Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

RESEARCH ARTICLE

Overall manifestations and survival of pediatric patients with Langerhans cell histiocytosis. A middle-income country (mic) national multicenter study

Liliana Velasco-Hidalgo[1], Alejandro González-Garay[2], Roberto Rivera-Luna[1], Marta Zapata-Tarrés[3], Cesar Galván-Diaz[1], Araceli López-Facundo[4], Farina Arreguín-González[5], José León-Espitia[6], Daniel Ortiz-Morales[7], Luis Juárez-Villegas[8], Oscar González-Llano[9], Daniela Covarrubias-Zapata[10], Alejandro Reséndiz-López[5], Miguel Palomo-Colli[8], Luisa Ma. Duarte-Arroy[1], José De J. Loeza-Oliva[11], Isidoro Tejocote-Romero[12], Laura García-Segura[13], Pablo González-Montalvo[14], Silvia Chávez-Gallegos[15], Eloy Pérez-Rivera[15], Iris Gallardo-Gallardo[16], Daniela Olvera-Caraza[17], Cinthia Cruz-Medina[18], Lourdes Vega-Vega[19], Lourdes Romero-Rodríguez[19], Citlali Simón-González[20], Diana Reyes-Morales[11], Rosalba Bellido[6], Guillermo Gaytán-Fernández[6], Martha Velázquez-Aviña[21], Gabriel Peñaloza-González[21], Kenya S. Carmona-Jaimez[2], and Nubia Macías-García[22]*

[1]*Servicio de Oncología, Instituto Nacional de Pediatría, Mexico City;* [2]*Departamento de Metodología de la Investigación, Instituto Nacional de Pediatría, Mexico City;* [3]*Coordinación de Investigación, Fundación Instituto Mexicano del Seguro Social (IMSS), AC, Mexico City;* [4]*Servicio de Oncología, Hospital Materno Infantil del Instituto de Seguridad Social del Estado de México y Municipios (ISSEMYM), Toluca, State of Mexico;* [5]*Servicio de Oncología, Centro Médico Nacional 20 de Noviembre, Mexico City;* [6]*Servicio de Oncología, Hospital General de León, León Guanajuato;* [7]*Servicio de Oncología, Hospital General de México, Mexico City;* [8]*Servicio de Oncología, Hospital Infantil de México Federico Gómez, Mexico City;* [9]*Departamento de Hematología Pediátrica, Hospital Universitario Dr. José E. González, Universidad Autónoma de Nuevo León, Monterrey, N. L.;* [10]*Servicio de Oncología Pediátrica, Centro Estatal de Oncología de Campeche "Dr. Luis González Francis," San Francisco de Campeche, Camp.;* [11]*Servicio de Oncología pediátrica, Centro Estatal de Cancerología "Dr. Miguel Dorantes Mesa," Xalapa, Ver.;* [12]*Servicio de Oncología Pediátrica, Hospital Para El Niño del Instituto Materno Infantil del Estado de México (IMIEM), Toluca, State of Mexico;* [13]*Servicio de Oncología, Hospital General de Celaya, Celaya, Gto.;* [14]*Servicio de Oncología pediátrica, Hospital General Dr. Agustín O'Horán, Servicios de Salud de Yucatán, Mérida, Yuc.;* [15]*Servicio de Hemato-oncología, Hospital Infantil de Morelia Eva Sámano de López Mateos, Morelia, Mich.;* [16]*Servicio de Oncología, Hospital Para el Niño de Morelense, Emiliano Zapata, Cuernavaca, Mor.;* [17]*Servicio de Oncología, Hospital Para el Niño Poblano, Puebla, Pue.;* [18]*Servicio de Transplante, Hospital Para el Niño Poblano, Puebla, Pue.;* [19]*Hospital Infantil Teletón de Oncología, Querétaro, Qro.;* [20]*Jefatura del Servicio de Oncología Pediátrica, Hospital Regional de Alta Especialidad del Niño Dr. Rodolfo Nieto Padrón, Villahermosa, Tab.;* [21]*Servicio de Oncología, Hospital Juárez de México, Mexico City;* [22]*Servicio de Oncología Pediátrica, Hospital del Niño Federico Gómez Santos, Torreón, Coahuila. México*

Abstract

Background: *Langerhans cell histiocytosis (LCH) is a rare neoplastic disease characterized by clonal proliferation of dendritic cells. It is Mexico's ninth most frequent malignancy in patients under 18 years of age. The aim of the study was to determine the clinical characteristics, treatment, and survival of Mexican pediatric patients diagnosed with LCH treated from January 2010 to December 2018.* **Methods:** *We conducted a retrospective study of LCH using data from 19 accredited hospitals throughout the Mexican Republic. Patients < 18 years who were diagnosed with LCH between January 2010 and December 2018 were included (253 patients) in the study.* **Results:** *All patients had a histopathological diagnosis, and extension studies were performed at their treatment centers. The median age at diagnosis was 19 months. The most frequently*

