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# Causes of treatment failure for children with LCH in Morocco

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## Abstract:

*Background: Langerhans Cell Histiocytosis (LCH) is a rare disease with high survival rate. We noted poor outcomes in Morocco and thus this study was conducted to identify causes of preventable treatment failure in children. Patients & Methods: This study includes cases of children LCH followed in six Pediatric Oncology Units part of the Moroccan LCH Study Group (Groupe Marocain d'Etude de l'Histiocytose) between 2000 and 2009. Patients were categorized into risk group or low risk group as per the International Histiocyte Society classification. Results: Forty-two patients were included in the present study. The median age at diagnosis was 20.5 months. The sex-ratio M/F was 5. The onset symptom was a skin lesion in 20% of the cases and bone involvement in 17%. Seventeen patients had unifocal LCH (40%). The most common site of unifocal LCH was bone (65%) and the mean duration of the first episode treatment was 3 months. Complete or partial remission was achieved in 58% of the cases. Among 20 patients who had risk organ involvement, 11 died from progressive disease and 2 died from septic shock. The overall survival rate was 40% at 5 years. Conclusion: The most common cause of treatment failure was refractory disease in 26%. However, toxic death and abandonment caused an additional 24% of patients to fail treatment. Reducing this preventable failure requires carefully designed interventions. Thus, the Moroccan LCH Study Group was established in March 2010 and set as main objective the improvement of the therapeutic management.*

**Keywords:** Langerhans cell histiocytosis, children, therapy, treatment failure

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## Introduction

Langerhans cell histiocytosis (LCH) is a rare non-malignant disease characterized by proliferation and accumulation of clonal dendritic cells in various organs [1,2]. The clinical picture of LCH can vary widely. Often, it involves only a single organ such as skin or bone. Other patients can present with multi-system disease. Evolution course may vary from a

limiting disease to a rapidly progressive one frequently fatal. [2-4]. Children with LCH in high-income countries are treated with standard protocols and have high survival rate (80-99%) [5-12]. Although the prognosis is good, late sequels are often described [12,13].

In Morocco, we noted poor outcomes for these patients. We conducted this study to identify causes of preventable treatment failure in children with LCH in Morocco.

### Patients and Methods

This observational multicenter descriptive study is covering all cases of LCH which occurred on children under the age of 18 between January 2000 and December 2009 and reported in the six hematology and pediatric oncology Moroccan Units part of the Moroccan LCH study group.

Demographic and clinical data as well as treatment and outcomes were retrospectively collected from medical records.

Patients were categorised into two groups according to international Histiocyte Society. Risk group (defined by the involvement of risk organs: liver, spleen, lungs or hematopoietic system) and low risk group.

Survival rates were estimated by Kaplan Meier method.

### Results

During the study period, 42 patients with confirmed diagnosis of LCH were included. The median age at diagnosis was 20,5 months with an age range of 5 months to 13 years. The sex-ratio M/F was 5. The onset symptom was a skin lesion in 20% of cases, and bone involvement in 17% of cases. Diabetes insipidus and otitis revealed disease in 5 cases respectively.

**Table I. Distribution of LCH by risk group and age at diagnosis.**

	Low risk group		Risk group		Total	
	N	%	N	%	N	%
	< 1 year	5	39	8	61	13
1-4 years	10	48	11	52	21	50
> 5 years	7	87,5	1	12,5	8	19
<b>Total</b>	<b>22</b>	<b>52</b>	<b>20</b>	<b>48</b>	<b>42</b>	<b>100</b>

The diagnosis was confirmed by histological examination. Immuno-chemistry with anti CD1a was performed in 49% of cases. In one case, the LCH was

**Table II. Treatment according to episodes (number of patients)**

	First episode	Second or more episodes
<b>No treatment</b>	5	
<b>Vinblastine+ steroids</b>	27	5
<b>Vinblastine+ steroids+ cytarabine</b>	9	2
<b>VP 16 alone or in combination</b>		4
<b>methotrexate</b>		2
<b>cladribine</b>		1

