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A RETROSPECTIVE COHORT ANALYSIS OF CHILDREN AND ADOLESCENTS WITH LYMPHOBLASTIC LYMPHOMA IN LATIN AMERICA.

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Abstract

BACKGROUND AND AIMS: There is scarce information about pediatric lymphoblastic lymphoma (LLy) in low and middle-income countries. We describe the clinical characteristics, treatment and outcome of a cohort of children and adolescents with LLy in Latin America (LA). METHODS: Retrospective study analyzing pediatric patients with LLy in 10 institutions of the St. Jude Global Alliance from nine LA countries between 2007 and 2017. RESULTS: One-hundred and twenty-six patients were included. Sixty (47.6%) had T-LLy, 49 (38.9%) B-LLy and in 17 (13.5%) the immunophenotype was unknown. Ninety-seven (77%) presented with stage III/IV disease, and 42 (33.3%) in critical conditions. In 30 cases (23.8%), the results of pathology diagnosis exceeded 15 days from biopsy, and 23 patients (18%) required a review at another institution. The EFS and OS at 5 years were 73% (SE 0.047) and 78% (SE 0.0435), respectively. Five-year abandonment-sensitive EFS and OS were 65% (SE 0.0477) and 70% (SE 0.0459), respectively. Events included relapse/progression (n=22), refractory disease (n =1) abandonment (n=11), induction death (n=4), death in complete remission (n=4), and second malignancies (n=1). CONCLUSIONS: A balanced proportion of LLy-T and B phenotypes was observed. Diagnosis was a challenge. Most of the patients presented with high-risk disease, and many in critical conditions. Toxic deaths and abandonment represented nearly half of the events. Improvements in diagnosis, supportive measures and follow up are imperative to improve the outcomes of pediatric LLy in Latin America.

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ABSTRACT

BACKGROUND AND AIMS: There is scarce information about pediatric lymphoblastic lymphoma (LLy) in low and middle-income countries. We describe the clinical characteristics, treatment and outcome of a cohort of children and adolescents with LLy in Latin America (LA).

METHODS: Retrospective study analyzing pediatric patients with LLy in 10 institutions of the St. Jude Global Alliance from nine LA countries between 2007 and 2017.

RESULTS: One-hundred and twenty-six patients were included. Sixty (47.6%) had T-LLy, 49 (38.9%) B-LLy and in 17 (13.5%) the immunophenotype was unknown. Ninety-seven (77%) presented with stage III/IV disease, and 42 (33.3%) in critical conditions. In 30 cases (23.8%), the results of pathology diagnosis exceeded 15 days from biopsy, and 23 patients (18%) required a review at another institution. The EFS and OS at 5 years were 73% (SE 0.047) and 78% (SE 0.0435), respectively. Five-year abandonment-sensitive EFS and OS were 65% (SE 0.0477) and 70% (SE 0.0459), respectively. Events included relapse/progression (n=22), refractory disease (n =1) abandonment (n=11), induction death (n=4), death in complete remission (n=4), and second malignancies (n=1).

CONCLUSIONS: A balanced proportion of LLy-T and B phenotypes was observed. Diagnosis was a challenge. Most of the patients presented with high-risk disease, and many in critical conditions. Toxic deaths and abandonment represented nearly half of the events. Improvements in diagnosis, supportive measures and follow up are imperative to improve the outcomes of pediatric LLy in Latin America.

Abbreviations

LLy	Lymphoblastic Lymphoma
NHL	Non-Hodgkin Lymphoma
ALL	Acute Lymphoblastic Leukemia
BFM	Berlin Frankfurt Munich
SJGA	St. Jude Global Alliance
SJCRH	St. Jude Children's Research Hospital
AHOPCA	Asociación de Hemato-Oncología Pediátrica de Centro América
IRB	Institutional Review Board
CNS	Central Nervous system
BM	Bone Marrow
OS	Overall survival
EFS	Event-free survival
ASOS	Abandonment sensitive overall survival
ASEFS	Abandonment sensitive event-free survival

INTRODUCTION

Lymphoblastic lymphoma (LLy) accounts for 15% to 20% of all pediatric non-Hodgkin lymphomas (NHL) based on statistics from North America and Western Europe[1]. The prevalence of LLy in other regions of the world is less well defined and there may be important epidemiological and biological variations across different continents[2]. Even though its epidemiology and outcome is well-characterized in the northern hemisphere[2], there is scant information from low and middle-income countries, and no large cohorts of pediatric patients with LLy from Latin America have been previously reported.