***Correspondence:**
Liliana Velasco-Hidalgo
E-mail: lilianavh@hotmail.com

Date of reception: 04-05-2024
Date of acceptance: 16-08-2024
DOI: 10.24875/BMHIM.24000061

Available online: 21-11-2024
Bol Med Hosp Infant Mex. 2024;81(6):328-336
www.bmhim.com

affected sites included the bone (178 cases; 70%) and the skin (131 cases; 51.7%). Of the patients in Group 1, 48 (42%) had bone marrow involvement, 62 (53%) had splenomegaly, and 39 (34.8%) had liver involvement. Of the patients who underwent chemotherapy treatment, 61.2% exhibited a complete response, and 36 patients (14.2%) relapsed after complete remission. The most frequent sites of relapse were the skin, bone, lymph nodes, and liver. The overall survival rate was 91.3% and was lower for patients in Group 1 (77%) compared with those in Groups 2 (97%) and 3 (100%), p = 0.001. **Conclusion:** *The current report aims to demonstrate the findings of a multicenter study conducted on Mexican children with LCH; consequently, these treatment results for a relatively infrequent disease merit further research.*

Keywords: *Langerhans cell histiocytosis. Mexico. Children.*

Manifestaciones clínicas generales y supervivencia de pacientes pediátricos con histiocitosis de células de Langerhans. Un estudio nacional multicéntrico en un país de medianos ingresos (mic)

Resumen

Introducción: *La histiocitosis de células de Langerhans (HCL) es una enfermedad neoplásica rara, caracterizada por una proliferación clonal de células dendríticas. Constituye la novena neoplasia maligna más frecuente en México en menores de 18 años. El objetivo de este estudio fue conocer las características clínicas, tratamiento y supervivencia de pacientes pediátricos con diagnóstico de HCL atendidos desde enero de 2010 a diciembre de 2018.* **Métodos:** *Se realizó un estudio retrospectivo de HCL en 19 hospitales acreditados en toda la República Mexicana. Se incluyeron pacientes menores de 18 años diagnosticados de HCL entre enero de 2010 y diciembre de 2018.* **Resultados***: Todos los pacientes tuvieron diagnóstico histopatológico y se les realizaron estudios de extensión en sus centros de tratamiento. Se incluyeron en el estudio 253 pacientes con HCL. La mediana de edad en el momento del diagnóstico fue de 19 meses. Los sitios de afectación más frecuentes fueron hueso en 178 (70%) y piel en 131 (51,7%). De los pacientes del grupo 1,48 (42%) tenían afectación a médula ósea, 62 (53%) esplenomegalia y 39 (34,8%) afectación hepática. De los pacientes que recibieron tratamiento de quimioterapia, 61.2% tuvo respuesta completa y 36 pacientes (14,2%) tuvieron recaída de la enfermedad después de haber entrado en remisión completa. Los sitios de recaída más frecuentes fueron la piel, huesos, ganglios linfáticos e hígado. La supervivencia global fue del 91,3% y fue menor para los pacientes del grupo de riesgo 1 (77%) en comparación con los de grupos de riesgo 2 (97%) y 3 (100%) con p = 0.001.* **Conclusión:** *El fin del presente informe es demostrar los hallazgos de un estudio multicéntrico realizado en niños mexicanos con HCL; en consecuencia, los resultados del tratamiento de una enfermedad relativamente infrecuente merecen más investigación, especialmente en términos de tratamiento.*

Palabras clave: *Histiocitosis de células de Langerhans. México. Niños.*

Introduction

Histiocytic disorders (HDs) are diverse diseases derived from myeloid progenitors of monocytic, histiocytic, and dendritic lines. According to the current classification, these disorders can be divided into C, H, L, M, and R groups. Langerhans cell histiocytosis (LCH) belongs to the L group, which also includes Erdheim-Chester disease (ECD), indeterminate cell histiocytosis, and mixed HDs (ECD-LCH)[1,2]. In Mexico, the incidence of HDs is 4.3 cases per million children under 18 years of age[3].

The clinical presentation of LCH is heterogeneous, ranging from single lesions to the involvement of multiple organs, including the liver, spleen, and bone marrow. Similar findings have been noted in different countries[4-6].

The Histiocyte Society has observed in its studies that the administration of vinblastine and prednisone confers a survival rate of up to 99% in patients without at-risk organs; the survival rate falls to 84% in patients with liver, spleen, and/or bone marrow involvement[7]. Other studies have demonstrated the usefulness of other drugs, such as cytarabine, and the importance of prolonged treatments of up to 12 months[8,9].

The $BRAF^{V600]E}$ somatic mutation was recently described in up to 57% of patients with LCH[10,11]. This mutation has been linked to greater involvement in organs at risk (88%), more significant reactivation at 5 years (43% vs. 28%), and increased resistance to chemotherapy (22% vs. 3%)[12,13]. The disease relapses frequently, so new treatment strategies are constantly being explored based on drugs such as cladribine, clofarabine, bisphosphonates, vemurafenib, and dabrafenib[14-21].

