19.7% in those WDS-ALL (p = 0.6894). No second malignancies were described in patients with DS-ALL.

The EFS and EFI were significantly lower among the patients with DS-ALL, p = 0.006 and p = 0.0297, respectively (Figure 3). The mean duration of follow-up of patients with DS was 54 months (range: 15-189).

Within the DS-ALL group, the EFI was analyzed by classifying patients by age group; lower intervals were observed in children aged 6-9 years (p = 0.7885). Also, a tendency towards an improved EFS was observed among patients with DS-ALL in the last 10 years of treatment, although such difference was not significant (p = 0.18) (Figure 4). This result was associated with a lower TRMM of 40% versus 15% and with higher rates of CR of 45% versus 64% in the ALL-90/-96 protocols versus ALLIC 2002/2009 protocols, respectively.

**DISCUSSION**

As described in the bibliography, this study found clinical and biological differences between patients with DS-ALL and those WDS-ALL. However, it is not possible to correlate the increased mortality of patients with DS-ALL to differences in the prevalence of certain factors used at present for the risk stratification of survival for this disease but to the higher treatment-related mortality.

Patients with DS had an increased risk for acute leukemia, and the incidence of ALL is 1/300 children with DS versus 1/3500 children WDS.1 Although acute myeloblastic leukemia

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**FIGURE 2. Distribution of acute lymphoblastic leukemia by immunophenotype and recurrent cytogenetic abnormalities among patients with Down syndrome (n= 54) versus patients without Down syndrome (n= 1632) older than 1 year**

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**TABLE 2. Response of acute lymphoblastic leukemia to induction among patients with Down syndrome (n= 53) versus patients without Down syndrome (n= 1491) eligible for assessment and older than 1 year**

<table>
<thead>
<tr>
<th>Patients</th>
<th>CR</th>
<th>DS-ALL (n= 53) Deaths in induction</th>
<th>M2/M3</th>
<th>WDS-ALL (n= 1491) Deaths in induction</th>
<th>M2/M3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>46</td>
<td>7</td>
<td>0</td>
<td>1446</td>
<td>22</td>
</tr>
<tr>
<td>Percentage</td>
<td>86.8</td>
<td>13.2</td>
<td>0</td>
<td>96.98</td>
<td>1.48</td>
</tr>
</tbody>
</table>

Acute lymphoblastic leukemia in patients with Down syndrome (DS-ALL); acute lymphoblastic leukemia in patients without Down syndrome (WDS-ALL); pro-B (EARLY B); pro-B immunophenotype; pre-B (PRE-B); pre-B immunophenotype; common B (COM B); undetermined B (undet. B); ambiguous lineage (LALA); unknown (UNK.).
in children with DS is characterized by the presence of a GATA-1 gene mutation acquired pre-leukemia, the genetic bases that may lead to the development of DS-ALL are unclear. It has been proposed that constitutional trisomy 21 may cause an alteration of hematopoiesis and thus alter its microenvironment as much as precursor cells, which may account for the increased incidence of ALL in patients with DS.\textsuperscript{6,22} Interestingly, trisomy 21 is the most commonly acquired numerical abnormality in leukemia cells, which occurs, as observed in our study, in 20\% of patients, either alone or combined.\textsuperscript{23}

The clinical and biological characteristics of the cases analyzed in this study are consistent with those previously described in the bibliography, as well as the lower EFS and EFI among patients with DS-ALL. It is worth noting that these last two findings cannot be attributed to a higher number of relapses but to an increased rate of TRMM. The OS of patients with DS-ALL was similar to the EFS, which may be explained by the difficulty of rescuing these patients due to the treatment intensity required to achieve a second remission following a relapse.

