American Journal of
Health, Medicine and Nursing Practice
(AJHMN)

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American Journal of Health, Medicine and Nursing Practice
ISSN 2520-4017 (Online)
Vol.6, Issue 1, pp 38-50, 2021
www.ajpojournals.org

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ISSN 2520-4017 (Online)
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www.ajpojournals.org

Abstract

Background: Langerhans cell histiocytosis (LCH) is a rare disease affects any age and any organ; its presentations and outcome vary from self-healing lesions to life-threatening disseminated disease. This study evaluated the outcome of treating children diagnosed with Langerhans cell histiocytosis (LCH) at Oncology Center, Saudi Arabia.

Methodology: Through a retrospective study design, the researchers reviewed the medical records and electronic files of all children (aged from 0-≤ 14 years) who had been diagnosed and treated for LCH at Princess Norah Oncology Center (PNOC), King Abdelaziz Medical City, Saudi Arabia, in the period from January 2000 to December 2019 (n=33).

Findings: Males constituted (66.7%), with remarkable dominance of Saudis (93.9%). The median age at diagnosis was 28 months (IQR=49 months); (42.4%) were diagnosed before reaching their second birthday**.** Fourteen patients (42.4%) had multisystem (MS-LCH) involvement, of which 13 patients with risk organ (RO) (+) and one patient without risk organ (RO) (-). Most of the patients received LCH III protocols. Reactivation occurred in 11 patients (33.3%), and two deaths (6.1%) occurred in cases with MS (RO) (+) progressive disease. The overall survival was 93.9%; with no statistically significant difference in event free survival observed between patients with multisystem compared to single system involvement.

Conclusion and recommendations: Excellent outcome of LCH is associated with single system involvement and worse outcome (reactivations, or morality) is determined by multi-organ involvement especially at younger age less than 24 months. Better understanding of pathophysiology and genetic molecular background could lead to a striking transformation to novel therapy that warrants a prospective clinical trial. A high mortality in patients with progressive disease demands an earlier aggressive salvage in such group. Prospective clinical trials are required for improved treatment strategies in these subgroups.

Keywords*: Survival, Pediatric, Langerhans histiocytosis, Multi-system LCH, Single-system LCH.*

1. Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder characterized by a reactive clonal proliferation and accumulation of dendritic cells with a wide range of clinical presentations ranging from a self-healing unifocal single system involvement to a fatal multisystem disease involving lungs, liver, spleen, and the hematopoietic system (Abla et al., 2010; Nezelof & Basset, 2004). The etiology of LCH is undetermined. Consistent data on incidence are difficult to obtain, only a few international and regional reports and studies of the disease have been presented (Cotterill et al., 2000; Kaatsch et al., 1995). For single bone lesions, a biopsy or curettage at the time of diagnosis is enough for the treatment. If surgical excision is not feasible, or multisystem disease involvement, other treatment modalities, such as chemotherapy or radiotherapy, are required (Broadbent et al., 1994).

Due to the heterogeneity of the clinical presentations of LCH among the pediatric age group and the need to determine the proper therapy to prevent recurrence and progression, we determine to evaluate the clinical presentations, frequency of disease reactivations, prognostic factors, the treatment outcome, and the sequalae of this disorder among Saudi children during a 20-year period.

2. Methodology

Through a descriptive record based study design, all pediatric cases aged from 0-≤ 14 years who had been diagnosed and treated for LCH, at Princess Norah Oncology Center (PNOC), King Abdelaziz Medical City, Jeddah, in the period from January 2000 to December 2019 were eligible for inclusion in the study (n=33). the researchers reviewed the medical records and electronic files of the cases. SPSS ver 24 was used for data analysis, Chi square was used for testing significance of difference in distribution of system involvement (categorical) and Kaplan Meier was used for testing the overall and event free survival of the cases. Significance was considered for $p<0.05$.

3. Results:

Table 1: Characteristics of the patients (n=33).