Since 2010, treatment for children with LCH in Mexico has been based on the provisions of the LCH III protocol of the Histiocyte Society and the National Technical Protocols of the National Council for the Prevention and Treatment of Cancer in Childhood and Adolescence[22].

This study evaluated pediatric patients' clinical characteristics, treatment, and survival across 19 hospitals accredited for caring for children with cancer in Mexico. This investigation focused on diagnoses between January 2010 and December 2018.

Table 1. Treatment protocol in children with LCH in Mexico

Induction If there is a complete response at the end of the first induction, maintenance is performed; if there is not, another 6 weeks are given.	Vinblastine 6 mg/m^2 IV weekly for 6 or 12 weeks Prednisone 40 mg/m^2 oral for 6-12 weeks
Maintenance Low risk - 25 weeks High risk - 52 weeks	Vinblastine 6 mg/m^2 IV every 3 weeks Prednisone 40 mg/m^2 oral for 5 days, every 3 weeks

Methods

An observational retrospective study was conducted in hospitals accredited for treating children with cancer. All centers throughout Mexico were invited to participate, of which nineteen hospitals accepted this invitation. All patients included were newly diagnosed with LCH, under 18 years of age, and diagnosed between 2010 and 2018. The patients' diagnoses were based on histopathology and immunohistochemistry and, in some cases, electron microscopy (6.3%). Extension studies were performed at the patients' treatment centers. All participants were classified according to a clinical group: (1) Group 1 presented involvement of at-risk organs (liver, spleen, and bone marrow); (2) Group 2 did not exhibit at-risk organ involvement; and (3) Group 3 exhibited involvement of the central nervous system and spinal cord. We collected information regarding initial clinical manifestations, affected sites, laboratory studies at diagnosis, histopathology studies, relapse or progression, survival, and mortality. Since 2010, most institutions in Mexico have followed the national protocol based on the Histiocyte Society's LCH III described in table 1: Patients in Group 1 are given a 12-month course of chemotherapy, and patients in Groups 2 and 3 receive 6 months of chemotherapy. The patients were followed up at the discretion of each center.

Relapse was defined as disease reactivation after a documented complete response, defined as the disappearance of all metabolic activity in the evaluation after treatment through imaging studies.

Since this study was retrospective, our sample was determined by convenience; patients registered at each center during the study period were included.

Patients whose records contained at least 80% of the required information were included in the study.

Statistical analysis

We performed univariate analysis using central-tendency tests to better understand the characteristics of the patient sample and to establish how each variable was distributed. We calculated means and standard deviations for continuous numerical variables with normal distributions. We calculated the median and either the minimum or maximum value for variables that were not normally distributed. In the case of qualitative variables, we calculated frequencies and proportions.

The frequencies among the risk groups were determined using X^2, Fisher's exact, and Kruskal–Wallis tests according to the type of variable and its distribution. We presumed that $p < 0.05$ indicated statistical significance. We also used a Cox proportional hazard model with mortality as the event. Overall and event-free survival was analyzed using the Kaplan–Meier method, and a log-rank test was used to assess whether there were significant differences between the groups.

Results

Clinical features

From January 2010 through December 2018, 253 patients with LCH were diagnosed at the 19 participating institutions (Table 2). The median age at diagnosis was 19 months. Patients in Group 1 had a mean age at diagnosis of 15 months (range 0.75-120 months), patients in Group 2 had a mean age at diagnosis of 25.5 months (range 0.62-192 months), and patients in Group 3 had a mean age at diagnosis of 28 months (range 0.2-180 months) ($p = 0.0001$). The male-female ratio of the total cohort was 1.3:1. The most frequently affected sites were the bone (178 cases; 70%) and the

