RESEARCH ARTICLE

Editorial Process: Submission:02/09/2024 Acceptance:05/08/2024

Nationwide Study of Factors Impacting Survival Outcome and Consequences in Children with Reactivation/Refractory Langerhans Cell Histiocytosis

Chalinee Monsereenusorn[1]*, Kunanya Suwannaying[2], Jassada Buaboonnam[3], Lalita Sathitsamitphong[4], Piti Techavichit[5], Samart Pakakasama[6], Su-on Chainansamit[7], Usanarat Anurathapan[6], Patcharee Komvilaisak[2], Chanchai Traivaree[1], Kleebsabai Sanpakit[3], Pimlak Charoenkwan[4], Panya Seksarn[5]

Abstract

Background: Disease reactivation/refractory remains a major challenge in managing Langerhans cell histiocytosis (LCH). Outcomes and late sequelae should be explored. **Methods:** A multi-institutional retrospective study was conducted to describe clinical characteristics, predictive factors, outcomes and late sequelae of pediatric reactivation/refractory LCH in Thailand. **Results:** In all, 47 patients were studied, 25 (53.2%) patients had disease reactivation and 22 (46.8%) patients had refractory LCH. The median reactivation and refractory time were 1.59 and 0.33 years from diagnosis, respectively ($p < 0.001$). The most common site of reactivation/refractory was the bone (n = 26, 55%), and 20 (42.6%) patients developed late sequelae. The 5-year overall survival (OS) was 76.1%. Patients with reactivation and refractory LCH performed similarly in 5-year OS (88% vs. 63%, $p = 0.055$). Prognostic factors associated with mortality were liver, spleen, hematopoietic system and lung reactivation ($p < 0.05$). Lung reactivation was the only independent risk factor associated with the survival outcome ($p = 0.002$). **Conclusions:** The outcomes of pediatric patients between reactivation and refractory LCH in Thailand were similarly desirable and mortality was minimal although late sequelae may evolve. Pulmonary reactivation/refractory was an independent risk factor associated with survival.

Keywords: Langerhans cell histiocytosis- reactivation/refractory- mortality- pulmonary- sequelae

Asian Pac J Cancer Prev, **25 (5)**, 1831-1839

Introduction

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder characterized by clonal expansion of myeloid precursor cells containing a cluster of differentiation antigens (CD) 1a or CD207 (Langerin) histiocytes [1]. The nature of disease can occur at all ages with heterogeneous degrees and systems involvement, ranging from self-resolution single lesion to disseminated disease with life-threatening sequelae [2]. However, the 5-year overall survival of pediatric LCH among the Thai population was desirable at 91.3%, [3] which was comparable to those in developed countries [4].

The incidence of disease reactivation (23.6%) of patients with LCH was tolerably observed in Thailand [3]. However, reactivation remains a major challenge in LCH management, especially among patients aged <2 years at diagnosis and multisystem (MS) LCH patients with risk-organ involvement (RO+). These were addressed as unfavorable risk factors associated with reactivation or progressive disease among the Thai population reported by Monsereenusorn et al. [3].

Although disease refractories have been exhibited in limited illustrations, the miserable outcomes and subsequently adverse sequelae development remain substantial, reflecting major morbidities affecting various organ functions and leading to difficult management [5, 6]. Therefore, the disease characteristics, risk factors, treatment and outcomes of reactivation and refractory LCH should be clarified and well described.

*[1]Division of Hematology-Oncology, Department of Pediatrics, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand. [2]Division of Hematology-Oncology, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. [3]Division of Hematology/Oncology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. [4]Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [5]Integrative and Innovative Hematology/Oncology Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. [6]Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. [7]Department of Pediatrics, Khon Kaen Hospital, Khon Kaen, Thailand. *For Correspondence: chalinee_monsereenusorn@pedpmk.org*

The present study aimed to evaluate the clinical characteristics, risk factors and treatment outcomes of pediatric patients with LCH experiencing reactivations/refractories and to explore the sequelae after disease reactivations/refractories at seven main oncology centers in Thailand.

Materials and Methods

Patient selection

The medical records of 199 newly diagnosed LCH patients were retrospectively reviewed. One hundred and twenty-seven (63.8%) LCH patients have been previously reported by Monsereenusorn et al. [3]. The patients were treated primarily at 7 tertiary pediatric oncology centers in Thailand between January 1, 1999 and December 31, 2019. These centers were Srinagarind and Khon Kaen Hospitals, Khon Kaen; Chiang Mai University Hospital, Chiang Mai; Phramongkutklao; Chulalongkorn; Siriraj and Ramathibodi Hospitals, Bangkok, Thailand.

The inclusion criteria comprised patients with reactivation/refractory LCH aged <18 years old whose diagnosis of reactivation/refractory LCH was confirmed by histopathology with a positive result for CD1a/Langerin or radiological progression or deterioration of diabetes insipidus (DI). Patients without evidence of disease reactivation/refractory, incomplete medical records, uncertain diagnoses, and those who were lost to follow-up were excluded from the study.

Written informed consent and assent were waived. This study was approved by the Ethics Committee and Institutional Review Board of Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand (reference number: IRBRTA 232/2565) and other institutional research ethics committees from other six institutions following the ethics principles of the Declaration of Helsinki (1975) and its revision.

Clinical definitions

Patients were classified according to the Histiocyte Society LCH-IV guidelines, [7] which consider the number of lesions, number and system involvements and whether the disease involves "risk organ(s)" (the liver, spleen or hematopoietic system) as a single system (SS) or MS. SS is characterized by the involvement of one system and no risk organ involvement (RO-). MS is characterized by the involvement of ≥ 2 systems, consisting of MS with RO- or low risk, and MS with RO+ or high risk [1].