Characteristics	No.	Percentage
Gender:		
Male	22	66.7
Female	11	33.3
Nationality:		
Saudi	31	93.9
Non-Saudi	2	6.1
Age at diagnosis:		
<24months	14	42.4
≥24 months	19	57.6
Presenting clinical findings:		
Swelling	23	69.7
Pain	10	30.3
Skin rash	9	27.3
Liver dysfunction	5	15.2
Ear dysfunction	5	15.2
Polyurea/Polydipsia	5	15.2
Diarrhea and failure to thrive	3	9.1
Others	10	30.3
Organ involved:		
Bone unifocal	20	60.6
Bone multifocal	14	42.4
Soft tissue	15	45.5
Liver	10	30.3
Skin	9	27.3
Lymph nodes	6	18.2
Spleen	5	15.2
Lung	4	12.1
Pituitary gland	1	3.0
Special site involvement:		
CNS	15	45.5
Vertebrae	6	18.2
Femur	2	6.1
Lab results at diagnosis:		
ESR >20	21	63.6
Hb <10 or infant < 9	8	24.2
Bilirubin >18	5	15.2
PLT <100	4	12.1
ALT >2xULN	4	12.1
AST >2xULN	4	12.1
Albumin <25	2	6.1
WBC <4000	1	3.0
LDH >500	1	3.0
Classification of the disease:		
Multisystem RO (+)	13	39.4
Single system unifocal	12	36.4
Multifocal single system	7	21.2
Multisystem RO (-)	1	3.0

Males constituted two thirds of the patients (66.7%), (M:F ratio =2) with remarkable dominance of Saudis (93.9%). The median age at diagnosis was 28 months (IQR=49 months); and slightly less than one half of the patients (42.4%) were diagnosed before reaching their second birthday. The median follow-up time was 72.1 months (IQR=86.3). Clinically, the most prominent presenting clinical findings were swelling (69.7%), bone related pain (30.3%), skin rash (27.3%), and polyurea/polydipsia (15.2%). The most involved organs were the bones, whether unifocal (60.6%) or multifocal (42.4%), skull bones (n = 12) most frequently affected bones, followed by vertebrae (n = 6) and femur (n = 5). Other organs involved the soft tissue (45.5%) and the liver (30.3%); with special site involvement of CNS (45.5%) and vertebrae (18.2%). The lab results showed that almost two thirds of the patients had ESR>20, and (24.2%) with lower Hb level, while 15.2% had increased bilirubin level >18. Fourteen patients (42.4%) had multisystem involvement, of which 13 patients (39.4%) with risk organ involvement (RO) (+) and one patient (3.0%) without risk organ (RO) (-). Six patients (18.2%) patients with multisystem disease had 2 organs involvement, one patient (3.0%) had 3 organs, one patient (3.0%) had 4 organs, and 6 patients (33.3%) had 5 organs involvement. Twelve patients (36.4%) were staged as single system unifocal, while 7 patients (21.2%) were classified as multifocal single system **[Table 1]**.

Table 2: Comparing multisystem and single system involvement according to demographic characteristics and outcome.

Characteristics	System involvement				X^2	P*
	Multisystem (n=14)		Single system (n=19)			
	No	%	No	%		
Gender:						
Male	8	57.1%	14	73.7%		
Female	6	42.9%	5	26.3%	0.992	0.319
Age categories:						
<24 months	10	71.4%	4	21.1%		
≥24 months	4	28.6%	15	78.9%	8.375	0.004**
Reactivation:						
Yes	7	50.0%	4	21.1%		
No	7	50.0%	15	78.9%	3.039	0.086
Outcome						
Alive in CR	12	85.7%	16	84.2%		
Alive with disease	0	0.0%	3	15.8%	NA	NA
Died	2	14.3%	0	0.0%		

** Based on Chi Square ** Statistically significant NA not applicable*

No statistically significant difference was detected between multisystem and single system patients according to their gender p>0.05 **[Table 2]**; yet multisystem risk organ involvement was significantly more observed among patients aged < 24 months (71.4%) compared to patients with single system (21.1%) p<0.05. Although statistically not significant (p>0.086), one half of the patients with multisystem involvement (50.0%) had more reactivations compared to 21.1% of single system patients. Two multisystem patients died, one of them died after liver transplant and the other died during reactivation.