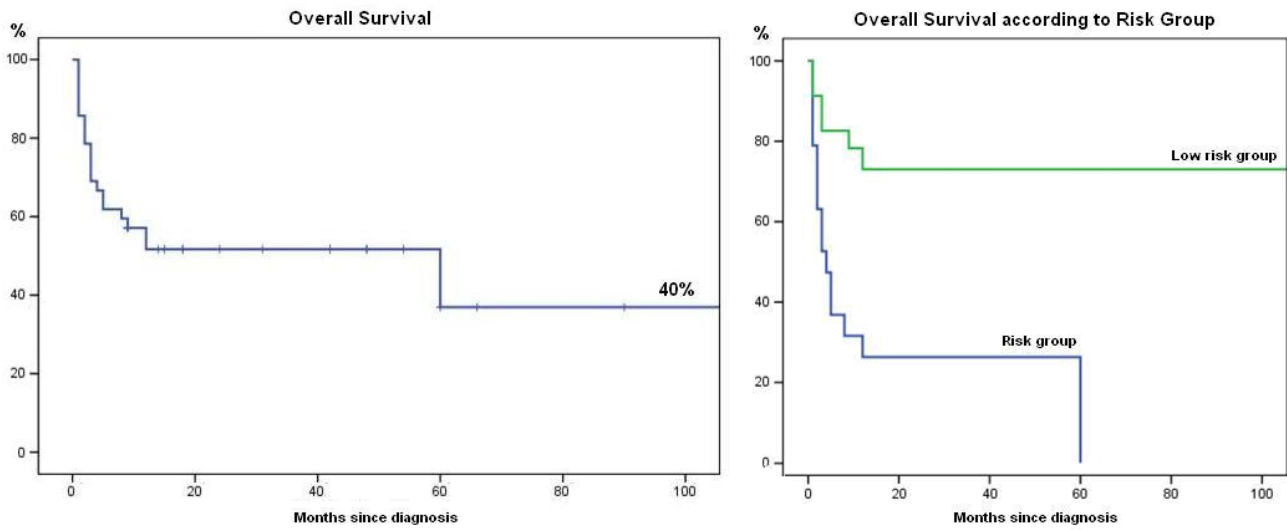
retained on the clinical and radiological data. Seventeen patients had unifocal LCH (40%). The most common site of unifocal LCH was bone (65%). The distribution of LCH by age and risk group is given in table I.

Table II shows the treatments administered during initial and subsequent episodes. The mean duration of first episode treatment was 3 months (0.5-15).

Therapeutic results and outcomes after a mean follow up of 36 months (1 month-11 years) are summarized in table III.