Multifocal bones (MFB) is defined as bone involvement including at least two lesions [2].

Clinical response is categorized according to the Thai Pediatric Oncology Group (ThaiPOG): ThaiPOG-LCH-1401 protocol, [3, 8] which was adapted from the Histiocyte Society LCH-III study protocol [2]. The good response (GR) was defined as the resolution of all signs and symptoms. Partial response (PR) was defined as regression of signs or symptoms, without new lesions developing. No response (NR) was defined as persistent signs or symptoms, without developing new lesions. Progressive disease (PD) was defined as the progression of signs or symptoms and/or the appearance of new lesions.

Reactivation was defined as the reappearance of signs and symptoms of active disease after either a period of disease control that persisted for >3 months or complete disease resolution, with pathological or radiological confirmation.

Refractory disease was defined as the progression or the reappearance of signs and symptoms of active disease after a period of disease control ≤ 3 months during the treatment, with pathological or radiological confirmation.

Sequelae were defined as any irreversible clinical condition developing during the active disease or after completing treatment, with direct association with the natural history of LCH, or treatment-related.

Chemotherapy regimens

Between 1999 and 2013, patients were treated as per the experience of individual institutional oncologists. Chemotherapy regimens were based on the three consortiums as follows;

The DAL-HX83 protocol (12 months of vinblastine [VBL], etoposide, 6-mercaptopurine [MP], methotrexate [MTX] and prednisolone [Pred]), [9, 10] The Japan LCH Study Group-96 (JLSG-96) [11] and JLSG-02 protocols [12, 13] (7.5 or 12 months of cytarabine, vincristine, Pred, MTX, doxorubicin and cyclophosphamide) and the International Collaborative Treatment Protocol for Children and Adolescents with LCH including LCH-I [14] and LCH-II studies [15] (6 months of VBL and Pred based regimens).

Between 2014 and 2017, ThaiPOG-LCH-1401 (12 months of VBL, Pred and 6-MP-based regimen) was launched and used as a national protocol for Thai children with LCH. Then ThaiPOG-LCH-1801 (12 or 24 months of VBL, Pred and 6-MP-based regimen)[3] was substituted and has been used since 2018 until the present time.

Outcome definition

Overall survival (OS) was defined as the period from the date of diagnosis either to the time of death resulting from any causes or to the last follow-up for surviving patients.

Statistical analysis

Patient demographic data were analyzed using descriptive statistics, presented as mean with standard deviation (normal distribution) or median with range (nonnormal distribution) for continuous variables, and calculated using frequency and percentage for categorical variables. Categorical and continuous variables were compared using Fisher's exact and Mann–Whitney U tests, respectively. The survival function was calculated using the Kaplan–Meier method. Univariate and multivariate analyses were performed to analyze the impact of possible factors on defined outcomes using Cox's Proportional Hazard Model to evaluate the effect of covariates on hazard ratio (HR). Statistical and survival analyses were performed using STATA/BE, 17.0 Software, and $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Among the 199 patients with LCH eligible for this study, 152 patients were excluded due to no evidence of disease reactivation/refractory. Therefore, a total of 47 patients (23.6%) with reactivation/refractory LCH were subsequently enrolled in this study. Among these 47 patients, there were 25 (53.2%) patients with reactivation and 22 (46.8%) patients with refractory LCH. Patient characteristics including age, sex, DI, organ and system involvement, primary and secondary treatment, the reactivation/refractory characteristics and subsequence sequelae are described in Table 1.

The patients' ages ranged from 1 month to 16 years with a median age of 1.37 years. Sex was equally distributed. Eight (17%) patients had DI at diagnosis, and the SS-to-MS ratio was 1:5. Single bone was the most common primary site (n = 4, 50%) among SS reactivation/refractory LCH. MS involvement had a RO+ of 82% (n = 32) and RO− at diagnosis of 18% (n = 7).

In total, 46 (98%) patients received chemotherapy as a primary treatment. The most commonly used chemotherapy regimen was ThaiPOG-LCH-1401. Surgery was primarily performed among 10 (21%) patients. Regarding the reactivation/refractory characteristics, fifty-one percent (n = 24) and 83% (n = 39) of patients with reactivation/refractory LCH experienced disease reactivation/refractory within one and two years after diagnosis, respectively. The median time from diagnosis to primary refractory (4 months) was shorter than the first reactivation (1.59 years) (p <0.001). The latest reactivation and refractoriness occurred 6.33 and 1.79 years after the first diagnosis, respectively.

The most common site of disease reactivation/refractory was the bone (n = 26, 55%). Patients with refractory LCH experienced liver and spleen reactivation rather than patients with LCH reactivation (p = 0.028 and 0.002, respectively). After reactivation, 39 (83%) patients received single secondary treatment, and 8 (17%) patients received combined therapy. Salvage therapies after refractory disease or reactivation included high-dose cytarabine, JLSG-96/02, Pred and VBL, 6-MP and MTX, relying on individualized institutional experts' experience and ThaiPOG-LCH-1801 protocols for patients who had disease recurrence after 2018. The clinical response after 1st reactivation/refractory of GR: non-GR (PR, NR, PD) was 1:1. Most patients had one episode of disease reactivation/refractory (n = 34, 72%). Patients with LCH reactivation had disease status at the last follow-up as GR rather than patients with refractory LCH (p = 0.008) (Table 1).

