Acute lymphoblastic leukemia in infants: 20 years of experience

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Abstract
Objective: To analyze patients younger than 2 years with acute lymphoblastic leukemia, treated in the period between 1990 and 2010 in a state reference center.
Methods: This was a clinical-epidemiological, cross-sectional, observational, and descriptive study. It included patients younger than 2 years with acute lymphoblastic leukemia, treated in the period of 1990 to 2010 in a pediatric oncology unit of a state reference center, totaling 41 cases.
Results: All patients were white ethnicity, and 60.9% were females. Regarding age, 24.38% were younger than 6 months, 17.07% were between 6 months and 1 year, and 58.53% were older than 1 year. The age of 6 months was statistically significant for the outcome of death. Predominant signs and symptoms were fever, bruising, and petechiae. A leukocyte count > 100,000 was found in 34.14% of cases, hemoglobin count < 11 in 95.13%, and platelet count < 100,000 in 75.61. Infiltration of central nervous system was present in 12.91% of patients. According to the lineage, B-cell lineage predominated (73%), but the T-cell line was statistically significant for death. 39% of patients had disease recurrence. In relation to vital status, 70.73% of the patients died; septic shock was the main cause.
Conclusions: Acute lymphoblastic leukemia in infants has a high mortality rate, especially in children under 1 year and those with T-cell derived lineage.

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Introduction

Approximately 10% of all cancers affecting children under 15 years correspond to those diagnosed in the first year of life.¹ Leukemia is the second most common cancer in children under 1 year of age, and acute lymphoblastic leukemia (ALL) the most frequently observed type.²

Some possible risk factors are genetic syndromes (Down, Noonan, trisomy 9), high birth weight (> 3.5 kg), previous abortion, maternal behavior (use of antihistamine, metronidazole, dipyrone, estrogen, alcohol consumption, use of marijuana and hallucinogenic drugs, radiation, and exposure to insecticides and pesticides).³,⁴

Leukemia in children under 1 year of age has distinct epidemiological, clinical, and biological characteristics, and is associated with unfavorable factors such as hyperleukocytosis and central nervous system (CNS) infiltration.⁵,⁶ In this age range, there is a predominance of gene rearrangements that present as 11q23 translocation, leading to the coexistence of the lymphoid and myeloid phenotypes, known as mixed lineage leukemia (MLL) translocation. The presence of this type of translocation is associated with worse prognosis.⁶,⁷

Regarding the immunophenotype, these children’s blast cells have a very young precursor B-cell (CD34+ / CD 19+) with CD 10 negativity.⁸

To treat leukemia in this age range, specific protocols are used, which have been developed by international cooperative groups, as childhood leukemias do not usually respond to traditional treatments, showing resistance to drugs such as corticosteroids and asparaginase.⁹,¹⁰ With the use of therapy intensification, survival has increased, but so has toxicity; in the CCG-1953 protocol of the Children’s Cancer Group, 29% of deaths occur during induction.¹²

The use of allogeneic bone marrow transplantation in these patients is still controversial, showing no difference in survival when compared to chemotherapy alone.¹³

In spite of all the therapeutic approaches, overall survival remains poor. In the CCG-1953 protocol of the Children’s Cancer Group, overall survival at five years ranged between 22% and 30%, while for the Interfant-99 protocol, it was 53.8%.¹⁰,¹² More recently, a group from Taiwan reported a survival rate of 18%.¹⁴

This study aimed to assess patients younger than 2 years of age with ALL, treated in the pediatric oncology unit of the Hospital Infantil Joana de Gusmão (HIJG) from 1990 to 2010.

Methods

This was a clinical-epidemiological, cross-sectional, observational, and descriptive study. The research protocol was approved by the Research Ethics Committee of the HIJG. The study included patients younger than 2 years diagnosed with ALL, treated at HIJG between January, 1990 and December, 2010. Exclusion criteria were loss at follow-up, transfer to another department for treatment, and insufficient data in the medical record.