American Journal of Health, Medicine and Nursing Practice
ISSN 2520-4017 (Online)
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www.ajpojournals.org

Table 3: Treatment protocols and outcomes (n=33).

Treatment protocols and outcome	No.	Percentage
Treatment provided:		
Surgery	6	18.2
Radiotherapy	1	3.0
Observation	1	3.0
Chemotherapy	26	78.8
Chemotherapy protocol name		
LCHIII Arm A*	25	75.7
LCHIII Arm B*	1	3.0
Initial therapy		
VBL/PDN*	26	78.8
6 MP Given	17	51.5
Salvage	4	12.1
Duration of initial therapy (n=26):		
6 months	2	7.7
12 months	22	84.6
24 months	2	7.7
Response after 6 weeks:		
Active disease better	15	45.5
Active disease intermediate	10	30.3
Active disease worse	1	3.0
NA	7	21.2
Response after 12 weeks:		
Active disease better	20	60.6
Active disease intermediate	2	6.1
Active disease worse	1	3.0
NA	10	30.3
Response at the end of therapy:		
Complete remission	25	75.8
Active disease	5	15.1
NA	3	9.1
Duration till complete remission:		
End of therapy	20	60.6
After 12 weeks	3	9.1
After surgical resection	3	9.1
Postradiotherapy	1	3.0
NA	6	18.2
Reactivation (n=11):		
Number of reactivations		
Once	9	81.8
Twice	1	0.9
Thrice	1	0.9
Duration from remission to reactivations		
Between 3-6 months	6	54.5
>6 months	5	45.5

**VBL: Vinblastine. PDN: Prednisone. LCH III: Langerhans Cell Histiocytosis protocol III*

Table 3 illustrates the treatment modalities provided to the patients, the great majority received chemotherapy (78.8%) with six-week initial therapy of Vinblastine and Prednisone

(VBL/PDN), according to LCH III protocol arm A **[Appendix]**, only one patient (3%) received LCH III Arm B (with addition of Methotrexate 500 mg/m2) protocols. The initial therapy was given for an average of 12 months for the overwhelming majority of the patients (84.6%), while only two patients (7.7%) received the treatment for a shorter duration (6 months) and another two received it for a longer duration (24 months). On the other hand, six patients (18.2%) underwent surgical operation and only one patient (3.0%) received radiotherapy, while only one patient was set under observation. After six weeks of treatment, slightly less than one half of the patients (45.5%) achieved active disease-better, while in one third (30.3%) of the patients the active disease was intermediate and only one patient became worse. Moreover, after 12 weeks, there was increase in the proportion of patients who achieved disease better up to 60.6%. At the end of therapy, complete remission was observed three out of every four treated patients (75.8%). On estimating the duration between starting treatment and complete remission, it was found that it was achieved after 12 weeks in 9.1% of the patients and achieved at the end of therapy in 60.6% of the patients. Reactivation occurred in 11 patients (33.3%), slightly more than one half of them (54.5%) had reactivation in the first six months after remission, while the rest (45.4%) had reactivation after six months of remission. Most of patients (81.8%) had reactivations once, while one patient had two episodes, and another one patient had thrice episodes of reactivation.

