OUTCOME OF TREATING PEDIATRIC LANGERHANS HISTIOCYTOSIS WITH LCH III IN TERTIARY CENTER, SAUDI ARABIA

Abrar Salamah Almohammadi
Khalid Abdalla Khalid
Moussa Mohamed Shehadah
Abdullah. A. Baothman
OUTCOME OF TREATING PEDIATRIC LANGERHANS HISTIOCYTOSIS WITH LCH III IN TERTIARY CENTER, SAUDI ARABIA

1Abrar Salamah Almohammadi  
Assistant consultant of Pediatric Hematology and Oncology.  
Princess Norah Oncology Center.  
King AbdulAziz Medical City-Jeddah (KAMC-J)

2Khalid Abdalla Khalid  
Consultant of Pediatrics Hematology and oncology  
Princess Norah Oncology Center

3Moussa Mohamed Shehadah  
Associate consultant of Pediatric Hematology and Oncology.  
Princess Norah Oncology Center.  
King AbdulAziz Medical City-Jeddah (KAMC-J)

4Abdullah. A. Baothman  
Consultant of Pediatrics Hematology and oncology  
Princess Norah Oncology Center  
King AbdulAziz Medical City-Jeddah (KAMC-J)  
Assistant professor of pediatric  
King Saud Bin AbdulAziz University for Health Science (KSAU-HS)

Corresponding Author’s Email: baothmanaa@ngha.med.sa
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 sequelae 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:**                                |     |            |
| <24 months                                           | 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 | X² | P* |
|-----------------|--------------------|----|----|
|                 | Multisystem (n=14) | Single system (n=19) |    |    |
| No | % | No | % |   |    |
| Gender:         |                    |                |    |    |
| Male | 8 | 57.1% | 14 | 73.7% | 0.992 | 0.319 |
| Female | 6 | 42.9% | 5 | 26.3% |    |    |
| Age categories: |                    |                |    |    |
| <24 months | 10 | 71.4% | 4 | 21.1% | 8.375 | 0.004** |
| >24 months | 4 | 28.6% | 15 | 78.9% |    |    |
| Reactivation:  |                    |                |    |    |
| Yes | 7 | 50.0% | 4 | 21.1% | 3.039 | 0.086 |
| No | 7 | 50.0% | 15 | 78.9% |    |    |
| Outcome        |                    |                |    |    |
| Alive in CR | 12 | 85.7% | 16 | 84.2% | NA | NA |
| Alive with disease | 0 | 0.0% | 3 | 15.8% |    |    |
| 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.
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.

![Classification of the disease](image)

**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].
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 2: Fate of the patient at last follow up.**

- Alive in CR, 28, 84.8%
- Alive with disease, 3, 9.1%
- Died, 2, 6.1%
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 sequelae (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.

References

Abla, O., Egeler, R. M., & Weitzman, S. (2010). Langerhans cell histiocytosis: Current concepts and treatments. *Cancer Treatment Reviews, 36*(4), 354–359.

Abla, O., & Weitzman, S. (2015). Treatment of Langerhans cell histiocytosis: Role of BRAF/MAPK inhibition. *Hematology (United States), 2015*, 565–570.

Al-Mulhim, I., Sabbah, R. S., & Al-Akkad, S. (1991). Histiocytosis-X in Saudi children. *Indian Journal of Cancer, 28*(2), 53–60.

Arico, M., & Egeler, R. M. (1998). Clinical aspects of Langerhans cell histiocytosis. *Hematology/Oncology Clinics of North America, 12*(2), 247–258.

Azouz, E. M., Saigal, G., Rodriguez, M. M., & Podda, A. (2005). Langerhans’ cell histiocytosis: Pathology, imaging and treatment of skeletal involvement. *Pediatric Radiology, 35*(2), 103–115.

Belgaumi, A. F., Pathan, G. Q., Siddiqui, K., Ali, A. A., Al-Fawaz, I., Al-Sweedan, S., Ayas, M., & Al-Kofide, A. A. (2019). Incidence, clinical distribution, and patient characteristics of childhood cancer in Saudi Arabia: A population-based analysis. *Pediatric Blood and Cancer, 66*(6), 53–60.

Broadbent, V., Egeler, R. M., & Nesbit, M. E. (1994). Langerhans cell histiocytosis - clinical and epidemiological aspects. *British Journal of Cancer, 33*, S11–6.

Cotterill, S. J., Parker, L., Malcolm, A. J., Reid, M., More, L., & Craft, A. W. (2000). Incidence and survival for cancer in children and young adults in the North of England, 1968-1995: A report from the Northern Region Young Persons’ Malignant Disease Registry. *British Journal of Cancer, 83*(3), 397–403.

