



**Original Article**

**Langerhans Cell Histiocytosis: Single Center Experience of 25 Years**

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**Abstract. Objectives:** To review a single center outcome of patients with Langerhans Cell Histiocytosis diagnosed at a tertiary referral hospital from Turkey.

**Methods:** The files between 1989 and 2015 of 80 patients with LCH were retrospectively analyzed.

**Results:** During the 25 years, 80 patients were diagnosed with LCH. The median age at diagnosis was 53 months (2-180 months) and the median follow-up time of patients was 10 years and 9 months (24 months-25 years). Bone was the most frequently affected organ (n:60, 75%). Initially, 43 patients (54%) had single system (SS) disease, 20 patients (25%) had multisystem (MS) disease without risk organ involvement (MS-RO<sup>-</sup>), and 17 patients (21%) had a multisystem disease with risk-organ involvement (MS-RO<sup>+</sup>). The overall survival (OS) rate was 91%, and event-free survival (EFS) rate was 67% at 10 years. 10-year OS rate was lower for patients with MS-RO<sup>+</sup> (65%) when compared to those with, MS-RO<sup>-</sup>, and SS (100%, 97%, p value=<0.001). The overall survival rate was also lower in patients with lack of response to systemic chemotherapy on 12th week (p=<0.001), younger age (<2 years) at presentation (p=<0.02), skin involvement (<0.001) and lack of bone lesions at presentation (<0.001).

**Discussion:** In the group with MS-RO<sup>+</sup>, OS is significantly low compared to other groups. Further efforts are warranted to improve survival in MS-RO<sup>+</sup> patients.

**Keywords:** Langerhans cell; Pediatric Oncology; Prognosis; Chemotherapy.

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**Introduction.** Langerhans cell histiocytosis (LCH) is a rare neoplasm caused by an abnormal oligoclonal proliferation of Langerhans cells and their accumulation at various tissues and organs.<sup>1,2,3</sup> The overall incidence rate for LCH was reported as 2.6 cases per million child years, and males are affected to a higher degree than females.<sup>4</sup> Langerhans cell histiocytosis is categorized into two major categories

based on the extent of disease:<sup>5</sup> single-system (SS) and multisystem (MS). The clinical presentation and outcome of the disease are diverse, and treatment options differ according to the extent and severity of disease.<sup>6-8</sup>

In this article, we present a retrospective analysis of LCH cases diagnosed at a tertiary referral hospital in Turkey over the past 25 years. Our aim was to describe

the course of the disease and evaluate the factors that have an effect over survival in our cohort.

**Materials and Methods.** The data of patients with LCH, treated at Istanbul University, Cerrahpasa Medical School Hospital Pediatric Hematology-Oncology Department between 1989 and 2015, were retrospectively analyzed from the medical records. A total of 80 patients were included. Their files were reviewed for demographic characteristics, clinicopathological features, laboratory findings, treatment regimens, and outcome.

Disease staging and organ dysfunctions were evaluated by disease history, physical examination, laboratory tests, and imaging studies. Complete blood count, liver and kidney function tests, serum electrolytes, ferritin, total bilirubin, PT, a PTT, urine osmolality were checked in all patients. Bone marrow aspirate and biopsy were performed only in multisystem patients. The radiological examination included at least chest X-ray and skeletal radiograph survey. Other further imaging modalities such as ultrasonography, computerized tomography, magnetic resonance imaging, bone scintigraphy, positron emission tomography and pulmonary function tests were performed when evaluation of the extent of disease was required.

LCH can be clinically be classified in two general groups, single system and multisystem. Risk organ involvement in the multisystem group is considered to be the most aggressive form of the disease.<sup>4,5</sup> While preparing the manuscript for publication, patients were retrospectively staged according to currently ongoing LCV IV trial of Histiocyte Society<sup>9</sup> even though different protocols have been used for classification and treatment of these patients. According to LCH IV trial, in monosystemic (single system) form, one organ or system is involved; such as bone (either as a single bone; monosystem unifocal bone or more than one bone; monosystem multifocal bone), skin or lymph nodes. In multisystemic form two or more organs or systems are involved; either with or without risk organs (hematopoietic system involvement, spleen and liver). Different from the previous protocols, the lung is not considered as a risk organ in LCH IV trial.