ALL diagnosis was based on morphology, cytochemistry, and flow cytometric immunophenotyping of bone marrow aspirate. The treatment protocols used were those...
of national (GBTI-II-85, GBTI-II-93, and GBTI-II-99) and international cooperative groups (ALL III-85, Interfant-99, and ALL-IC BFM 2002).

The variables analyzed were age at diagnosis (stratified age range as ≤ 6 months; 6 months < age < one year; and ≥ one year); gender; birth weight (greater and less than 3,500 grams); ethnicity according to the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística – IBGE) (white, black, mixed-race, Asian, and Native Brazilian); origin according to the state of Santa Catarina according to the IBGE, as established by IBGE (Greater Florianópolis, Northern Santa Catarina, Western Santa Catarina, Uplands, Southern Santa Catarina, Itajaí Valley); parental contact with pesticides; signs and symptoms at diagnosis (fever, bone pain, lymphadenopathy, hepatosplenomegaly, skin and mucosal membrane bleeding); laboratory assessment at diagnosis (leukocyte, hemoglobin, and platelet counts); CNS involvement at diagnosis; presence and type of genetic alterations precursor phenotype (B or T derived); vital status (alive or deceased); death (immediate cause, in remission or not of neoplastic disease, treatment period); relapse (medullary, extra-medullary or combined); time of follow-up.15

Data were collected from the medical records and statistics service (Serviço de Arquivo Médico e Estatística) and from the hospital cancer registry of the HJIG.

Statistical analysis was performed using the GraphPad Prism 5® software. The results were analyzed using Pearson’s chi-squared test with 95% level of significance, thereby analyzing the relationship between two variables.

### Results

The total number of patients evaluated was 41, all whites, of which 60.97% were females. The mean age at diagnosis was 12.5 months, with a median of 13 months. Regarding the age range at diagnosis, 24.39% were younger than 6 months, 17.07% were older than 6 months and younger than 1 year, and 58.53% were older than 1 year of age. The mean birth weight was 3,367 g, with a median of 3,400 g.

History of parental contact with pesticides was described in 19.51% of cases. A total of 39% of cases denied history of contact with pesticides, and in 41.5% of the cases the data were not available. Signs and symptoms at the diagnosis are summarized in Table 1.

As for the geographic origin, considering the sub regions of the state of Santa Catarina according to the IBGE, 34.14% (n = 14) of the patients came from the Itajaí Valley, 24.39% (n = 10) from Greater Florianópolis, 17.07% (n = 7) from Southern Santa Catarina, 9.75% (n = 4) from Western Santa Catarina, 7.32% (n = 3) from Northern Santa Catarina, and 7.32% (n = 3) from the Uplands. The overall mean follow-up time was 2 years; in surviving patients, this time was 4.6 years.

CNS infiltration at diagnosis was present in 12.19% of patients. Three patients did not undergo CSF analysis, as they died before the exam. CNS infiltration, when compared with vital status, was not statistically significant (p = 0.54). Hematological alterations at diagnosis are detailed in Table 2.

Cytogenetic assessment was performed in 48.78% of cases (n = 20). Of these, 17.07% had genetic alterations, including 11q23:3, chromosome trisomy 8:1, terminal deletion of the long arm of chromosome 7:1 and t (15, 17). Data were not available in 51.22% of the cases.

In 73.17% of cases the precursor phenotype was derived from B-lineage, and in 14.63%, from T-lineage cells.

Regarding the vital status, 29.27% of the patients were alive (two patients undergoing treatment). The outcome of death occurred in 70.73% of patients (two patients off treatment and in clinical remission). Leukocyte count at diagnosis and its comparison with vital status are described in Table 3. Age at diagnosis and its association with vital status is described in Table 4.

Of the patients who died (n = 29), only five of them were in clinical remission, and three deaths occurred during treatment induction. The main cause of death was septic shock (41% of deaths). Disease relapse occurred in 39.02% of cases (n = 16); 12 patients presented medullary relapse, three presented CNS relapse, and one patient presented combined relapse (medullary and CNS). Only two patients underwent allogeneic bone marrow transplant; of these, one is alive and in remission.
When comparing the precursor phenotype with vital status, 40% of patients with B-lineage-derived cells survived and 60% died. All patients with T-lineage-derived cells died. Using the chi-squared test to compare the lines with vital status, a p-value = 0.0006 was obtained, and thus, T-lineage was statistically significant for death. There was no statistical significance when comparing birth weight (< and > 3,500 g) with vital status (p = 0.31).