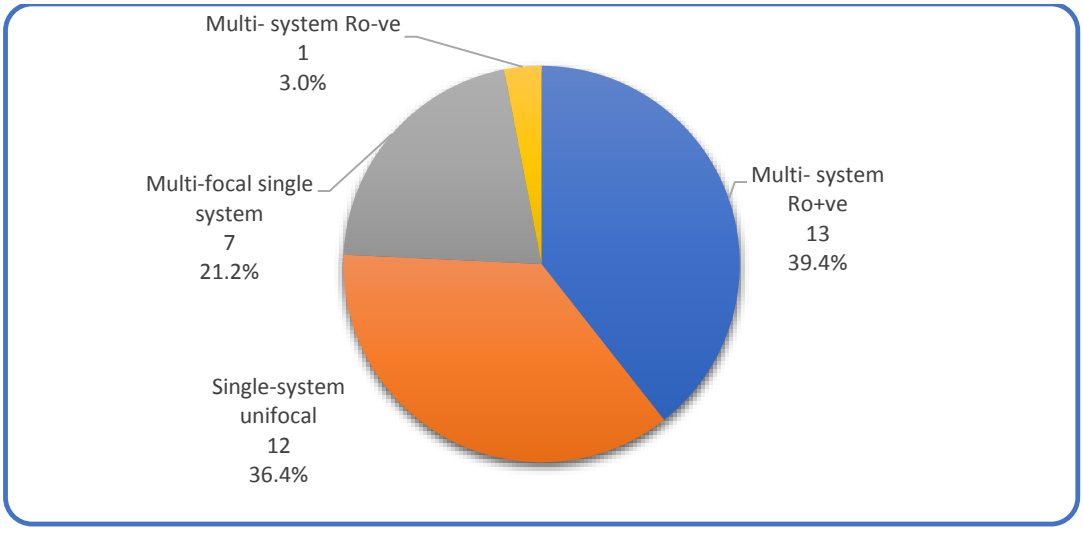


Figure 1: Classification of the disease (n=33).

The survival function at last follow up of the patients shows that the overwhelming majority (84.8%) were alive in complete recession, while only three patients (9.1%) were alive with disease and two patients (6.1%) died **[Figure 1]**.

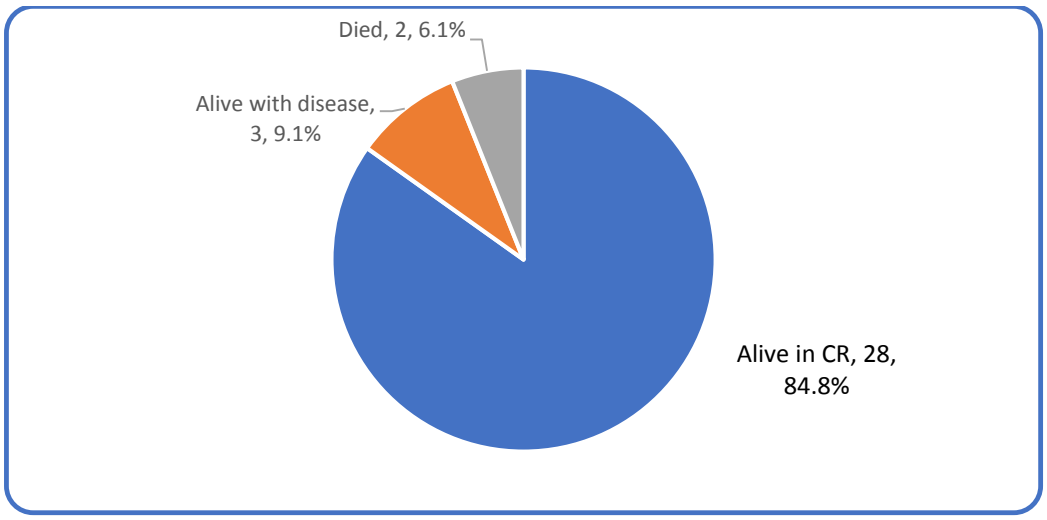
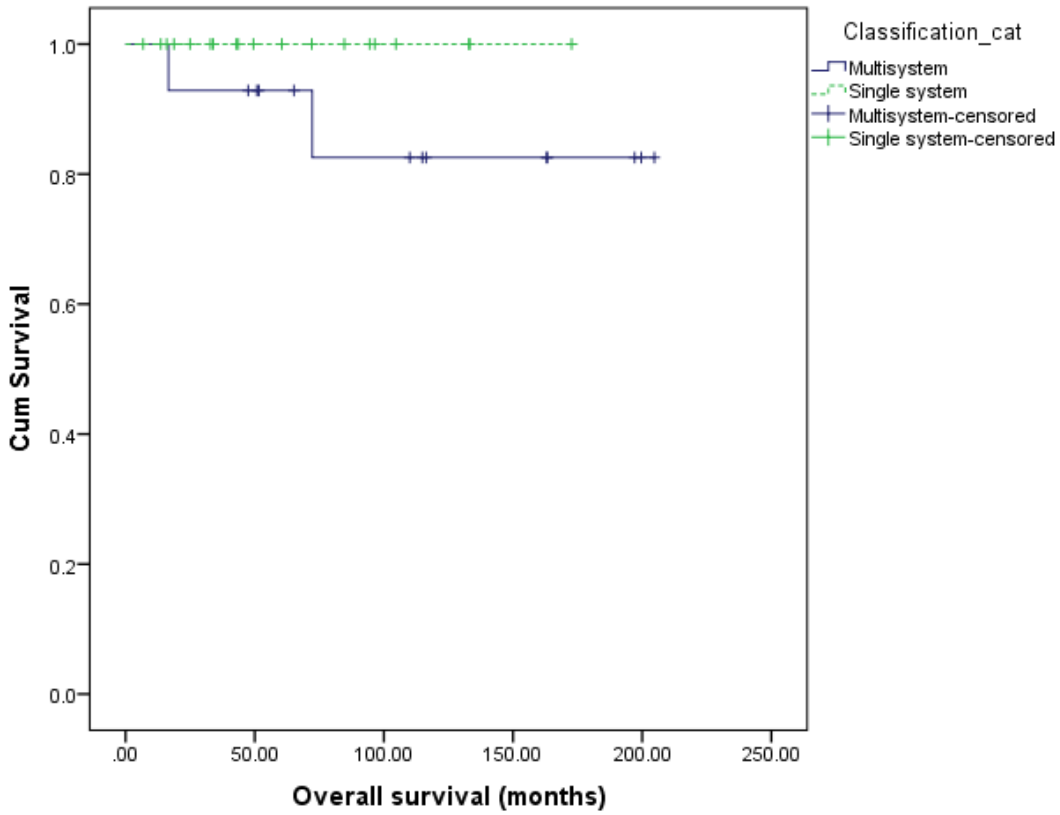