Table 2. Age and reference hospital

Variable	Group 1 (n = 112)	Group 2 (n = 71)	Group 3 (n = 70)
Age (years)	Median (min-max) 1.2 (0.06-10)	Median (min-max) 2.12 (0.05-16)	Median (min-max) 2.3 (0.01-15)
Reference hospital	**n (%)**	**n (%)**	**n (%)**
Instituto Nacional de Pediatría	23 (20.5)	21 (29.5)	6 (8.57)
Hospital Infantil Teletón de oncología	1 (0.89)	4 (5.6)	2 (2.85)
Centro Médico Nacional 20 de noviembre	2 (1.78)	6 (8.4)	4 (5.71)
Hospital Ángeles del Pedregal	1 (0.89)	1 (1.40)	0 (0)
Centro Estatal de Oncología de Campeche	2 (1.78)	3 (4.22)	1 (1.42)
CECAN, Veracruz	7 (6.25)	2 (2.81)	3 (4.28)
Hospital General de Celaya	1 (0.89)	2 (2.81)	1 (1.42)
Hospital para el niño del IMIEM	24 (21.4)	2 (2.81)	4 (5.71)
Hospital Materno Infantil del ISSEMyM	2 (1.78)	2 (2.81)	3 (4.28)
Hospital General de México	2 (1.78)	2 (2.81)	0 (0)
Hospital General de León	5 (4.46)	1 (1.40)	2 (2.85)
Hospital General "Dr. Agustín O'Horán"	8 (7.14)	9 (12.6)	7 (10)
Hospital para el Niño Poblano	2 (1.78)	2 (2.81)	0 (0)
Hospital del Niño "Federico Gómez Santos," Saltillo	2 (1.78)	0 (0)	0 (0)
HNRNP Tabasco	3 (2.67)	0 (0)	2 (2.85)
Hospital Infantil de Morelia	2 (1.78)	1 (1.40)	3 (4.28)
Hospital Infantil de México	22 (19.6)	9 (12.6)	26 (37.14)
Hospital Juárez de México	0 (0)	1 (1.40)	3 (4.28)
Hospital Universitario UANL	3 (2.67)	3 (4.22)	3 (4.28)

skin (131; 51.7%). Table 3 lists the primary clinical manifestations at diagnosis.

The most frequent sites of bone involvement were the skull (127; 50.1%), spine (32; 12.6%), femur (28; 11%), pelvis (14; 5.5%), and humerus (11; 4.3%).

The most frequently positive immunohistochemistry markers for diagnosis included CD1a (199; 78.6%), S100 (166; 65.6%), CD207 (71; 28%), CD68 (41; 16.2%), and Birbeck granules, determined by electron microscopy (16; 6.3%).

Pulmonary involvement was observed in 13 patients (11.6%) in Group 1 and 5 patients (7%) in Group 2, mainly presenting as alveolar infiltrate in 16 cases (8.7%), bullae in one case (0.54%), and bronchiectasis in one case (0.54%).

Forty-eight patients (42%) in Group 1 had bone marrow involvement, 62 (53%) had splenomegaly, and 39 (34.8%) had liver involvement. The values of hemoglobin, leukocytes, and platelets at diagnosis were statistically significantly different among the patient groups. Platelet levels (median 204,000 cells/μL) and hemoglobin (median 7.6 g/dL) were lower in patients in Group 1 ($p = 0.0001$).

Treatment

Two hundred and thirty-five patients (92.5%) received treatment according to the national protocol based on the LCH III protocol with 6 mg/m² vinblastine and 40 mg/m² prednisone for 6 or 12 months, depending on the risk group. Ten patients (3.9%) received first-line treatment with vincristine (1.5 mg/m²), cytarabine (100 mg/m²), and prednisone (20 mg/m²). Six patients (2.3%) received the LCH II protocol, three patients

Table 3. Clinical characteristics by group in patients with LCH according to the risk group at diagnosis

Variable	Group 1 Frequency (%) (n = 112)	Group 2 Frequency (%) (n = 71)	Group 3 Frequency (%) (n = 70)	p-value
Gender				
Male	58 (0.51)	47 (0.66)	40 (0.57)	0.15
Female	54 (0.48)	24 (0.33)	30 (0.42)	
Clinical manifestations				
Skin lesions	69 (0.61)	42 (0.59)	19 (0.27)	0.000
Adenopathy	76 (0.67)	33 (0.46)	18 (0.25)	0.000
Diabetes Insipidus	14 (0.12)	10 (0.14)	12 (0.17)	0.68
Lung involvement	16 (0.14)	5 (0.07)	0 (-)	0.003
Bone lesions	66 (0.58)	56 (0.8)	55 (0.78)	0.002
Otitis	15 (0.13)	10 (0.14)	1 (0.01)	0.016
Weight loss	24 (0.21)	6 (0.08)	3 (0.04)	0.002
Proptosis	7 (0.06)	12 (0.17)	7 (0.10)	0.07
General symptoms	65 (0.58)	20 (0.28)	15 (0.21)	0.000
Tumor	1 (0.009)	2 (0.02)	0 (-)	0.28
Retinal gliosis	0 (-)	1 (0.01)	0 (-)	0.27
Medullary Syndrome	0 (-)	0 (-)	1 (0.01)	0.26
Pain	0 (-)	2 (0.02)	1 (0.01)	0.22
Vasculitis	1 (0.008)	0 (-)	0 (-)	0.53
Diarrhea	0 (-)	1 (0.01)	0 (-)	0.27
Gingival hyperplasia	1 (0.008)	0 (-)	0 (-)	0.53
Hematopoietic condition	89 (0.79)	0 (-)	0 (-)	0.000

Test statistic = X^2.

(1.1%) received treatment with etoposide 100 mg/m² as a single drug, and five patients (1.9%) underwent surgical treatment only. Three patients (1.1%) received no treatment.