Since 2017, the Department of Global Pediatric Medicine at St. Jude Children's Research Hospital (St. Jude) actively promotes the St. Jude Global Alliance to centers across Latin America that provide care to children with cancer in the region. This collaboration provides among others, the opportunity to conduct descriptive clinical studies to analyze the cancer characteristics and outcome of Latin American patients in a large transnational population.

The primary objective of the present study is to describe the outcome of children and adolescents treated for LLy at institutions in Latin America participating in the St. Jude Global Alliance. Secondary objectives include describing the clinical characteristics at presentation and assessment of the treatment strategies.

METHODS

This was an international, multicentric retrospective cohort study. Ten Latin-American oncologic centers providing care to children and adolescents with LLy participated, collecting and recording the clinical data of their patients. As a retrospective study of de-identified secondary use of clinical data the St. Jude IRB determined an exempt research status, and this determination was provided to the site principal investigator for local study submission and approval at each one of the participating institutions.

Study inclusion criteria were a diagnosis of LLy of any phenotype between January 1, 2007 and December 31, 2017; age less than 19 years; and clinical medical records available for review and abstraction. For each patient variables collected included age, gender, lymphoma immunophenotype, stage and sites of disease, treatment regimen administered and clinical status. Data was collected in a case report form and then transcribed to an electronic password-secure REDCap database. Study staff at St. Jude periodically reviewed the data

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entered and queried sites for missing data or for clarifications. Online meetings were held for training, progress evaluation and other discussions.

Statistical analysis

Event-free survival (EFS) was calculated from the time of diagnosis until death, relapse, progression, abandonment or the occurrence of a second malignancy. Patients with no events were censored at the date of last follow-up. Overall survival (OS) was defined as time from diagnosis to death or date of last follow-up for those who were still alive. The EFS and overall survival (OS) were calculated using the Kaplan–Meier method, and groups were compared using a log-rank test. Induction deaths were defined as those occurring in the first 30 days after admission, before remission evaluation. Deaths in complete remission included those attributed to any cause other than LLy after achieving a complete remission. Abandonment was defined as failure to adhere to scheduled or unscheduled visits during therapy for at least four consecutive weeks. Follow-up was updated as of March 1, 2020, thus each patient had at least 3 years of follow-up.

Categorical data are expressed in absolute frequencies and percentages. Continuous variables are expressed as medians (range). The χ^2 or Fisher exact test was used for the analysis of categorical variables and Mann-Whitney test for continuous variables.

RESULTS

Ten centers of nine countries participated in the study. Among these, 126 children and adolescents with LLy were identified and included for analysis; 77 (61.1%) were males and 49 (38.9%) females. Sixty children (47.6%) presented T-LLy and 49 (38.9%) B-precursor LLy by immunohistochemical analysis and/or flow cytometry and in 17 (13.5%) the phenotype unknown/in conclusive (Table 1). Median age at diagnosis was 9.6 years (range, 0.8 - 17.7); patients with T-LLy were slightly older (median, 10.4 years; range, 1.7 to 17.8 y) than those with B-LLy (median 7.7 years; range, 0.84 – 17.4 y). Patients with B-precursor phenotype tended to present with lower stage disease with 18 (36.7%) patients having stage I/II in contrast to 3 (5%) for T-cell phenotype. Fifty-five patients (91.6%) with T-cell phenotype had stage III-IV disease, in contrast 29 (59.1%) with B-precursor phenotypes ($p<0.05$). Median lactate dehydrogenase (LDH) values were also significantly higher in patients with T-cell phenotype (726 IU/L versus 548 IU/L, $p<0.05$). Detailed patient data is described in Table 1.