Overall survival outcomes

Eleven (23.4%) patients expired, 10 (91%) patients died from disease reactivation/refractory (6 patients from multiorgan failure, 3 patients from septic shock led to cardiopulmonary compromise, and 1 patient from septicemia with acute respiratory distress syndrome) and 1 (9%) patient died from necrotizing fasciitis at both hands and subsequently developed Streptococcus pyogenes septicemia during re-induction therapy with VBL and Pred.

The median time to death was 8 months from diagnosis (range, 10 days to 3.24 years). Five-year OS among patients with reactivation/refractory LCH was 76.1% (95% confidence interval [CI], 61 to 86%) (Figure 1). The median follow-up time was 6.15 years (range, 10 days to 19.5 years).

Outcomes of patients with reactivation vs. refractory LCH

The 5-year OS of the patients with reactivation LCH was higher (88% [95% CI, 67.3%–96%]) than refractory LCH (63% [95% CI, 39.4%–79.6%]) despite

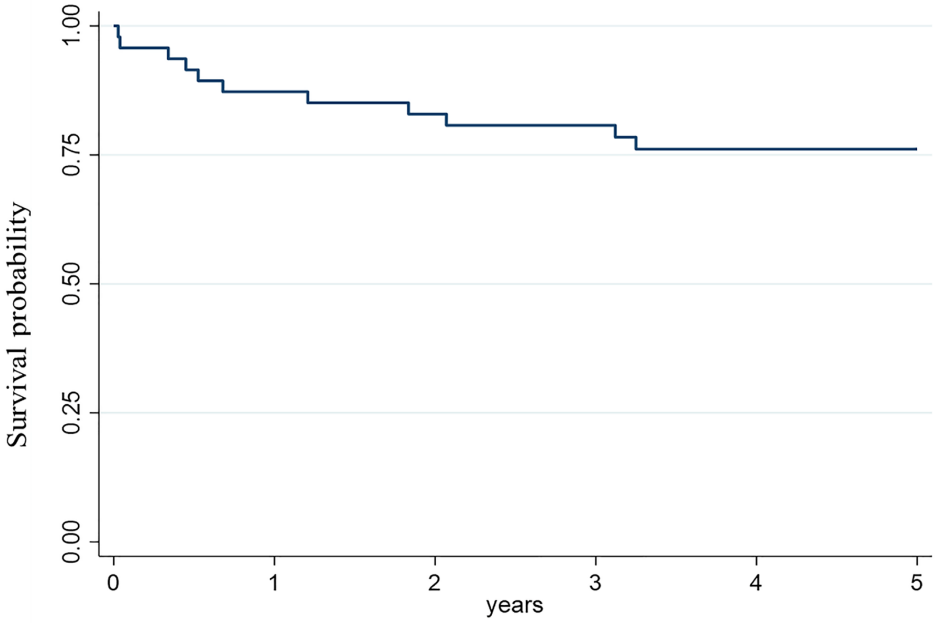

Figure 1. Overall Survival among Reactivation/Refractory LCH Patients (n=47). Note: Survival outcome was calculated using the Kaplan-Meier method. Abbreviation: LCH, Langerhans cell histiocytosis

Table 1. Patient Demographic Data (n=47)

	Reactivation (n=25) N(%)	Refractory (n=22) N(%)	Total (n=47) N(%)	p-value
Age at diagnosis (years)				0.354
Mean±SD	2.51±2.98	2.44±3.6	2.48±3.25	
Median (range)	1.48(0.42-13.95)	1.21(0.07-15.59)	1.37(0.07-15.59)	
Gender				0.302
Female	11 (45.8)	13 (54.2)	24 (51.1)	
Male	14 (60.9)	9 (39.1)	23 (48.9)	
DI at diagnosis	5 (62.5)	3 (37.5)	8 (17)	0.562
Primary system involvement				
Single system	6 (75)	2 (25)	8 (17)	0.175
Single bone	4 (100)	0 (0)	4 (50)	0.108
Multifocal bones	2 (66.7)	1 (33.3)	3 (37.5)	
Lung	0 (0)	1 (100)	1 (12.5)	
Multisystem	19 (48.7)	20 (51.3)	39 (83)	0.175
High risk (organ involvement)	14 (43.8)	18 (56.3)	32 (82.1)	0.184
Liver	13 (46.4)	15 (53.6)	28 (71.8)	0.648
Hematopoietic	11 (40.7)	16 (59.3)	27 (69.2)	0.135
Spleen	11 (45.8)	13 (54.2)	24 (61.5)	0.648
Low risk	5 (71.4)	2 (28.6)	7 (17.9)	
Primary treatment				
Chemotherapy	24 (52.2)	22 (47.8)	46 (97.9)	0.133
ThaiPOG-LCH-1401	8 (53.3)	7 (46.7)	15 (32.6)	
ThaiPOG-LCH-1801	4 (36.4)	7 (63.6)	11 (23.9)	
LCH-II	6 (66.7)	3 (33.3)	9 (19.6)	
DAL-HX-83	3 (75)	1 (25)	4 (8.7)	
ITP*	3 (100)	0 (0)	3 (6.5)	
JLSG-96/02	0 (0)	2 (100)	2 (4.3)	
LCH-I	0 (0)	2 (100)	2 (4.3)	
Surgery	8 (80)	2 (20)	10 (21.3)	0.056
Curettage	7 (87.5)	1 (12.5)	8 (80)	
Partial resection	0 (0)	1 (100)	1 (10)	
Total resection	1 (100)	0 (0)	1 (10)	
Radiation	1(50)	1 (50)	2 (4.3)	0.926
Topical steroid	4 (80)	1 (20)	5 (83.3)	0.121
Bisphosphonate	0 (0)	1 (100)	1 (16.7)	
Time from diagnosis to first reactivation/primary refractory (years)				<0.001
Mean±SD	2±1.31	0.51±0.45	1.3±1.25	
Median (range)	1.59 (0.69-6.33)	0.33(0.02-1.79)	0.99(0.02-6.33)	
Organ reactivation/refractory				
Bone	14(53.8)	12 (46.2)	26 (55.3)	0.92
Hematopoietic	6 (40)	9 (60)	15 (31.9)	0.215
Liver	4 (28.6)	10 (71.4)	14 (29.8)	0.028
Spleen	2 (18.2)	9 (81.8)	11 (23.4)	0.002
Skin	6 (54.5)	5 (45.5)	11 (23.4)	0.918
Lung	3 (33.3)	6 (66.7)	9 (19.1)	0.184
CNS risk lesion/special sites^	6 (66.7)	3 (33.3)	9 (19.1)	0.368
Endocrine	4 (66.7)	2 (33.3)	6 (12.8)	0.479
Lymph nodes	3 (75)	1 (25)	4 (8.5)	0.361