Figure 2: Fate of the patient at last follow up.

The Kaplan Meier survival analysis showed that there was no statistically significant difference in survival of the patients according to the age of diagnosis p>0.05 **[Figure 2]**.



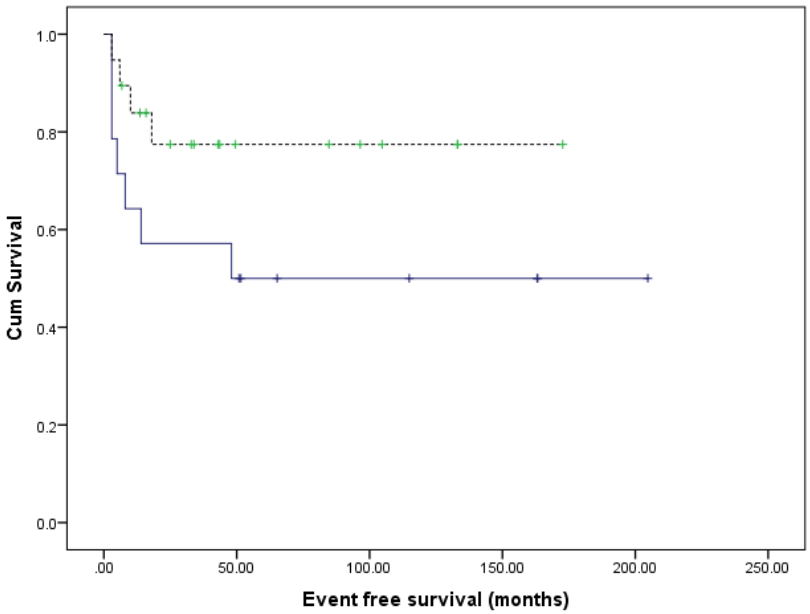


Figure 3: Overall and event free survival of LCH patients.