Of the patients who underwent chemotherapy, 61.2% had a complete response with the first induction; this rate increased to 87% after the second induction treatment. Nineteen patients (7.9%) had no response or experienced disease progression after the second induction; they switched to a second-line of treatment. That treatment included cytarabine (100 mg/m²), prednisone (40 mg/m²) or cladribine (5 mg/m²), and cytarabine 100 mg/m² (Table 4).

Relapse

Thirty-six patients (14.2%) experienced disease relapse after presenting complete remission. The most frequent sites of relapse included the skin, bone, lymph nodes, and liver (Table 5). The second-line treatments consisted of several combinations: (1) cytarabine, vincristine, and steroids in 14 cases (38.8%); (2) vinblastine and prednisone in 11 cases (30.5%); (3) clofarabine in one case (2.7%); (4) cladribine in four cases (11.1%); (5) etoposide and cytarabine in five cases (13.8%); and (6) no treatment in one case (2.7%).

Twenty-two patients (8.6%) died. The causes of death included refractory disease in six patients (27.2%), septic shock in 10 patients (45.4%), infection in two patients (9%), hematological alteration in one patient (4.5%), pneumonia in one patient (4.5%), and intracranial hemorrhage in one patient (4.5%).

The overall survival rate was 91.3%, and it was lower for patients in Group 1 (77%) compared with patients in Groups 2 (97%) and 3 (100%) (p = 0.001; Fig. 1). Event-free survival was 66% for patients in Group 1, 74% for patients in Group 2, and 93% for patients in Group 3 (p = 0.0012; Fig. 2).

The mortality risk of each independent variable was analyzed by calculating the hazard ratios (HR) with a 95% confidence interval (CI); statistically significant differences were incorporated into a broad multivariate Cox proportional hazard model. We then used the stepwise backward method to reduce those differences until the best-fit model was obtained (log-likelihood = –25.94, X^2 (3) = 33.83, p = 0.000). Finally, the reduced model was verified using tests and diagnostics for a proportional hazard model with p = 0.10. In this model, variables associated with mortality included an age under 1 year (HR 5.037, p = 0.001), splenomegaly (HR 6.494, p = 0.000), and refractory disease (HR = 2.80, p = 0.005) tables 6 and 7.

Table 4. Treatment response, relapse and deaths by groups

Variable	Group 1 Frequency (%) (n = 112)	Group 2 Frequency (%) (n = 71)	Group 3 Frequency (%) (n = 70)	p-value
1st induction	109	65	66	
Complete response	40 (0.35)	41 (0.57)	53 (0.75)	0.000
Very Good partial	36 (0.32)	14 (0.19)	10 (0.14)	0.016
Partial	11 (0.09)	12 (0.16)	6 (0.08)	0.25
No response	12 (0.10)	4 (0.05)	1 (0.01)	0.03
Progression	12 (0.10)	0 (-)	0 (-)	0.00
2nd induction				
Complete response	84 (0.75)	61 (0.86)	64 (0.91)	0.012
Very good partial	13 (0.11)	4 (0.05)	2 (0.028)	0.092
Partial	2 (0.017)	1 (0.014)	0 (-)	0.791
No response	6 (0.05)	1 (0.014)	3 (0.02)	0.391
Progression	4 (0.035)	3 (0.042)	2 (0.028)	1.0
Relapse	23 (20.5)	10 (14.1)	3 (4.28)	0.009
Death	19 (16.9)	2 (2.81)	1 (1.42)	0.000

Test statistics: Fisher×s exact test.

Table 5. Relapse sites in patients with LCH according to the group

Variable	Group 1 Frequency (%) (n = 112)	Group 2 Frequency (%) (n = 71)	Group 3 Frequency (%) (n = 70)	p-value
Skin	3 (0.02)	2 (0.02)	3 (0.04)	0.900
Bone	10 (0.08)	8 (0.11)	0 (-)	0.007
Lymph nodes	5 (0.04)	0 (-)	1 (0.01)	0.14
Liver	3 (0.02)	1 (0.01)	4 (0.05)	0.38
Spleen	2 (0.01)	1 (0.01)	2 (0.02)	0.73
Lung	1 (0.008)	0 (-)	1 (0.01)	0.75
Middle ear	1 (0.008)	0 (-)	0 (-)	1.0
Orbit	1 (0.008)	0 (-)	1 (0.01)	0.75
Pituitary gland	0 (-)	1 (0.01)	0 (-)	1.0
Bone marrow	0 (-)	1 (0.01)	0 (-)	1.0

Test statistic: Fisher×s exact test; LCH: langerhans cell histiocytosis.

The primary factors associated with mortality included belonging to Group 1 (HR 8.23; 95% CI 2.4-27.9; p = 0.001) and the involvement of the skin, bone, liver, spleen, or bone marrow.

Discussion

LCH is a rare disease; its incidence in Mexico is similar to that reported in other countries. The aberrant differentiation of mononuclear cells through the mitogen-activated protein kinase pathway characterizes LCH and conditions its activation[23].