Treatment included local steroid therapy, radiotherapy, chemotherapy, surgical excision of the lesion (even though it is not recommended any longer), or a combination of these modalities. Depending on the year of admission, patients were treated by DAL-HX 83 protocol<sup>10,11,12</sup> between 1989 and 1991, LCH-I protocol<sup>12</sup> between 1992 and 1996, LCH-II protocol<sup>7</sup> between 1996 and 2004 and LCH-III protocol<sup>13</sup> after 2004.

For the evaluation of response, the response criteria of LCH-I Study<sup>6</sup> were employed. Responders had a complete resolution (NAD) or continuous regression of

disease; intermediate responders were patients with active disease who had either stable disease or a mixed response (a regression of disease but the appearance of new lesions in another site or organ system), and non-responders had progression of the disease. Reactivation was defined as a reappearance of disease signs or symptoms after complete disease resolution.<sup>11</sup>

**Statistics.** Continuous variables are presented as median (mean-max) deviation, while categorical variables are given as percentages. The Shapiro Wilk test was used to verify the normality of the distribution of continuous variables. Statistical analysis of clinical characteristics between two groups consisted of unpaired t-tests for parametric data and Mann Whitney U test, whereas the chi-square/Fisher's exact tests were used for categorical variables. The Kaplan-Meier method was used to estimate survival as a function of time, and the log-rank test analyzed survival differences. Analyses were performed with PASW 18 (SPSS/IBM, Chicago, IL, USA) software and two-tailed P value less than 0.05 was considered statistically significant.

## Results.

*Patient Characteristics.* Among 80 eligible patients with LCH, 56 of them were male, and 24 were female (M/F: 2.3). Median age at diagnosis was 36 months (2 months to 15 years). Patients in the SS group had a higher median age at diagnosis when compared to MS-RO<sup>-</sup> and MS-RO<sup>+</sup> groups (p=0.01 and p=0.0001 respectively). General characteristics of patients are shown in **Table 1**.

*Initial symptoms.* At the time of diagnosis, swelling (n: 33, 41%) was the most recorded referral symptom followed by pain (n: 24, 30%) in which 21 were related to bone and 7 presented with limping gait. Skin rash or eruption was noted in 16 (20%) of the patients while polyuria and polydipsia was the presenting symptom in 7 (8.7%) of the patients.

*Physical examination and organ involvement.* The most frequently affected organ was bone (n: 60, 75%). In MS-RO<sup>+</sup> group, besides risk organ infiltration, skin involvement was also statistically higher (n:14; p=0.0001) compared to the other two groups. Bone involvement was statistically high in the SS group (n: 36; p=0.01), and soft tissue involvement was statistically higher in MS-RO<sup>-</sup> group (n:10; p=0.0001). Distribution of organ involvement varied significantly by patient age. Status of patients according to age is illustrated in **Table 2**.

*Diagnosis.* Among 80 patients enrolled to study, 76 (95%) had a histological diagnosis of LCH based on characteristics histological appearance of LCH lesions