**Table III. Therapeutic results and outcomes**

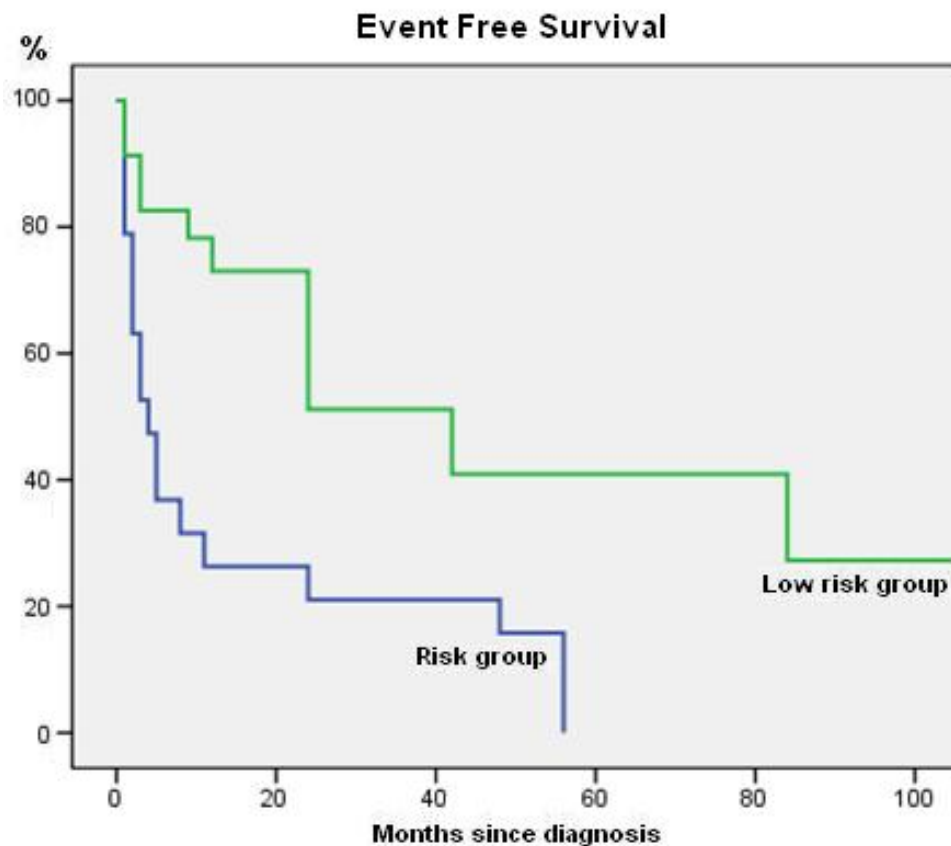
	Low risk group		Risk group		Total	
	N	%	N	%	N	%
<b>Complete / partial remission</b>	17	77	7	35	24	<b>58</b>
<b>Failure</b>	1		4	20	5	<b>12</b>
<b>Relapse</b>	5	23	4	20	9	<b>21</b>
<b>Maintained complete remission/ stable disease</b>	17	77	4	20	21	<b>50</b>
<b>Death</b>	0		13	65	13	<b>30</b>
<b>Lost to follow up</b>	5	23	3	15	8	<b>19</b>
<b>Total</b>	<b>22</b>		<b>20</b>			<b>42</b>



**Figure 1. Overall Survival Curves**

Among 20 patients who had risk organ involvement, 11 died from progressive disease and 2 died from septic shock under cladribine and association of vinblastine and cytarabine in one case respectively.

The overall survival rate was 40% at 5 years. The survival curve for all patients and according to risk group is shown in fig 1 and 2.



**Figure 2. Event Free Survival curves**

Endocrine sequelae were not searched in all children during evolution. Growth hormone and thyroid deficiency were diagnosed in one case respectively.

Two children were followed for diabetes insipidus already present at diagnosis.

### Discussion

This retrospective study describes management of childhood LCH in Morocco. Strengths of this work are the ten years study period and the participation of six units from different regions of the country. However, we cannot claim to have all Moroccan cases and incidence rates cannot be estimated in the absence of exhaustive consultation of pathological databases.

Many descriptive and epidemiological studies are published reporting an incidence ranged from 2.2 to 8.9 cases per million per year [5-11]. This cohort is characterized by the young age at diagnosis with a median at 20.5 months as against 2 to 3.7 years in the studies cited above. The primary disease sites were similar in most studies, with bone and skin lesions predominating, as they did in our study.

We also noticed that only 49% of cases had immunohistochemistry with anti CD1a. The most common causes of treatment failure were refractory disease in 26%, as in HIC. However, toxic death and abandonment caused an additional 24 % of patients to fail treatment. Reducing this preventable failure requires carefully designed interventions. Thus, the Groupe Marocain d'Etude de l'Histiocytose (Moroccan LCH Study Group) was established in March 2010 under the auspices of the Société Marocaine d'Hématologie et d'Oncologie Pédiatrique (SMHOP). The Group set as main objectives diagnosis doubts resolution, risk group assignment, and improvement of the therapeutic management through improved knowledge of the disease, the homogenization of treatment and collaboration with international expertize groups.

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