The diagnosis of LLy was done by tissue biopsy in 110 cases (87%), cytology of body fluid plus immunophenotyping by flow cytometry in 17 (13%) and bone marrow aspirate in 19 (15%). The time between the diagnostic biopsy and the pathological diagnosis was less than 14 days in 96 patients (76%), between 15 and 30 days in 21(17%) and greater than 30 days in 9 patients (7%). In 23 patients (18%) the diagnosis of LLy was done after a second review of the pathology at a referral institution; in 5 cases (4%) the diagnosis of LLy was established after correction of a previous non LLy diagnosis.

At diagnosis, 24 patients (19%) presented with oncologic emergencies: 20 of them (15.9%) with upper vena cava syndrome and 4 (3.2%) with tumor lysis requiring dialysis and 18 (14.9%) with other severe complications. Seventeen (13.5%) required admission to an intensive care unit during the diagnostic interval due to these conditions. Overall, 23 children (18.4%) received treatment before the diagnosis was confirmed, including steroids (n=22) and less frequently cyclophosphamide (n=5) or radiotherapy (n=1). In 17 patients (28.8%) of the cases of T-LLy, the local team initiated treatment without biopsy confirmation whereas this occurred in 4 (8.1%) of cases with pre-B LLy.

Sixty-three (50%) patients received BFM-based protocol treatments, 59 (46.8%) received other regimens, and in 4 (3%) no therapy data was available. Radiotherapy was used in 18 children (14.2%); in 9 of the cases to the cranium, 2 craniospinal and 7 to other sites (paravertebral, mediastinal, bones, testicle). Eighty-seven (70.1%) children completed the prescribed therapy.

Events included relapse in 22 cases (17.4%), abandonment in 11 (8.7%), death in complete remission in 4 (3.1%), induction death in 4 (3.1%), induction failure in 1 (0.8%), and one patient presented a second malignancy (histiocytic sarcoma) (0.8%). Events according to phenotype are listed in Table 2. Treatment

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abandonment varied among the participating countries. Sites of relapse included 7 (31.8%) isolated central nervous system (CNS), 3 (13.6%) isolated bone marrow (BM), 5 (22.7%) extranodal (testicle, lymph node, orbit and other), 3 (13.6%) mediastinal, 1 (4.5%) in BM and mediastinum and 2 in other sites. Thirty-one patients (24.6%) had died at the time of case ascertainment for this study. Causes of death included refractory-relapsed disease 16 (51.6%), infection 9 (29%), toxicity 4 (12.9%) , unknown 1/other 1.

The event free survival (EFS) and overall survival (OS) at 5 years was 73% (SE 0.047) and 77% (SE 0.0435), respectively for the complete cohort. When abandonment of treatment was considered as an event, the ASOS and ASEFS were 70% (SE 0.0459) and 65% (SE 0.0477), respectively. No statistically significant difference was observed between B- and T-cell phenotypes or between patients treated with BFM-based protocols versus other regimens . The median follow-up time for patients with available follow-up data (n=124) is 5.58 years (Range: 0 to 14.58 years).

DISCUSSION

Our study showed a predominance of T-LLy phenotype similar to what is reported in other areas of the world, however, the proportion of B-LLy was higher. [3-5] In our Latin American cohort, 47.6 % of the patients had T-cell phenotype and 38.9% with B-LLy phenotype, while reported series from Europe and North America indicate a different distribution of phenotypes (around 75% and 20%, respectively).[3,5] This tendency to a balanced proportion of T-cell over B-cell phenotypes in Latin American LLy has been previously suggested in a smaller Brazilian report.[4] In our cohort most of the cases of B precursor phenotype LLy are diagnosed in Central America and the Andean countries. (Table 3). Similar distributions of T and B immunophenotypes have been observed in acute leukemias in some countries of Latin America.[6] These findings must be confirmed in further epidemiological studies and possible biological explanations and implications of these differences further investigated.