Table 1. Continued

	Reactivation (n=25) N(%)	Refractory (n=22) N(%)	Total (n=47) N(%)	p-value
Secondary treatment				NA
Single treatment	22 (56.4)	17 (43.6)	39 (83)	
Chemotherapy	21 (55.3)	17 (44.7)	38 (80.9)	
Pamidronate	1 (100)	0 (0)	1 (2.1)	
Combined treatment	3 (37.5)	5 (62.5)	8 (17)	
Chemotherapy and pamidronate	0 (0)	4 (100)	4 (8.5)	
Chemotherapy and radiation	3 (100)	0 (0)	3 (6.4)	
Radiation and pamidronate	0 (0)	1 (100)	1 (2.1)	
Clinical response after the first reactivation/primary refractory				
Good response	16 (64)	9 (36)	25 (53.2)	
Non-good response	9 (40.9)	13 (59.1)	22 (46.8)	
Number of total reactivations/refractories				0.453
1	19 (55.9)	15 (44.1)	34 (72.3)	
2	3 (33.3)	6 (66.7)	9 (19.1)	
3	2 (66.7)	1 (33.3)	3 (6.4)	
4	1 (100)	0 (0)	1 (2.1)	
Clinical response at last follow-up				0.008
Good response	21 (70)	9 (30)	30 (63.8)	
Partial response	1 (16.7)	5 (83.3)	6 (12.8)	
No response	1 (100)	0 (0)	1 (2.1)	
Progressive disease	2 (20)	8 (80)	10 (21.3)	
Sequelae				
DI	6 (66.7)	3 (33.3)	9 (19.1)	0.368
Liver**	1 (20)	4 (80)	5 (10.6)	0.116
Bone	2 (50)	2 (50)	4 (8.5)	0.894
Other endocrinopathies	1 (25)	3 (75)	4 (8.5)	0.237
Hearing	1 (50)	1 (50)	2 (4.3)	0.926
Skin	0 (0)	2 (100)	2 (4.3)	0.123
Lung#	0 (0)	1 (100)	1 (2.1)	0.281
CNS degeneration	1 (100)	0 (0)	1 (2.1)	0.343

*, Individualized treatment protocol (ITP) was the protocol used for individualized patients including cyclophosphamide, vincristine, cytarabine and prednisolone; ^, Central nervous system (CNS) risk lesions are those involving sphenoid, orbital, ethmoid, zygomatic or temporal bones. Special sites include intracranial soft tissue extension or vertebral lesions with intraspinal soft tissue extension.; **, Liver sequelae was defined as liver dysfunction (hyperbilirubinemia, hypoproteinemia, hypoalbuminemia, elevated alkaline phosphatase, elevated transaminases, gamma-glutamyl transferase (GGT), ascites, edema; #, Lung sequelae was defined as pulmonary dysfunction (abnormal pulmonary function test, pulmonary fibrosis, cystic lung disease); Notes: Data are presented as mean±SD or median (range) for continuous variables and number (%) for categorical variables. Comparison between two independent data sets was analyzed using Fisher's exact or Mann–Whitney U test (age at diagnosis and time from diagnosis to first reactivation/primary refractory). Statistical significance was considered at $p < 0.05$; Abbreviations: CNS, central nervous system; DI, diabetes insipidus; ITP, individualized treatment protocol; JLSG, The Japan Langerhans cell histiocytosis Study Group; LCH, Langerhans cell histiocytosis; NA, not available; SD, standard deviation; ThaiPOG, Thai Pediatric Oncology Group

the statistically insignificant (p = 0.055, HR, 3.676; 95% CI, 0.974–13.877) (Figure 2).

Factors associated with survival outcomes in reactivation/refractory LCH

The liver, spleen, hematopoietic system and lung reactivation/refractory were significantly associated with survival outcomes from univariate analysis ($p <0.05$). However, lung reactivation/refractory was the only independent risk factor associated with the survival outcome in subsequent multivariate analysis (p = 0.002) (Table 2).

Late sequelae

As a consequence, 20 (42.6%) patients developed late sequelae. The most common sequela was DI (n = 9, 19%). The development of sequelae was indifferent between patients with reactivation and refractory LCH ($p \geq 0.05$) (Table 1).

Discussion

The treatment outcomes of newly diagnosed LCH using the national ThaiPOG-LCH protocols were desirable [16, 3] compared to other developed countries [4, 17].