**Table 1.** General Characteristics of patients, treatment and survival outcomes.

	Total	SS (n:43)	MS-RO <sup>-</sup> (n: 20)	MS-RO <sup>+</sup> (n: 17)	<i>p</i>
<b>Patients (n)</b>	80	43	20	17	
<b>Gender [Male/Female (n)]</b>	56/24	31/12	15/5	11/6	0.776
<b>Median age on diagnosis (month) (min-max)</b>	36 (2-180)	81 (6-180)	29.5 (2-105)	18 (2-47)	<b>&lt;0.001</b>
<b>Age distribution [n (%)]</b>					
≤24 months	24	8 (%18.6)	7 (%35)	12 (%70.59)	<b>0.001</b>
>24 months	56	35 (%81.4)	13 (%65)	5 (%29.41)	
<b>Organ involvement [n (%)]</b>					
Bone Marrow	6	0	0	6 (%35.29)	<b>&lt;0.001</b>
Liver	14	0	0	14 (%82.35)	<b>&lt;0.001</b>
Lungs	5	0	0	5 (%29.41)	<b>&lt;0.001</b>
Spleen	4	0	0	4 (%23.53)	<b>&lt;0.001</b>
Bone	60	36 (%83.72)	17 (%85)	7 (%41.18)	<b>0.001</b>
Skin	25	2 (%4.65)	9 (%45)	14 (%82.35)	<b>&lt;0.001</b>
Soft tissue	14	3 (%6.98)	10 (%50)	1 (%5.88)	<b>&lt;0.001</b>
Lymph node	10	1 (%2.33)	5 (%25)	4 (%23.53)	0.012
Hypophysis	7	1 (%2.33)	4 (%20)	2 (%11.76)	0.061
<b>Chemotherapy protocol [n (%)]</b>					
DAL-HX 83	6	2 (%11.11)	1 (%6.67)	3 (%17.659)	0.218
LCH-1	10	4 (%22.22)	1 (%6.67)	5 (%29.41)	
LCH-2	10	3 (%16.67)	2 (%13.33)	5 (%29.41)	
LCH-3	24	9 (%50)	11 (%73.13)	4 (%23.53)	
<b>Chemotherapy response at 12 wk (n)</b>					
NAD or DR	43	17 (%94.44)	15 (%100)	11 (%64.71)	<b>0.007</b>
IR or DP	7	1 (%5.56)	0 (%0)	6 (%35.29)	

NAD: complete resolution, DR: continuous regression of disease, IR: intermediate responders, DP: disease progression.

**Table 2.** Status of patients in relation to age.

	≤2 years (n:18)	> 2 years	<i>p</i>
<b>Gender [Male/Female (n)]</b>	20/7	37/16	0.690
<b>Group [ n(%) ]</b>			
Single group	8 (29.63)	35 (66.04)	<b>0.002</b>
Multiple group	19 (70.37)	18 (33.96)	
<b>Risk group involvement [ n(%) ]</b>			
SS	8 (29.63)	35 (66.04)	<b>0.001</b>
MS-RO <sup>-</sup>	7 (25.93)	13 (24.53)	
MS-RO <sup>+</sup>	12 (44.44)	5 (9.43)	
<b>Organ Involvement [ n(%) ]</b>			
Bone marrow	6 (22.22)	0 (0)	<b>&lt;0.001</b>
Spleen	3 (11.11)	1 (1.89)	0.073
Liver	10 (37.04)	4 (7.55)	<b>0.001</b>
Lungs	4 (14.81)	1 (1.89)	0.024
Skin	17 (62.96)	8 (15.09)	<b>&lt;0.001</b>
Bone	15 (55.56)	45 (84.91)	<b>0.004</b>
Soft tissue	4 (14.81)	10 (18.87)	0.652
Lymph node	6 (22.22)	4 (7.55)	0.061
<b>Chemotherapy response at 12 wk [ n(%) ]</b>			
NAD or DR	17 (73.91)	26 (96.30)	0.023
IR or DP	6 (26.09)	1 (3.70)	
<b>Overall Survival</b>	%77.78	%98.11	<b>0.002</b>

NAD: complete resolution, DR: continuous regression of disease, IR: intermediate responders, DP: disease progression.

**Table 3.** Treatment Options according to the involvement of disease.

Extent of Disease (n);	Treatment Option (n/survival)				
	Surgical Curretage/Excision	Local Radiotherapy	Local Steroid	Chemotherapy	Combination therapy
Unifocal bone lesion (22)	16/100%	1/100%	-	5/100%	-
Soft Tissue involvement (3)	1/100%	-	-	2/100%	-
Skin Limited (2)	-	-	2/ 50%	-	-
Hyphophysis (1)	-	-	-	-	1/100%*
Solitary Lymph Node involvement (1)	1/100%	-	-	-	-
Single System Multifocal Bone (14)	2/100%	-	-	11/100%	1/100%‡
MS-RO <sup>-</sup> (20)	-	-	-	15/100%	5/100%§
MS-RO <sup>+</sup> (17)	-	-	-	17/65%	-

\*DDAVP and oral steroid, ‡ Intralesional steroid, surgical curretage and radiotherapy, ~ 3 patients; surgical curretage and radiotherapy, 1 patient; intralesional steroid and DDAVP, 1 patient; intralesional steroid and radiotherapy.

on hematoxylin and eosin and positive immunohistochemical staining with CD1a and/or S-100. The diagnosis was based on radiological and clinical findings in 4 (5%) patients, because of the surgical risk due to localization in the paravertebral area.