We have reported the results of the largest Mexican cohort to date (253 patients) diagnosed with LCH over 8 years at 19 institutions. Roughly half of the patients (44%) had high-risk organ disease. Patients in this group exhibited a survival rate of 77%, similar to that

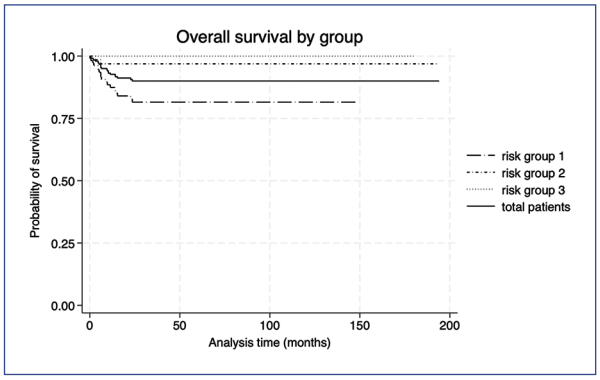

Figure 1. Global overall survival and by risk group. (2010-2018) n = 253.

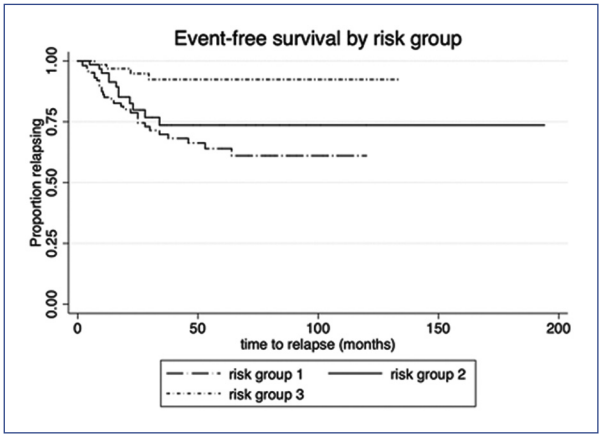

Figure 2. Event-free survival by risk group (2010-2018) n = 253.

Table 6. Cox proportional hazards model for mortality in pediatric patients with LCH in Mexico (2010-2018) n = 253

Variable	HR (IC95%)	p-value
Sex (female)	1.041 (0.43-2.47)	0.92
Risk Group		
Risk group 1	11.985 (2.78-51.66)	0.001
Risk group 2	0.292 (0.06-1.25)	0.09
Relapse	2.119 (0.85-5.25)	0.10
Clinical manifestations		
General symptoms	1.709 (0.72-4.02)	0.22
Dermatitis	4.160 (1.39-12.36)	0.010
Lymphadenopathy	2.088 (0.84-5.17)	0.11
Diabetes insipidus	1.382 (0.46-4.10)	0.56
Lung disorders	2.584 (0.86-7.67)	0.08
Otitis	1.586 (0.46-5.39)	0.46
Proptosis	1.066 (0.24-4.58)	0.93
Splenomegaly	6.821 (2.75-16.9)	0.000
Bone marrow infiltration	4.669 (1.98-10.99)	0.000
Bone lesions	0.246 (0.10-59.4)	0.002
Laboratory studies		
Hyperbilirubinemia	6.780 (2.73-16.83)	0.000
Hypoproteinemia	6.712 (2.59-17.37)	0.000
Hypoalbuminemia	4.466 (1.80-11.07)	0.001
Hemoglobin (mg/dL)	0.734 (0.62-0.86)	0.000
Leukocytes	0.983 (0.91-1.06)	0.66
Platelets	0.993 (0.990-0.996)	0.000

HR: hazard ratios.

Table 7. Reduced COX model

Variable	HR (IC95%)	p-value
Age < 1 year	5.037 (1.90 a 13.31)	0.001*
Splenomegaly	6.494 (2.48 a 16.96)	0.000*
Refractory disease	2.802 (1.00 a 7.84)	0.050*

Log likelihood: –90.17; X^2 (3): 33.87; p = 0.000*; HR: hazard ratios.

reported internationally (1 year of overall survival up to 99%)[7-24].

Validated risk-stratification criteria for children include disease sites and responses to initial therapy. Patients with lesions in "risk organs," including the bone marrow, spleen, or liver (Group 1), have a significantly higher risk of mortality than patients with lesions limited to "non-risk" sites (7). Risk stratification for LCH is based on the analysis of outcomes of prospective pediatric trials. Patients with high-risk LCH exhibit a survival rate of almost 90%. Still, outcomes are significantly worse if the disease progresses during the 1st 12 weeks of therapy[8].

In patients without risk organ involvement, the survival rate has been reported to be 98.2%, with a relapse rate of 26% for patients in Group 2[25]. We noted similar results in our population.

Gene alterations, such as the $BRAF^{V600E}$ mutation, have been shown in recent years to be a factor associated with high-risk characteristics, in addition to relapses and disease refractoriness[26]. However, it is not possible to routinely test for gene alterations in our population; this fact is a limitation of our study.