### Discussion

Leukemia in children younger than one year is more common in girls (1.17:1), a result confirmed by this study. In the SEER study, the white ethnicity was more affected, but no difference was observed regarding response to treatment when compared to the black ethnicity. In the present research, all patients were whites, consistent with the demographic characteristics of the state of Santa Catarina.1,2

Most patients came from the nearby regions, such as Itajaí valley and the state capital city, Florianópolis, as HIJG is a referral center for cancer treatment in the region.

According to Naumburg, exposure to pesticides is not a proven risk factor for the development of leukemia; however, Slate et al. found an association between leukemia in infants and gestational exposure to petroleum-derived products, such as benzene. Maternal exposure to pesticides was verified in 19% of the patients in this study.3,4

Leukemia in children younger than 1 year usually presents as hyperleukocytosis at diagnosis. Mann et al. and Tomizawa et al., evaluating this age range, showed that most patients presented more than 100,000 leukocytes at diagnosis, which is similar to the results found in the present study, where 34% had a leukocyte count > 100,000 cells.11,16

Pui et al. reported that CNS infiltration is more common in leukemia diagnosed in children younger than 1 year.6 In the Japanese group, 20% of patients showed CNS infiltration; the same was observed for 9% of patients in the Interfant-99 group8,11 Similar to that observed in the Interfant-99 group, CNS infiltration in the present study was not statistically significant for death.10 However, in the study by Rives et al., evaluating T-cell-derived leukemia, CNS infiltration at diagnosis was significant for death.17

Most patients in the present study had B-cell precursor phenotype. According to Ribeiro et al., T-cell-derived leukemias are more aggressive, a result corroborated by this study, where this lineage was statistically significant for death (p = 0.0006).18 Rives et al. achieved overall survival at five years of 74% in T-cell-derived leukemia, whereas Hunger et al. observed an overall survival of 90%
in B-cell derived leukemia, considering all age ranges of childhood.\(^{17,19}\)

Overall five-year survival rate can reach up to 90% in children older than 1 year, while in those younger than 1 year, the survival rate decreases dramatically. The Interfant-99 group had a survival rate of 47%; the Associazione Italiana Ematologia Pediatric Oncology (AIEOP 91-95), 45%; the Berlin-Frankfurt-Munster (BFM), 43%; the Children’s Cancer Group (CCG) 1953, 42%; and the Taiwan group, 18%.\(^{5,10,14,20}\)

This study found an overall survival of 29%. As in the aforementioned studies, of the patients who died, most were not in remission. The intensive use of chemotherapy in an attempt to remit the disease can cause long periods of severe neutropenia, exposing patients to diverse types of infection. In this study, the main cause of death was septic shock, probably due to the prolonged period of neutropenia. Therefore, intensification of supportive care, prevention, and prompt treatment of infections becomes an extremely important factor in the management of these patients.

The presence of genetic alterations as the MLL rearrangement is associated with a worse prognosis, and is more frequently observed in younger infants; according to Bueno, it may originate in the intrauterine period.\(^6\) Genetic evaluation was not possible in all patients in this study; however, age younger than 6 months showed statistical significance for death, suggesting a possible correlation with the presence of genetic alterations.\(^8\)

Considering the poor prognosis associated with ALL in children younger than 1 year, it is important to develop new therapeutic strategies. In this context, the literature describes new treatments, such as trans-retinoic acid, vitamin D3, histone deacetylase, and DNA-methyltransferase-inhibitors, which could improve clinical outcomes in patients younger than one year with leukemia.\(^{15,16}\) However, more studies are needed to demonstrate the efficacy of these agents.

**Conflicts of interest**

The authors have no conflicts of interest to declare.

**References**