**Staging.** Forty-three patients (53.75%) presented with SS disease and 37 patients (46.25%) presented with multisystem disease. Distribution of risk groups varied according to the age as is shown in **Table 2**.

**Treatment.** Patients were treated according to the extent of the disease. Details of treatment regimens are illustrated in **Table 3**. Among 22 patients with unifocal bone lesions 16 were treated with surgical curettage/excision and the rest 6, who had involvement of weight-bearing bones, skull base, temporal bones and vertebral column, were treated with chemotherapy (n:5) and local radiotherapy (n:1). For the patients in the multisystem low-risk group (n: 20), 15 were treated with chemotherapy, and the rest 5 were treated with combination treatments. All patients in the multisystem high risk group (n: 17) were treated with systemic chemotherapy. A total of 50 patients from all groups received chemotherapy as the treatment. According to chemotherapy response on week 12, 43 patients (86%) were classified as responders; of these, 33 (66%) had NAD, and 10 (20%) had DR. Seven patients (14%) were evaluated as non-responders; of these 3 (6%) had IR and 4 (8%) had DP. Chemotherapy response was statistically worse in MS-RO<sup>+</sup> group compared to the other two groups (p=0.007) and in patients, under 2 years of age (p=0.023) as is shown in **Table 1** and **2**.

**Treatment response and outcome.** The median follow up time was 10 years and 9 months (1 month to 25 years), 10-year overall survival (OS) rate in the entire patient cohort were 91.25 %, and EFS (event-free survival) rate was 67.5%. Seven patients died. One patient in the single system group (skin involvement) has developed reactivation of risk organ involvement

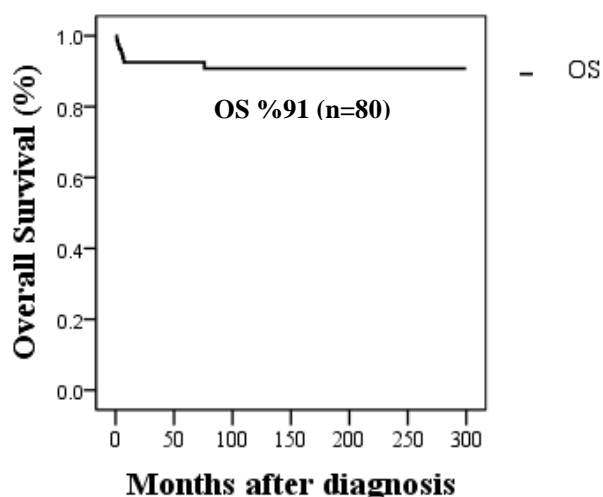
during follow up and was lost due to progressive disease. Besides this patient, the rest 6 were in MS-RO<sup>+</sup> group. 10-year OS rate was lower for patients with MS-RO<sup>+</sup> (65%) when compared to those with, MS-RO<sup>-</sup>, and SS (100%, 97%, p value=<0.001).

Regarding the age of patients' OS rate at 10 years from diagnosis was 77% for patients younger than 2 years of age and 98% for patients older than 2 years of age (p=0.02). Bone involvement was reported in 60 patients (75%). Ten year OS rate was significantly higher in patients with bone involvement than in those with extraosseous disease site involvement (100% vs. 65%; p=<0.001). Even among patients of MS-RO<sup>+</sup> group, presence of bone lesions was associated with better OS (% 100 vs. % 40; p=0.016). Ten year OS rate was significantly higher in patients who responded to initial treatment at 12 weeks compared to those who did not (100% vs. 14%; p=<0.001) and also in patients with skin involvement as is shown in **Table 4**. Due to the difference in the distribution of deaths among groups, we could not perform multivariate analysis.