In general, the treatment received by our patients is recommended by the Histiocyte Society based on vinblastine and prednisone, which has been the standard treatment used internationally[27]. The treatment duration is 12 months for patients with risk organ disease and 6 months for those without organ disease. The primary second-line treatments used in patients with relapsed or refractory disease include cytarabine, etoposide,

steroids, and other drugs[28,29]. The LCH-IV study is one of the largest LCH trials to date; the Histiocyte Society is currently carrying it out. This prospective multi-arm study will evaluate first- and second-line treatments and include patient follow-up[30]. There is no question that multisystem/multifocal bone involvement constitutes a recurring problem[31]. Our patients could access drugs, such as cladribine, which is currently recognized as yielding adequate outcomes.

Single bone lesions are effectively treated with limited curettage or corticosteroid injections[32]. Large pelvic or vertebral lesions not amenable to curettage may be treated with radiation therapy. Our patients were offered a similar chemotherapy regimen as children in Group 1 who relapsed. Recently, indomethacin has been considered an alternative for bone LCH[33].

Besides our inability to detect BRAF V600E, another limitation of this retrospective study was that the histopathological study and follow-ups were performed according to the protocols of each center.

Conclusion

This study represents the first effort in Mexico to conduct a national analysis of LCH. We observed that LCH is a pathology characterized by relatively homogeneous patient care across Mexico. It has been reported that survival is acceptable; however, the frequency of recurrence is still high. Therefore, increased access to second-line drugs with limited toxicity is necessary. The challenge now is to access BRAF V600E testing so that patients can benefit from effective targeted therapies and form a cooperative group that involves most institutions.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

References

1. McClain KL, Bigenwald C, Collin M, Haroche J, Marsh RA, Merad M, et al. Histiocytic disorders. Nat Rev Dis Primers. 2021;7:73.
2. Leung AK, Lam JM, Leong KF. Childhood Langerhans cell histiocytosis: a disease with many faces. World J Pediatr. 2019;15:536-45.
3. Rivera-Luna R, Velasco-Hidalgo L, Zapata-Tarrés M, Cárdenas-Cardos R, Aguilar-Ortiz MR. Current outlook of childhood cancer epidemiology in a middle-income country under a public health insurance program. Pediatr Hematol Oncol. 2017;34:43-50.
4. Wang D, Chen XH, Wei A, Zhou CJ, Zhang X, Ma HH, et al. Clinical features and treatment outcomes of pediatric Langerhans cell histiocytosis with macrophage activation syndrome-hemophagocytic lymphohistiocytosis. Orphanet J Rare Dis. 2022;17:151.
5. Hu X, Buhtoiarov IN, Wang C, Sun Z, Zhu Q, Huang W, et al. Langerhans cell histiocytosis: a population-based study of anatomical distribution and treatment patterns. J Bone Oncol. 2022;36:100454.
6. Bagnasco F, Zimmermann SY, Egeler RM, Nanduri VR, Cammarata B, Donadieu J, et al. The international dataset on the association between Langerhans Cell Histiocytosis and other malignancies. Data Brief. 2022;45:108604.
7. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood. 2020;135:1319-31.
8. Gadner H, Minkov M, Grois N, Pötschger U, Thiem E, Aricò M, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood. 2013;121:5006-14.
9. Morimoto A, Shioda Y, Imamura T, Kudo K, Kawaguchi H, Sakashita K, et al. Intensified and prolonged therapy comprising cytarabine, vincristine and prednisolone improves outcome in patients with multisystem Langerhans cell histiocytosis: results of the Japan Langerhans Cell Histiocytosis Study Group-02 Protocol Study. Int J Hematol. 2016;104:99-109.
10. Berres ML, Lim KP, Peters T, Price J, Takizawa H, Salmon H, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med. 2014;211:669-83.
11. Milne P, Abhyankar H, Scull B, Singh P, Chakraborty R, Allen CE, et al. Cellular distribution of mutations and association with disease risk in Langerhans cell histiocytosis without BRAFV600E. Blood Adv. 2022;6:4901-4.
12. Héritier S, Emile JF, Hélias-Rodzewicz Z, Donadieu J. Progress towards molecular-based management of childhood Langerhans cell histiocytosis. Arch Pediatr. 2019;26:301-7.
13. Héritier S, Emile JF, Barkaoui MA, Thomas C, Fraitag S, Boudjemaa S, et al. BRAF mutation correlates with high-risk Langerhans cell histiocytosis and increased resistance to first-line therapy. J Clin Oncol. 2016;34:3023-30.
14. Donadieu J, Bernard F, Van Noesel M, Barkaoui M, Bardet O, Mura R, et al. Cladribine and cytarabine in refractory multisystem Langerhans cell histiocytosis: results of an international phase 2 study. Blood. 2015;1261415-23.
15. Simko SJ, Tran HD, Jones J, Bilgi M, Kwon Beaupin L, Coulter D, et al. Clofarabine salvage therapy in refractory multifocal histiocytic disorders, including Langerhans cell histiocytosis, juvenile xanthogranuloma and Rosai-Dorfman disease. Pediatr Blood Cancer. 2014;61:479-87.
16. Morimoto A, Shioda Y, Imamura T, Kanegane H, Sato T, Kudo K, et al. Nationwide survey of bisphosphonate therapy for children with reactivated Langerhans cell histiocytosis in Japan. Pediatr Blood Cancer. 2011;56:110-5.
17. Donadieu J, Larabi IA, Tardieu J, Visser J, Hutter C, Sieni E, et al. Vemurafenib for refractory multisystem langerhans cell histiocytosis in children: an international observational study. J Clin Oncol. 2019;37:2857-65.
18. Kieran MW, Geoerger B, Dunkel IJ, Broniscer A, Hargrave D, Hingorani P, et al. A phase I and pharmacokinetic study of oral dabrafenib in children and adolescent patients with recurrent or refractory BRAF V600 mutation-positive solid tumors. Clin Cancer Res. 2019;25:7294-302.
19. Yang Y, Wang D, Cui L, Ma HH, Zhang L, Lian HY, et al. Effectiveness and safety of dabrafenib in the treatment of 20 Chinese children with BRAF-V600E-mutated Langerhans cell histiocytosis. Cancer Res Treat. 2021;53:261.
20. Eder SK, Schwentner R, Ben SP, Abagnale G, Attarbaschi A, Minkov M, et al. Vemurafenib acts as a molecular on-off switch governing systemic inflammation in Langerhans cell histiocytosis. Blood Adv. 2022;6:970-5.