Toxic deaths (including induction death and death in complete remission) occurred in 6.3% of our patients. This is higher than the observed rates in high income countries which describe toxic mortality between 1 to 3.7% in lymphoblastic lymphomas. However these rates are lower than the recently reported 6.4% induction mortality rate and 3.8% deaths in complete remission for patients with acute lymphoblastic leukemia (ALL) in Latin America. [6,7] Several factors may explain this finding, seventy-six percent of our cohort presented with advanced high-risk disease, many had severe clinical complications like mediastinal compression or tumor lysis syndromes, and 3.2% of the patients required dialysis. In contrast, tumor lysis was reported in only 4% of patients included in a recent prospective European study, and impaired renal function occurred in 2.8% of the cases.[7] Notably our institutions had limited resources for diagnosis and supportive care, and this may partly explain the higher risk of fatal toxic events and the delay in diagnosis confirmation. Local physicians were keen to use empirical tratments prior to the diagnosis in 18.4% of our cases, a higher proportion compared to other reports and more frequent than in ALL in a Latin American cohort that reported a 5%.[6] This prephase approach may explain the relative low percentage of induction deaths observed especially in T-LLy.

Diagnosis of LLy still constitutes a challenge in our setting.[8] A delay between biopsy and definitive diagnosis greater than 15 days was reported in 23.8% of our patients. This factor influenced the therapeutic decisions that were made in cases with high risk disease. Approximately one fourth of our patients had the diagnosis confirmed by immunocytology in fresh tissue or fluids, presenting the opportunity to establish a more timely diagnosis. However, in approximately one quarter of the cases, the diagnosis of LLy was achieved after a second pathological consultation.

The fact that in our cohort, patients presented with higher stages of the disease and with severe clinical complications may be explained by multiple contextual factors. One of the possible causes is the absence of optimal local diagnostic techniques like flow cytometry or molecular biology in some institutions delaying diagnosis and risk stratification assignment. Additionally, there is insufficient supportive care treatment in some centers, with drugs like rasburicase not being available, lack of access to urgent hemodialysis implementation , restricted ICU admissions, and/or insufficiently trained pediatricians and surgeons in the

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management of oncologic diseases and their emergency complications.

Treatment regimens used were diverse and were categorized as BFM and non BFM based ones. There was no significant difference in outcomes, but there was a tendency favoring BFM-based protocols (Figure 2). The CNS relapse rate was 5.5%, higher than reports from Europe and North America reporting less than 3%.[7,9] There was wide variation among institutions participating in our study regarding CNS-directed therapy and prophylactic cranial radiotherapy was not used routinely.[9] In fact, CNS radiotherapy was applied to only 11 children (8.7%), including the 4 cases with initial CNS involvement at diagnosis, and the remaining as CNS cranial prophylaxis with 1200Gy.

Survival results of patients treated for LLy in our cohort can be considered acceptable but lower than that observed in high income countries.[7,9-11] Moreover, considering the abandonment-adjusted outcome it is imperative that we develop strategies to decrease abandonment rates. Recent work by the PAHO regional working group as part of the Global Initiative for Childhood Cancer recommends strategies that could be implemented to address this problem.[12] Among the events observed in this cohort, there was an increased proportion of non-disease related mortality and abandonment and may be explained by lack of optimal resources and socio-economic and cultural factors. Abandonment is a relevant and prevalent problem in LA countries, occurring in 8.7 % of our cases, representing a quarter of all clinical events, and has a heterogeneous distribution being less prevalent in Brazil and Uruguay, as reported previously for ALL or mature B-cell malignancies.[6,13,14]

Lastly, despite being a retrospective study that did not include patient sensitive information and was considered exempt by USA regulations, 9 of the 16 centers in Latin America initially invited to participate in the study had difficulties in obtaining local IRB approval. Inconsistency and non-harmonized IRB approaches to the review and approval of retrospective data to answer important research questions constitutes a barrier to research initiatives in Latin America, even for the collection of non-sensitive data like in the present study.[15]

Limitations of our study include the retrospective design that may have missed cases and incomplete clinical data, heterogeneous resources among participating centers and no uniform therapeutic approach. With these limitations prognostic factors could not be assessed. Despite these limitations, our transnational study provides important findings to establish the landscape of lymphoblastic lymphoma in children across a wide-range of representative countries in Latin America.

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Conflict of interest: none to declare

Table 1: Clinical characteristics of patients with LLy.