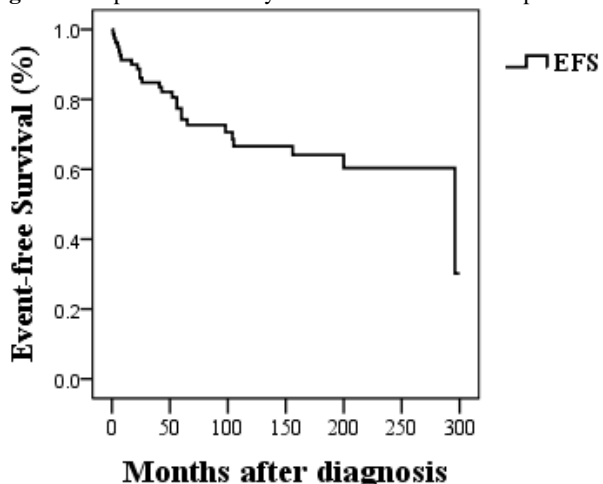
**Reactivation.** Out of 80 patients, 20 (25%) experienced at least one reactivation. The first reactivation occurred 2-46 months (median: 11 mo) after the initial diagnosis. Regarding the timing, one patient (5%) reactivated during induction treatment, 4 (20%) patients reactivated during continuation treatment and 15 patients (75%) reactivated while on follow up. Among these reactivations, 4 occurred in the first year and the rest 11 afterward (2-46 months, median: 17 months after the initial diagnose). Among the patients with first reactivation, 7 patients had SS MFB, 6 patients had SS SS (single system, single side), 4 patients had MS-RO<sup>+</sup>, and 3 patients had MS-RO<sup>-</sup> disease. The most clinical pattern of reactivation was limited to the bone. Bone reactivation was observed in 16 of the 20 patients (7 patients unifocal, 4 patients multifocal bone and in 5 patients reactivation was associated with other organs' involvement). Risk organ reactivation was observed in only 3 patients (15%). Patients with reactivated disease were treated with

**Table 4.** Univariate analysis of Factors Correlated With Overall Survival.

	(n)	OS 5 year (%)	OS 10 year (%)	p
Age at diagnosis	≤2 years (24)	82	77	0.02
	>2 years (56)	98	98	
Risk group	Single System (43)	100	97	<0.001
	MS RO (-) (20)	100	100	
	MS RO (+) (17)	65	65	
Response to treatment on 12 <sup>th</sup> week	Responder (43)	100	100	<0.001
	Non responder (7)	14	14	
Bone involvement	Yes (60)	100	100	<0.001
	No (20)	70	65	
Skin involvement	Yes (25)	76	71	<0.001
	No (55)	100	100	

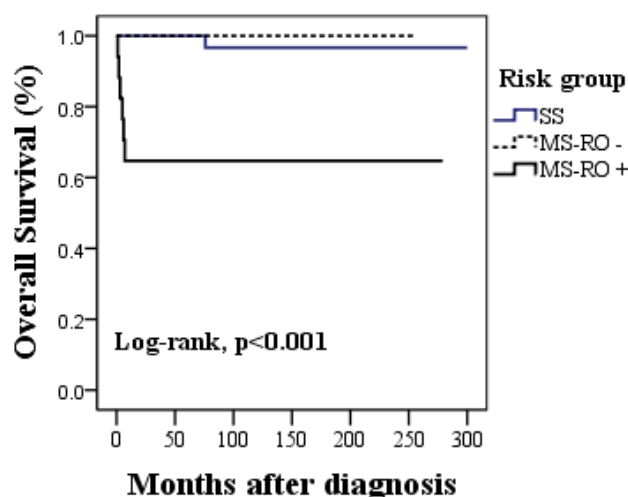


**Figure 1.** Kaplan Meier analysis of overall survival for patients.



**Figure 2.** Kaplan Meier analysis of event free survival for patients.

chemotherapy (n:17), or local therapy (radiotherapy (n:1), curettage (n:1) and intralesional steroid (n:1). Five patients experienced multiple reactivations: one patient experienced 2, three patients experienced 3, and one patient experienced 4 reactivations in the follow-up; within a mean period of 17 (9-26 mo) months. The 10-year reactivation rates for SS-SS, MS-RO<sup>-</sup>, and MS-RO<sup>+</sup> patients were 30%, 15%, and 23.5% respectively. Reactivation rate did not differ statistically according to the involved organs or risk groups. Reactivation did not affect mortality except for one patient in group SS-SS (MFB) who relapsed in follow-up with