21. Eckstein O, McAtee CL, Greenberg J, Kumar A, Fein-Levy C, Smith T, et al. Rituximab therapy for patients with Langerhans cell histiocytosis-associated neurologic dysfunction. Pediatr Hematol Oncol. 2018;35:427-33.
22. Rivera-Luna R. Protocolos Técnicos. 1st ed. Mexico: Editores de Textos Mexicanos; 2010.
23. Kvedaraite E, Milne P, Khalilnezhad A, Chevrier M, Sethi R, Lee HK, et al. Notch-dependent cooperativity between myeloid lineages promotes Langerhans cell histiocytosis pathology. Sci Immunol. 2022;7:eadd3330.
24. Liu H, Stiller CA, Crooks CJ, Rous B, Bythell M, Broggio J, et al. Incidence, prevalence and survival in patients with Langerhans cell histiocytosis: a national registry study from England, 2013–2019. Br J Haematol. 2022;199:728-38.
25. Cui L, Wang CJ, Lian HY, Zhang L, Ma HH, Wang D, et al. Clinical outcomes and prognostic risk factors of Langerhans cell histiocytosis in children: results from the BCH-LCH 2014 protocol study. Am J Hematol. 2023;98:598-607.
26. Kemps PG, Zondag TC, Arnardóttir HB, Solleveld-Westerink N, Borst J, Steenwijk EC, et al. Clinicogenomic associations in childhood Langerhans cell histiocytosis: an international cohort study. Blood Adv. 2023;7:664-679.
27. Allen CE, Ladisch S, McClain KL. How I treat Langerhans cell histiocytosis. Blood. 2015;126:26-35.
28. Sakamoto K, Kikuchi K, Sako M, Kato M, Takimoto T, Shioda Y. Pilot study to estimate the safety and effectiveness of hydroxyurea and methotrexate recurrent Langerhans cell histiocytosis (LCH-HU-pilot). Medicine (Baltimore). 2022;101:e31475.
29. Tardieu M, Néron A, Duvert-Lehembre S, Larabi IA, Barkaoui M, Emile JF, et al. Cutaneous adverse events in children treated with vemurafenib for refractory BRAFV600E mutated Langerhans cell histiocytosis. Pediatr Blood Cancer. 2021;68:e29140.
30. North American Consortium for Histiocytosis. (2016-2025). LCH-IV, International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis. Identifier NCT02205762. Available from: https://clinicaltrials.gov/study/NCT02205762
31. Sakamoto K, Morimoto A, Shioda Y, Imamura T, Imashuku S. Relapses of multisystem/multifocal bone Langerhans cell histiocytosis in paediatric patients: data analysis from the JLSG-96/02 study. Br J Haematol. 2022;200:769-775.
32. Nauert C, Zornoza J, Ayala A, Harle TS. Eosinophilic granuloma of bone: diagnosis and management. Skeletal Radiol. 1983;10:227-35.
33. De Benedittis D, Mohamed S, Rizzo L, Santopietro M, Palumbo G, Cardarelli L, et al. Indomethacin is an effective treatment in adults and children with bone Langerhans cell histiocytosis (LCH). Br J Haematol. 2020;191:e109-13.