The overall survival of all studied patients was 93.9% and was comparable in patients with multisystem compared to single system involvement (85.7% versus 100% respectively, p=0.168). Meantime, there was no statistically significant difference in event free survival between the two groups (50.0% versus 79.9% respectively, p=0.114) **[Figure 3]**.

4. Discussion

Once, LCH was considered as an immune dysregulation disorder, however with advances in molecular biology and genetics, 50-60% LCH patients were found to have a proto-oncogene mutation in BRAF-V60E, and almost 100% had a cellular signal transduction phosphorylation defects of MEK/ERC. This lead to consider LCH as a dendritic cell neoplasm with a strong inflammatory component (Abla & Weitzman, 2015). The course of disease is unpredictable, varying from self-limited disease to rapid progression and death or frequent recurrence and reactivation with the risk of disease related permanent, predictable and often with irreversible sequalae (Donadieu, 1996). The exact incidence of LCH in Saudi Arabia is uncertain, however, data from the National Cancer Registry, Saudi Arabia (SA-NCR), for pediatric patients (age 0-14 years) diagnosed between 2005 and 2009 reported an incidence of 0.12% (Belgaumi et al., 2019). Al-Mulhim et al -twenty-nine years ago- reported the outcome of 21 Saudi children with Histiocytosis-X. At the median of 3 years follow up 3 patients died, three had recurrences and eight patients had various disabilities (38%).

Overall disease free survival was 84.2% (Al-Mulhim et al., 1991). The paucity of confirmed LCH may suggest a degree of under-reporting or under-diagnosis in these previous studies, or cases that may be treated without chemotherapy are not included in SA-NCR. LCH has a wide clinical variety and outcome. Localized disease is usually seen in older patients, whereas a more aggressive form of disease with organ dysfunction is typical in children younger than 24 months of age (Broadbent et al., 1994). The data support this, with more patients younger than 2 years presented with MS-LCH than older ones. The distribution between sexes in patients accords most of previous studies that showed ratios from 1.1 to 2 boys to every one girl

(Donadieu, 1996; Gadner et al., 2001; Hamre et al., 1997). Age is one of the important prognostic factors in MS-LCH. Majority of our younger (<2 years) patients (71.4%) presented with MS-LCH (P<0.004). Due to small number of our series, age at diagnosis was not associated with outcome. Skin rash may present as the first sign of LCH (Howarth et al., 1999). In the current study, out of the nine children who had initial skin lesions, three received previous treatments for other pathologies, that could resulted in a diagnostic deferral.

Ear involvement was described in five patients, that was often misdiagnosed as otitis infection. It is more common among younger children with multisystem disease; therefore, the presence of persistent otitis, not responding to common treatments, should increase the suspicion of LCH (Surico et al., 2000). Bony lesions were the commonest initial manifestation of the disease, almost 70% of the patients had bone-related swelling and pain. which is consistent with literature data (Arico & Egeler, 1998; Azouz et al., 2005; Broadbent et al., 1994; Del Río et al., 2007). The reported two deaths occurred in cases with liver dysfunction, one of them died after liver transplantation which asserts what had been documented before that liver dysfunction is associated with worst outcome (Donadieu, 1996; Gadner et al., 1994; Kilpatrick et al., 1995; Lahey, 1975).

Grois et al (1995) pointed that diabetes insipidus (DI) is a common manifestation in LCH, due to infiltration of hypothalamic-pituitary axis; it may precede the disease or manifest itself later during the disease course (N. Grois et al., 1995). DI varies considerably, with rates between 5% and 50% (N. Grois et al., 1995; Salotti et al., 2009). In our patient population, five (15%) patients had long duration of diabetes insipidus before the diagnosis was made, mostly associated with multiple system involvement. Previous researches claimed that MS-LCH patients especially those with craniofacial involvement at diagnosis are 4-6 times more at risk of developing DI than those with single-system disease (N. Grois et al., 1995; Nicole Grois et al., 2010). LCH clinical outcomes of LCH have improved markedly over the past decades through cooperative randomized national and international clinical trials (Cotterill et al., 2000). In the current study, the overall survival was 93.9% and was comparable in patients with multisystem compared to single system involvement (85.7% versus 100% respectively, p=0.168).