**Figure 3.** Kaplan Meier analysis of overall survival for patients according to risk groups. SS, single system; MS-RO<sup>-</sup>, multi system without risk organ involvement; MS-RO<sup>+</sup>, multi system with risk organ involvement.

risk-organ involvement and died due to disease progression despite the combined chemotherapy protocols in 6 months. The EFS of the cohort is shown in **Figure 2**.

**Discussion.** Because LCH is a rare disease, disease-related publications in the literature are usually multi-institutional. This report is one of the rare single-center studies within 25 years including 80 pediatric patients with sufficient follow up duration. Our aim was to describe the course of the disease and evaluate the outcomes.

The demographic features of LCH patients in our cohort were comparable with previous reports showing early onset of disease and male predominance.<sup>14,15</sup> The median age of our patients at diagnosis was 36 months; more than 1/3 of patients were under 2 years, and the male/female ratio was 2.3.

In concordance with previous reports, the majority of our patients presented with symptoms related to bone (71%) including swelling, pain and limping gait.<sup>16,17,18</sup> The most affected organs by disease in our study after bone were skin, soft tissue and liver retrospectively and which was also in line with the previously reported series in the literature.<sup>17,18</sup> Presence



of bone lesions at diagnosis was associated with better OS in our cohort as was described in the literature before.<sup>19</sup> Even among MS-RO<sup>+</sup> group, OS was significantly better in patients with bone disease (% 100 in the presence of bone disease and 40% in the absence of bone disease;  $p=0.016$ ). Even though this is in concordance with previous reports showing the superiority of bone involvement among MS-RO<sup>+</sup> patients, in our opinion, our number of patients is too low ( $n:17$ ) to contribute to this hypothesis.<sup>20</sup>

In our cohort, group involvement differed according to age, while the children older than 2 years mostly presented with SS disease and bone involvement, the younger group ( $\leq 2$  years of age) presented with more multisystem disease, skin and risk organ involvement. This was in concordance with previous studies in the literature.<sup>16,17,19</sup>

Kim et al. described "bone" as the most common site of involvement in their study among the patients between 1 to 5 years of age.<sup>16</sup> In 2012, Postini et al. reported their 40 years of experience with pediatric LCH patients. Single system unifocal bone involvement was the most observed clinical presentation in patients over 2 years of age.<sup>20</sup> In a nationwide survey from Korea, young age at diagnosis ( $< 2$  years) was associated with multisystem risk organ involvement resulting in higher mortality.<sup>16</sup>

In LCH, the course of the disease is highly heterogeneous and it is related to the extent of organ involvement. In 2014, Lee et al. reported the outcome of 22 years' experience. The OS rate was significantly low in patients with risk-organ involvement.<sup>19</sup> In the study by Yagci et al. where the outcome of 217 LCH patients was described OS and EFS rates were significantly worse in MS-RO<sup>+</sup>.<sup>17</sup> In our study, patients with SS disease and MS-RO<sup>-</sup> had excellent survival rates. All patients except one survived in these two groups. The only patient dead was a boy who had a reactivation of risk organ involvement during follow up. Besides this patient, all the other deaths were observed in the MS-RO<sup>+</sup>. Our findings support the hypothesis that risk organ involvement is a strong negative predictor of outcome in LCH patients.

Skin involvement was observed in 25 (31%) of our cohort. Age  $< 2$  years and MS-RO<sup>+</sup> were associated with skin involvement ( $p < 0.001$ ) as was shown in the literature before.<sup>21</sup> Several studies revealed the presence of somatic BRAF-V600E mutation on skin biopsy.<sup>22</sup> The existence of BRAF-V600E in circulating blood has been associated with disease recurrence.<sup>23</sup> In our cohort, a skin biopsy or peripheral blood were not available for analyses of BRAF-V600E mutation. However, in univariate analyses patients with skin involvement had lower EFS and OS. Due to the close association of skin disease with risk-organ involvement and the low number of patients enrolled we cannot conclude whether skin involvement is an independent

predictor of poor outcome. Prospective multicenter trials are needed to determine the effect of skin involvement over the outcome in LCH patients.