Table 2. Predictive Factors Associated with Survival Outcomes in Pediatric Patients with Reactivation/Refractory LCH (n=47)

	Total (n=47) N (%)	Survive (n=36) N (%)	Expired (n=11) N (%)	Crude HR	Crude 95%CI	Crude p value	Adjusted HR	Adjusted 95%CI	Adjusted p value
Disease status at the first recurrence									
Reactivation	25 (53.2)	22 (88)	3 (12)	1			1		
Primary refractory	22 (46.8)	14 (63.6)	8 (36.4)	3.676	0.974-13.877	0.055	1.169	0.215-6.357	0.856
Primary system involvement									
Single-system and multisystem low-risk	15 (31.9)	13 (86.7)	2 (13.3)	1			1		
Multisystem high risk	32 (68.1)	23 (71.9)	9 (28.1)	1.814	0.392-8.401	0.446	0.26	0.023-2.994	0.28
Liver reactivation/refractory									
None	33 (70.2)	30 (90.9)	3 (9.1)	1			1		
Involvement	14 (29.8)	6 (42.9)	8 (57.1)	7.982	2.101-30.328	0.002	5.045	0.42-60.549	0.202
Spleen reactivation/refractory									
None	36 (76.6)	31 (86.1)	5 (13.9)	1			1		
Involvement	11 (23.4)	5 (45.5)	6 (54.5)	4.799	1.457-15.806	0.01	1.51	0.322-7.09	0.601
Hematopoietic system reactivation/refractory									
None	32 (68.1)	28 (87.5)	4 (12.5)	1			1		
Involvement	15 (31.9)	8 (53.3)	7 (46.7)	4.495	1.309-15.433	0.017	4.134	0.791-21.594	0.092
Lung reactivation/refractory									
None	38 (80.9)	33 (86.8)	5 (13.2)	1			1		
Involvement	9 (19.1)	3 (33.3)	6 (66.7)	8.333	2.516-27.602	0.001	10.036	2.378-42.351	0.002

Notes: Data is presented as number (%) for categorical variables. Univariate analysis and multivariate analysis were calculated using Cox's Proportional Hazard Model. P <0.05 is considered statistical significance; Abbreviations: CI, confidence interval; HR, Hazard ratio; LCH, Langerhans cell histiocytosis

However, the incidence of disease reactivation in patients with LCH remained high at 23.6% in Thailand, [3] which may have been due to limited resources to detect disease reactivation [18, 19]. The other factors associated with reactivation rate were SS-to-MS ratio, BRAFV600E status, [20, 21] and chemotherapy regimens applied, which may vary in distinct study populations.

Reactivation/refractory LCH is a challenging clinical course with a dismal prognosis, affecting unsatisfactory consequences. Most studies reported the characteristics and outcomes among patients with reactivation LCH, but rarely with refractory LCH. However, the characteristics and outcomes between these two entities should be elucidated to predict the outcomes and providing appropriate management. Reactivation of MFB and MS-LCH has previously been described by the Histiocyte

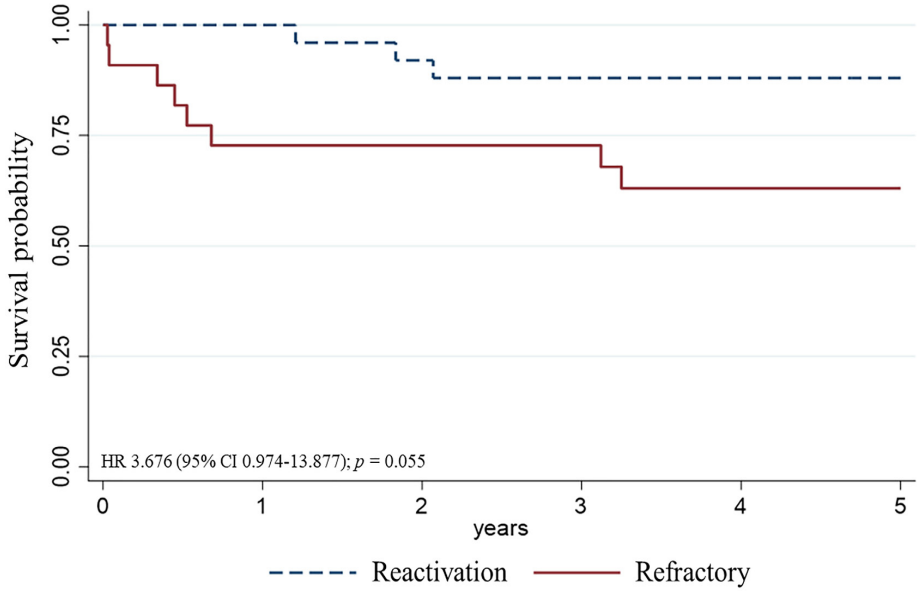

Figure 2. Overall Survival between Reactivation vs. Refractory LCH Patients (n=47). Notes: The survival function was calculated using the Kaplan-Meier method and compared using Cox's Proportion Hazard Model. P-value <0.05 is considered as statistical significance. Abbreviation: LCH,Langerhans cell histiocytosis

Society [22] and Japan LCH Study Group [23]. Moreover, the disease reactivation was observed particularly in patients with RO+ MS-LCH compared with those of RO- MS-LCH and SS-LCH in Thailand [3]. However, our study found that the primary system involvement was not clinically significant observed between patients with reactivation and refractory LCH.