An excellent survival rate (100%) was detected in SSD group. However, the probability of EFS at 16 years for this group of patients (50%) shows some predilection for disease relapse. Reactivation is one of the potential challenges encountered in the management of LCH. In our study, recurrence occurred in nearly one-third of the patients, yet the majority attained remission after second line therapies. The two patients who received treatment for six months had shorter duration of CR, emphasizing the importance of prolonged duration of treatment course; they responded to second line of therapies and survived. As reported by others, recurrence is not a predictive factor of worst outcome (Gadner et al., 1994). Among those patients with single system disease, only three (23%) had one reactivation episode which is comparable to other reposted studies (N. Grois et al., 1995; Histiocyte Society, 2002; Titgemeyer et al., 2001). No cases of secondary neoplasms were observed after long follow up, presumably post use of etoposide as described in few number of cases (Histiocyte Society, 2002).

Conclusion

Excellent outcome of LCH is associated with single system involvement and probably older age group. On the other hand, worse outcome (reactivations, or morality) of LCH is determined by multi-organ involvement especially at younger age less than 24 months. Single system LCH patients might benefit from only observational approach. Eventually, better understanding of pathophysiology and genetic molecular background could lead to a striking transformation to novel therapy that warrants a prospective clinical trial to solve the challenges of high mortality in younger age groups with organ dysfunctions, the high relapse rate especially among the MS-LCH patients and disease associated complications.

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Appendix

Summary of treatment components of LCH III protocol

	Treatment A	Treatment B
COURSE I	1. Prednisone (PDN): 40mg/m2 daily in 3 doses as a 4-week course, tapering over a period of 2 weeks 2. Vinblastine (VBL) 6 mg/m2 IV day 1 of week 1, 2, 3, 4, 5, 6.	1. Prednisone (PDN): 40mg/m2 daily in 3 doses as a 4-week course, tapering over a period of 2 weeks 2. Vinblastine (VBL) 6 mg/m2 IV day 1 of week 1, 2, 3, 4, 5, 6. 3. Methotrexate 500 mg/m2 24 hours-infusion with Folinic acid (leucovorin) rescue. 4. Folinic acid 12mg/m2 orally is given 24 hours and 30 hours after the stop of the MTX infusion.
*COURSE II	1. Prednisone (PDN): 40mg/m2 in 3 divided doses for 3 days every week, from week 7-12. 2. Vinblastine (VBL) 6 mg/m2 IV day 1 of week 7, 8, 9, 10, 11, 12.	1. Prednisone (PDN): 40mg/m2 in 3 divided doses for 3 days every week, from week 7-12. 2. Vinblastine (VBL) 6 mg/m2 IV day 1 of week 7, 8, 9, 10, 11, 12. 3. Methotrexate 500 mg/m2 24 hours-infusion with folinic acid (leucovorin) rescue. 4. Folinic acid 12mg/m2 orally is given 24 hours and 30 hours after the stop of the MTX infusion
Continuation treatment:	1. Oral 6-mercaptopurine (6-MP) 50mg/m2 daily until the end of month 12 from therapy start. 2. Pulses of oral prednisone PDN 40mg/m2 in 3 doses, day 1-5 q 3 weeks. 3. Vinblastine (VBL) 6mg/m2 IV bolus, day 1 q 3 weeks.	1. Oral 6-mercaptopurine (6-MP) 50mg/m2 daily until the end of month 12 from therapy start. 2. Pulses of oral prednisone PDN 40mg/m2 in 3 doses, day 1-5 q 3 weeks. 3. Vinblastine (VBL) 6mg/m2 IV bolus, day 1 q 3 weeks. 4. Methotrexate 20mg/m2 orally, once weekly until the end of month 12

* Starting without delay after course 1 for patients who are Active Disease (AD) better or intermediate after course 1. Patients who are Non-Active Disease (NAD) after course 1 proceed to continuation treatment