There is no current standard management protocol for patients whose disease is unresponsive to frontline therapy or who present with multiple reactivations. Even though patients with single bone or low-risk multisystem reactivation respond well to second-line treatments such as 6-mercaptopurine and methotrexate, patients with risk-organ reactivation have inadequate response even to salvage protocols. Treatment of refractory LCH patients with 2CdA as monotherapy has shown a higher response rate in patients with non-risk organs involvement, but limited activity in refractory patients with risk-organ involvement.<sup>26</sup> Combination of 2CdA with Cytarabine (Ara-C) as a salvage protocol has promising results. Even in the MS-RO<sup>+</sup> group, 5 year survival rate was reported to be 85% in the phase II study by Donadeiu et al.<sup>24</sup> The principal declared side effect of the treatment was severe hematologic toxicity and arising severe infection.<sup>24</sup> Currently, ongoing prospective LCH-IV study is evaluating the effect of 2CdA and Ara-C combination chemotherapy for risk organ involved refractory LCH patients.<sup>9</sup> In our cohort we treated 2 of our patients with a combination of 2CdA and Ara-C; one was a girl with single system bone involvement who relapsed during maintenance therapy from multiple bones. She achieved remission with 2CdA treatment until now. The second patient was initially staged in single system group (skin involvement) but had reactivation of risk organ involvement during follow up. He died because of progressive disease despite 2CdA treatment. In our study, the number of patients was too few to report 2CdA efficiency. In the literature, some case reports are showing the efficacy of Clofarabine as monotherapy in refractory LCH patients. Rodriguez-Galindo et al. showed complete remission in 2 refractory LCH patients (both without risk organ involvement) with Clofarabine therapy who were unresponsive to 2-CdA treatment.<sup>27</sup> This finding was in concordance with the recent study showing the superiority of Clofarabine treatment in non-risk organ involved refractory LCH patients.<sup>28</sup>

There are also promising reports regarding the Lenalidomide plus steroid treatment in refractory patients.<sup>29,30</sup> The main advantage of this protocol is the feasibility of treatment at an outpatient clinic, cost-effectivity of the drug and reported limited toxicity. However, literature regarding this protocol is scarce in the pediatric population.

After the description of recurrent oncogenic mutations affecting the MAPK pathway in LCH patients, targeted therapies such as BRAF, MEK or BRAF/MEK inhibitors were reported to be useful for patients with these mutations who even were unresponsive to salvage treatments.<sup>22,31,32</sup> However,

further studies are warranted to reveal the efficacy, safety, and long term outcome in the pediatric population for targeted therapies.

Reactivation is a common problem in the treatment of patients with LCH.<sup>25</sup> The total reactivation rate in our cohort was 25%. This rate is similar to the reported data.<sup>20,25</sup> Reactivations predominantly affected the bones as was shown in the literature before.<sup>19,20</sup> Even in the group with multifocal bone involvement or in patients with multiple reactivations, recurrence or the disease, were not associated with mortality. Only one patient with MS-RO<sup>+</sup> reactivation died despite rescue treatment, which suggests the severity of risk organ involvement also in disease reactivation. The 5-year reactivation rates of our patients did not differ between the groups, which was contradictory to the previous reports in where higher reactivation rates were reported

in the MS group.<sup>16</sup> In our opinion, this is related to poor outcome in MS-RO<sup>+</sup> group. Because most of these patients (5 of 6) could not get into remission, they died in early stages of treatment before developing any reactivation.

**Conclusions.** In conclusion, our study shows favorable disease course in SS and MS-RO<sup>-</sup> groups in LCH patients. Patients within these groups, survive with chemotherapy, even if they develop multiple reactivations. Risk organ involvement, younger age at presentation (<2 years), unresponsive to induction treatment, skin involvement, and absence of bone involvement at diagnosis remained subgroups of worse outcome in our cohort. Further improvement with more potent agents especially during induction is warranted for the treatment of this group.

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