The reactivations were detected more than once for 34.8% of patients with reactivation LCH from the report in Argentina, [5] and 20% of Egyptian children, [24] compared with 24% in the Thai population in our study. Nevertheless, the first reactivations were particularly (88%) observed within two years, [5, 25, 23] which agrees with our study (83%). On the other hand, we reported the latest reactivation developed six years after diagnosis.

Although reactivation generally occurred, the reactivation was associated with minimal mortality with a ratio of death of MS-to-SS of 2:1 [22]. Moreover, the five-year OS for newly diagnosed LCH was 91.3%, [3] compared to 76.1% among patients with reactivation/refractory LCH. These may relate to most patients achieving no active disease (NAD) status after effective salvage therapy [23] as well as no statistical distinction identified for the survival outcomes among patients with reactivation and refractory LCH, likewise addressed in our study. These results underlined the non-lethal nature of LCH reactivations/refractories, contrary to disease relapse in general malignant disorders.

Even though the mortality rate was slightly observed among patients with reactivation/refractory LCH, the associated factors impacting survival are mandatory to explore but have not been determined in any study report yet. Interestingly, our study determined the indistinctive outcomes after salvage therapy between SS/RO- and RO+ MS-LCH with reactivation/refractory although the outcomes of newly diagnosed RO+ MS-LCH are poor [3].

The factor associated with survival outcomes in reactivation/refractory LCH was a specific organ recurrence. The hematopoietic system, liver, spleen and pulmonary recurrence were subordinate risk factors associated with survival outcomes among patients with reactivation/refractory LCH. These findings may have resulted because most patients with reactivation/refractory LCH experience multiple organ recurrence. Also, LCH treatment outcomes were inferior by the number of RO+ [3]. Interestingly, pulmonary recurrence was the only independent risk factor related to survival outcomes in this study. Pulmonary LCH is rare in children but commonly occurs among smoking adults, [26] and isolated pulmonary LCH is also barely seen [2, 27] Children with pulmonary LCH are routinely observed in MS-LCH, [28, 29] and combined with other organ involvement for 48% [30]. Only 9% [28] to 50% [29] of patients with pulmonary LCH presented respiratory symptoms. Le Louet, S et al. [30] reported 14 of 17 (82%) patients with LCH who presented with respiratory failure in intensive care, had lung involvement. Also, 35% of those patients died from severe respiratory failure. Moreover, lung involvement RO+ MS-LCH exhibited an inferior outcome than RO- MS-LCH, [28]. Lung involvement caused severe pulmonary hypertension and finally required lung transplantation [31]. Therefore, death from pulmonary reactivation is possible due to severe lung involvement [30] leading to respiratory failure, combined with multiple organ failure from multi-organ involvement, [16] or concomitantly with infection such as invasive fungal disease [32].

Permanent sequelae have been addressed in 42 to 71% [33, 34, 5] of patients with LCH. A higher incidence of sequelae was observed in MS-LCH [35, 34] or patients with BRAFV600E mutation [36]. A strong prevalence (42.6%) was noticed in our study among patients with reactivation/refractory LCH [22, 5, 23]. However, sequelae were indifferently addressed between patients with reactivation and refractory LCH. The most common sequela was DI [34], followed by skeletal or ear abnormalities, [35, 5, 37, 17] similarly found in our study. These sequelae possibly developed anytime, either related to treatment [35] or after completed treatment. The various treatment protocols may affect the distinction of late sequelae. Nonetheless, reactivation remarkably affected the long-term sequelae [25, 23]. Herein, the lower incidence of reactivation perhaps from prolonged intensified upfront treatment may reduce the sequelae [25, 8]. Decreasing morbidity and disease consequences after disease reactivation is significantly warranted.

The present study is the first multicenter study to explore the clinical characteristics, factors associated with outcomes and late sequelae in patients with reactivation/refractory LCH using the ThaiPOG-LCH protocols. A standardized national protocol using prolonged intensive chemotherapy was well established to improve the outcomes of the long-term consequences.

Limitations

This study illustrated a retrospective study in which some data were unavailable. The study included only patients with reactivation/refractory LCH from seven main institutions that treated LCH might not elaborate on the whole picture of reactivation/refractory LCH in Thailand. Different timelines and duration of treatment according to different treatment protocols and distinctive follow-up times could also have affected the outcomes. Shortened follow-up time may be inadequate to access the late sequelae. Treatment-related mortality and treatment-associated long-term consequences should be further explored. Patients presenting SS-LCH not treated by pediatric oncologists, such as those with CNS-risk lesions or isolated cutaneous LCH, were not enrolled in this study. The unavailability of essential investigations such as BRAFV600E activating mutation testing, due to resource-limited settings, could relate to distinct outcomes. Prospective multicenter studies with molecular testing and longitudinal follow-up are mandatory to detect and monitor the consequence of disease, especially after disease reactivation/refractory.

In conclusions, the outcomes of pediatric patients between reactivation and refractory LCH in Thailand were similarly desirable and mortality was minimal, although late sequelae later evolved. Most patients presented disease reactivation within two years after initial diagnosis. Prognostic factors included liver,

spleen, hematopoietic system and pulmonary reactivation/refractory. Only pulmonary reactivation/refractory remained an independent risk factor significantly associated with survival outcomes.

Author Contribution Statement

CM conceptualized and designed the study, collected, analyzed, and interpreted data, and drafted and edited the manuscript. SP contributed to the conception and design of the work. PC assisted in conceptualizing the study. All authors contributed to patients' care, collected data and critically reviewed and approved the final manuscript.