The different protocols for the treatment of pediatric ALL have reported that the TRMM was 2-4\%. Among patients with DS, the increased TRMM was associated with a higher level of chemotherapy toxicity and an increased susceptibility to infections. Gastrointestinal toxicity, methotrexate-induced mucositis, and hematological disorders (higher and more prolonged myelosuppression) are more common and severe among patients with DS-ALL compared to those WDS-ALL.\textsuperscript{6,24-26} However,
the in vitro cytotoxicity of blast cells has been studied in DS-ALL but a higher sensitivity to different chemotherapy agents has not been observed.27 An increased rate of cardiotoxicity in association with anthracycline use has not been observed either.24 In our study, we did not observe TRMM exclusively associated with chemotherapy toxicity; on the contrary, all deaths were associated with infections and were homogeneously distributed across all treatment stages, as described in the bibliography.3,8 Immunodeficiency, together with respiratory and heart disorders associated with DS, increases the risk for severe complications. As mentioned before, constitutional trisomy 21 alters the development of B-cells, which causes moderate dysgammaglobulinemia and also moderate or severe T-cell disorder.9 The consensual recommendations for this group of patients suggest a strict clinical follow-up during the entire treatment, including maintenance; stronger controls during prolonged neutropenia; aggressive antibiotics for suspected infections, even if there is no fever or neutropenia; influenza vaccination for family members; IV gamma globulin treatment for children with low or moderate hypogammaglobulinemia; and antibiotic prophylaxis.9 Different abnormalities in gene expression have been associated with a worse prognosis in patients with DS. Approximately 60% of patients with DS-ALL had cytokine receptor-like factor 2 (CRLF2) overexpression3,6,8,28 versus 5% of those WDS-ALL; however, unlike what has been

**Figure 4. Event-free interval probability curves by age range and event-free survival probability curves by treatment protocol of acute lymphoblastic leukemia among patients with Down syndrome (n= 53)**

**a. Event-free interval (EFI) probability curves by age range**

- EFI > 9 years (n = 10): 67% (± 19%)
- EFI 1-6 years (n = 29): 77% (± 12%)
- EFI 6-9 years (n = 15): 29% (± 19%)

$\text{p = 0.7885}$

**b. Event-free survival (EFS) probability curves by treatment protocol**

- EFS ALLIC 2001 and 2009 (n = 33): 48% (± 11%)
- EFS ALL-90 and -96 (n = 21): 42% (± 11%)

$\text{p = 0.1838}$

Acute lymphoblastic leukemia among patients with Down syndrome (DS-ALL); ALLIC: Acute Lymphoblastic Leukemia Intercontinental.
observed in patients WDS and B-cell precursor ALL, this lacks prognostic value among those with DS-ALL, even if it is associated with JAK-2 kinase mutations. IKZF1 gene deletions, present in 30% of patients with DS-ALL, have demonstrated an adverse prognostic value in this group of patients, with an OS approximately 40% lower for patients with gene deletion. The Ponte di Legno study group associated the differences in the EFS by age group with the mean age of the population with IKZF1 gene deletions and concluded that the increased incidence of this mutation at an older age may be a genetic factor that would account for the lower EFS in patients aged 6-9 years. In our report, a lower EFS was also observed in this age group, but it was not possible to analyze the presence of IKZF1 gene deletions in our population.

The increased risk for morbidity and mortality observed in patients with DS hinders the possibility of designing treatment schemes because it is necessary to adapt the different international protocols so as to achieve a balance between an improved EFS and OS and a reduced TRMM. It is worth noting that 40-50% of patients with DS require treatment modifications (a reduction of more than 20% of the chemotherapy dose or an extension of more than 20% of treatment stages), which may have a negative impact on survival by increasing the possibility of a relapse. The most recent treatment protocols included in our report have demonstrated an improved EFS in relation to a reduced TRMM. Since TRMM does not occur in a particular treatment stage, it has been agreed that it would not be justified to reduce the chemotherapy dose. There is consensus in the bibliography that it is necessary to reduce the dose of methotrexate during the first treatment course with a gradual increase based on tolerance. Also, a reduced TRMM, which has resulted from a better clinical support over recent years, has brought about the use of intensive treatments that are adequate to the risk, thus increasing the number of patients with DS-ALL who achieve CR.

The future prospects for this group of patients are the analysis of new risk factors, such as IKZF1 gene mutation, and the need to develop institutional clinical support guidelines in accordance with the latest consensual recommendations for international reference groups.

CONCLUSIONS
This study confirms that patients with DS-ALL have their own set of clinical and cytogenetic characteristics. It corroborates that patients with DS in the age range between 6 and 9 years old tend to have a lower survival rate. Although children with DS-ALL showed a better initial treatment response, their EFS and EFI were significantly lower due to the high TRMM, exclusively in relation to sepsis.

REFERENCES