Median age in years (range):
Immunophenotype
Sites of disease: Mediastinum Lymph node Bone Marrow Thoracic/abdominal effusions CNS Extranodal: Bone Skin and
Median LDH (IU/L; range):
Stage I/II III/IV Unknown
Medical **complications at diagnosis** -Superior vena cava syndrome Tumor lysis syndrome Others

Table 2: Events according to phenotype of LLy.

Events	A
Death in induction Death in remission (infection/toxicity) Abandonment Relapse Refractory disease Second malignancy	4

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Table 3. Distribution of T and B LLY phenotype among institutions

Country	Institution	T-cell	B-cell precursor	Other	NA
Brazil	GRAACC/Instituto de Oncologia Pediatrica/UNIFESP	9	6	1	1
Brazil	Hospital de Cancer Infantojuvenil de Barretos	13	2	2	0
Peru	Instituto Nacional de Enfermedades Neoplásicas (INEN)	6	17	2	0
Guatemala	UNOP (Unidad de Oncologia Pediatrica)	12	12	1	0
Haiti	Hopital Saint-Damien	3	1	0	0
Honduras	Hospital Escuela Universitario	3	5	0	3
R. Dominicana	Hospital Infantil Dr. Robert Reid Cabral	2	2	0	1
Mejico	Hospital General de Tijuana	4	3	0	5
Panama	Hospital Del Niño Jose Renan Esquivel	1	1	0	0
Uruguay	Hospital Pereira Rossell - Fundación Perez Scremini	7	0	0	1

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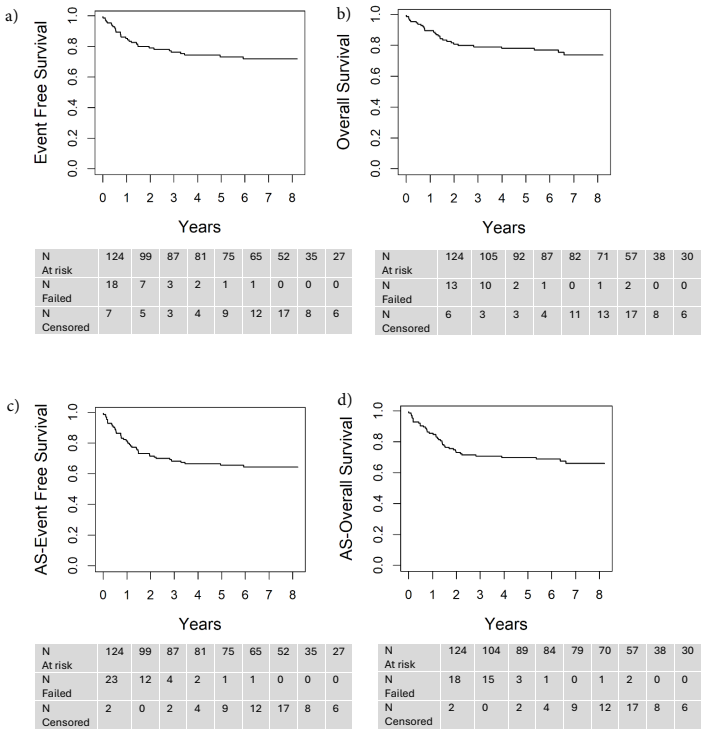

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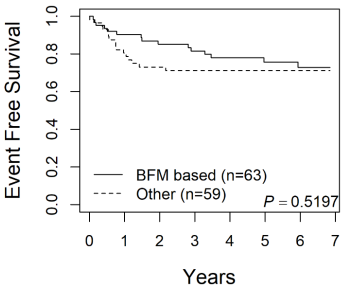

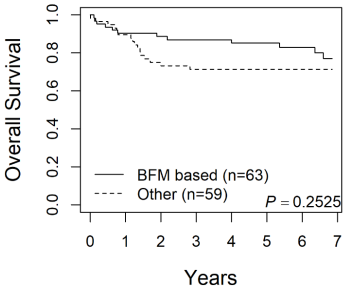

EFS events	Protocol	
	BFM based	Other
Induction Death	2	1
Relapse	10	12
Death In Remission	2	2
Induction Failure	1	0
Second Malignant Neoplasm	0	1
Total	15	16

OS events	Protocol	
	BFM based	Other
Deaths	12	16