Acknowledgements

The authors gratefully acknowledged Mrs. Supak Cae-Ngow, Office of Research and Development, Phramongkutklao College of Medicine for statistical analysis and ThaiPOG for supporting this study.

Funding

The funding to conduct the study was obtained from the Thai Society of Hematology and Phramongkutklao College of Medicine, Royal Thai Army.

Scientific content approval

The manuscript was reviewed and approved by the Office of Research and Development, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand. This manuscript was not a part of an approved student thesis.

Ethics approval

This study was approved by the Ethics Committee and Institutional Review Board of Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand (reference number: IRBRTA 232/2565) and other institutional research ethics committees from other six institutions following the ethics principles of the Declaration of Helsinki (1975) and its revision.

Data sharing statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy or ethical restrictions. The data are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood. 2020. https://doi.org/10.1182/blood.2019000934.
2. Monsereenusorn C, Rodriguez-Galindo C. Clinical characteristics and treatment of langerhans cell histiocytosis. Hematol Oncol Clin North Am. 2015;29(5):853-73. https://doi.org/10.1016/j.hoc.2015.06.005.
3. Monsereenusorn C, Suwannaying K, Techavichit P, Sathitsamitphong L, Komvilaisak P, Rujkijyanont P, et al. Clinical outcomes and screening for organ involvement in pediatric langerhans cell histiocytosis in thailand: Multicenter study on behalf of the thai pediatric oncology group. Int J Hematol. 2022;115(4):563-74. https://doi.org/10.1007/s12185-022-03293-0.
4. 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(5):728-38. https://doi.org/10.1111/bjh.18459.
5. Pollono D, Rey G, Latella A, Rosso D, Chantada G, Braier J. Reactivation and risk of sequelae in langerhans cell histiocytosis. Pediatr Blood Cancer. 2007;48(7):696-9. https://doi.org/10.1002/pbc.21145.
6. Veys PA, Nanduri V, Baker KS, He W, Bandini G, Biondi A, et al. Haematopoietic stem cell transplantation for refractory langerhans cell histiocytosis: Outcome by intensity of conditioning. Br J Haematol. 2015;169(5):711-8. https://doi.org/10.1111/bjh.13347.
7. Lch-iv, international collaborative treatment protocol for children and adolescents with langerhans cell histiocytosis. https://www.clinicaltrials.gov/ct2/show/NCT02205762.
8. Gadner H, Minkov M, Grois N, Potschger U, Thiem E, Arico M, et al. Therapy prolongation improves outcome in multisystem langerhans cell histiocytosis. Blood. 2013;121(25):5006-14. https://doi.org/10.1182/blood-2012-09-455774.
9. Gadner H, Heitger A, Grois N, Gatterer-Menz I, Ladisch S. Treatment strategy for disseminated langerhans cell histiocytosis. Dal hx-83 study group. Med Pediatr Oncol Suppl. 1994;23(2):72-80. https://doi.org/10.1002/mpo.2950230203.
10. Minkov M, Grois N, Heitger A, Potschger U, Westermeier T, Gadner H. Treatment of multisystem langerhans cell histiocytosis. Results of the dal-hx 83 and dal-hx 90 studies. Dal-hx study group. Klin Padiatr. 2000;212(4):139-44. https://doi.org/10.1055/s-2000-9667.
11. Morimoto A, Ikushima S, Kinugawa N, Ishii E, Kohdera U, Sako M, et al. Improved outcome in the treatment of pediatric multifocal langerhans cell histiocytosis: Results from the japan langerhans cell histiocytosis study group-96 protocol study. Cancer. 2006;107(3):613-9. https://doi.org/10.1002/cncr.21985.
12. Morimoto A, Shioda Y, Imamura T, Kudo K, Kitoh T, Kawaguchi H, et al. Intensification of induction therapy and prolongation of maintenance therapy did not improve the outcome of pediatric langerhans cell histiocytosis with single-system multifocal bone lesions: Results of the japan langerhans cell histiocytosis study group-02 protocol study. Int J Hematol. 2018;108(2):192-8. https://doi.org/10.1007/s12185-018-2444-0.
13. 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(1):99-109. https://doi.org/10.1007/s12185-016-1993-3.
14. Gadner H, Grois N, Arico M, Broadbent V, Ceci A, Jakobson A, et al. A randomized trial of treatment for multisystem langerhans' cell histiocytosis. J pediatr. 2001;138(5):728-34. https://doi.org/10.1067/mpd.2001.111331.
15. Gadner H, Grois N, Potschger U, Minkov M, Arico M, Braier J, et al. Improved outcome in multisystem langerhans cell histiocytosis is associated with therapy intensification.

Blood. 2008;111(5):2556-62. https://doi.org/10.1182/blood-2007-08-106211.
16. Kitticharoenjit P, Supakul N, Rujkijyanont P, Traivaree C, Photia A, Monsereenusorn C. Clinical characteristics and outcomes of langerhans cell histiocytosis at a single institution in thailand: A 20-year retrospective study. Asian Biomed. 2021;15(4):171-81. https://doi.org/doi:10.2478/abm-2021-0022.
17. Rigaud C, Barkaoui MA, Thomas C, Bertrand Y, Lambilliotte A, Miron J, et al. Langerhans cell histiocytosis: Therapeutic strategy and outcome in a 30-year nationwide cohort of 1478 patients under 18 years of age. Br J Haematol. 2016;174(6):887-98. https://doi.org/10.1111/bjh.14140.
18. Othman MY, Blair S, Nah SA, Ariffin H, Assanasen C, Soh SY, et al. Pediatric solid tumor care and multidisciplinary tumor boards in low- and middle-income countries in southeast asia. JCO Glob Oncol. 2020;6:1328-45. https://doi.org/10.1200/GO.20.00284.
19. Monsereenusorn C, Friedrich P, Alcasabas P, Lam C, Rodriguez-Galindo C. Burden of pediatric solid tumors management in south-east asia countries. Pediatr Blood Cancer. 2017;64:S416-S.
20. Heritier 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(25):3023-30. https://doi.org/10.1200/JCO.2015.65.9508.
21. Kemps PG, Zondag TCE, Arnardottir 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(4):664-79. https://doi.org/10.1182/bloodadvances.2022007947.
22. Minkov M, Steiner M, Potschger U, Arico M, Braier J, Donadieu J, et al. Reactivations in multisystem langerhans cell histiocytosis: Data of the international lch registry. J pediatr. 2008;153(5):700-5, 5 e1-2. https://doi.org/10.1016/j.jpeds.2008.05.002.
23. Sakamoto K, Morimoto A, Shioda Y, Imamura T, Imashuku S, Japan LCHSG. Relapses of multisystem/multifocal bone langerhans cell histiocytosis in paediatric patients: Data analysis from the jlsg-96/02 study. Br J Haematol. 2023;200(6):769-75. https://doi.org/10.1111/bjh.18583.
24. Sedky MS, Rahman HA, Moussa E, Taha H, Raafat T, Hassanein O. Langerhans cell histiocytosis (lch) in egyptian children: Does reactivation affect the outcome? Indian J Pediatr. 2016;83(3):214-9. https://doi.org/10.1007/s12098-015-1801-8.
25. Morimoto A, Kobayashi R, Maeda M, Asami K, Bessho F, Imashuku S, et al. Impact of reactivation on the sequelae of multi-system langerhans cell histiocytosis patients. Pediatr Blood Cancer. 2008;50(4):931-2; author reply 2. https://doi.org/10.1002/pbc.21315.
26. Vassallo R, Ryu JH. Pulmonary langerhans' cell histiocytosis. Clin Chest Med. 2004;25(3):561-71, vii. https://doi.org/10.1016/j.ccm.2004.04.005.
27. Varkki S, Tergestina M, Bhonsle VS, Moses PD, Mathai J, Korula S. Isolated pulmonary langerhans cell histiocytosis. Indian J Pediatr. 2013;80(8):700-3. https://doi.org/10.1007/s12098-012-0866-x.
28. Wang D, Cui L, Li ZG, Zhang L, Lian HY, Ma HH, et al. Clinical research of pulmonary langerhans cell histiocytosis in children. Chin Med J (Engl). 2018;131(15):1793-8. https://doi.org/10.4103/0366-6999.237400.
29. Odame I, Li P, Lau L, Doda W, Noseworthy M, Babyn P, et al. Pulmonary langerhans cell histiocytosis: A variable disease in childhood. Pediatr Blood Cancer. 2006;47(7):889-93. https://doi.org/10.1002/pbc.20676.
30. Le Louet S, Barkaoui MA, Miron J, Galambrun C, Aladjidi N, Chastagner P, et al. Childhood langerhans cell histiocytosis with severe lung involvement: A nationwide cohort study. Orphanet J Rare Dis. 2020;15(1):241. https://doi.org/10.1186/s13023-020-01495-5.
31. Dauriat G, Mal H, Thabut G, Mornex JF, Bertocchi M, Tronc F, et al. Lung transplantation for pulmonary langerhans' cell histiocytosis: A multicenter analysis. Transplantation. 2006;81(5):746-50. https://doi.org/10.1097/01.tp.0000200304.64613.af.
32. Monsereenusorn C, Sricharoen T, Rujkijyanont P, Suwanpakdee D, Photia A, Lertvivatpong N, et al. Clinical characteristics and predictive factors of invasive fungal disease in pediatric oncology patients with febrile neutropenia in a country with limited resources. Pediatric Health Med Ther. 2021;12:335-45. https://doi.org/10.2147/PHMT.S299965.
33. Chow TW, Leung WK, Cheng FWT, Kumta SM, Chu WCW, Lee V, et al. Late outcomes in children with langerhans cell histiocytosis. Arch Dis Child. 2017;102(9):830-5. https://doi.org/10.1136/archdischild-2016-312185.
34. Bernstrand C, Sandstedt B, Ahstrom L, Henter JI. Long-term follow-up of langerhans cell histiocytosis: 39 years' experience at a single centre. Acta Paediatr. 2005;94(8):1073-84. https://doi.org/10.1111/j.1651-2227.2005.tb02048.x.
35. Haupt R, Nanduri V, Calevo MG, Bernstrand C, Braier JL, Broadbent V, et al. Permanent consequences in langerhans cell histiocytosis patients: A pilot study from the histiocyte society-late effects study group. Pediatr Blood Cancer. 2004;42(5):438-44. https://doi.org/10.1002/pbc.20021.
36. Heritier S, Barkaoui MA, Miron J, Thomas C, Moshous D, Lambilliotte A, et al. Incidence and risk factors for clinical neurodegenerative langerhans cell histiocytosis: A longitudinal cohort study. Br J Haematol. 2018;183(4):608-17. https://doi.org/10.1111/bjh.15577.
37. Braier J, Chantada G, Rosso D, Bernaldez P, Amaral D, Latella A, et al. Langerhans cell histiocytosis: Retrospective evaluation of 123 patients at a single institution. Pediatr Hematol Oncol. 1999;16(5):377-85. https://doi.org/10.1080/088800199276921.