Del Río, L., Lassaletta, L., Martínez, R., Sarriá, M. J., & Gavilán, J. (2007). Petrous bone Langerhans cell histiocytosis treated with radiosurgery. *Stereotactic and Functional Neurosurgery, 85*(2–3), 129–131.

Donadieu, J. (1996). A multicentre retrospective survey of Langerhans’ cell histiocytosis: 348 cases observed between 1983 and 1993. *Archives of Disease in Childhood, 75*(1), 17–24.

Gadner, H., Grois, N., Arico, M., Broadbent, V., Ceci, A., Jakobson, A., Komp, D., Michaelis, J., Nicholson, S., Pötschger, U., Pritchard, J., & Ladisch, S. (2001). A randomized trial of treatment for multisystem Langerhans’ cell histiocytosis. *Journal of Pediatrics, 138*(5), 728–734.
Gadner, H., Heitger, A., Grois, N., Gatterer-Menz, I., & Ladisch, S. (1994). Treatment strategy for disseminated langerhans cell histiocytosis. *Medical and Pediatric Oncology, 23*(2), 72–80.

Grois, N., Flucher-Wolfram, B., Heitger, A., Mostbeck, G. H., Hofmann, J., & Gadner, H. (1995). Diabetes insipidus in langerhans cell histiocytosis: Results from the DAL- HX 83 study. *Medical and Pediatric Oncology, 24*(4), 248–256.

Grois, Nicole, Fahrner, B., Arceci, R. J., Henter, J. I., McClain, K., Lassmann, H., Nanduri, V., Prosch, H., & Prayer, D. (2010). Central Nervous System Disease in Langerhans Cell Histiocytosis. *Journal of Pediatrics, 12*(2), 287–305.

Hamre, M., Hedberg, J., Buckley, J., Bhatia, S., Finlay, J., Meadows, A., Nesbit, M., Smithson, A., & Robison, L. (1997). Langerhans cell histiocytosis: An exploratory epidemiologic study of 177 cases. *Medical and Pediatric Oncology, 28*(2), 92–97.

Histiocyte Society. (2002). Treatment protocol of the Third International Study for Langerhans Cell Histiocytosis. 2nd ed. *Vienna: Histiocyte Society*.

Howarth, D. M., Gilchrist, G. S., Mullan, B. P., Wiseman, G. A., Edmonson, J. H., & Schomberg, P. J. (1999). Langerhans cell histiocytosis diagnosis, natural history, management, and outcome. *Cancer, 85*(10), 2278–2290.

Kaatsch, P., Haaf, G., & Michaelis, J. (1995). Childhood malignancies in Germany—methods and results of a nationwide registry. *European Journal of Cancer, 31a*(6), 993–999.

Kilpatrick, S. E., Wenger, D. E., Gilchrist, G. S., Shives, T. C., Wollan, P. C., & Unni, K. K. (1995). Langerhans’ cell histiocytosis (histiocytosis X) of bone a clinicopathologic analysis of 263 pediatric and adult cases. *Cancer, 76*(12), 2471–2484.

Lahey, M. E. (1975). Histiocytosis X—an analysis of prognostic factors. *The Journal of Pediatrics, 87*(2), 184–189.

Nezelof, C., & Basset, F. (2004). An Hypothesis Langerhans Cell Histiocytosis: The Failure of the Immune System to Switch from an Innate to an Adaptive Mode. *Pediatric Blood and Cancer, 42*(5), 398–400.

Salotti, J. A., Nanduri, V., Pearce, M. S., Parker, L., Lynn, R., & Windebank, K. P. (2009). Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland. *Archives of Disease in Childhood, 94*(5), 376–380.

Surico, G., Muggeo, P., Muggeo, V., Conti, V., Novielli, C., Romano, A., Loiacono, G., Ceci, A., & Rigillo, N. (2000). Ear involvement in childhood langerhans’ cell histiocytosis. *Head and Neck, 22*(1), 42–47.

Titgemeyer, C., Grois, N., Minkov, M., Flucher-Wolfram, B., Gatterer-Menz, I., & Gadner, H. (2001). Pattern and course of single-system disease in langerhans cell histiocytosis data from the DAL-HX 83- and 90-study. *Medical and Pediatric Oncology, 37*(2), 108–114.
## 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 | 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.              | 2. Vinblastine (VBL) 6 mg/m² IV day 1 of week 1, 2, 3, 4, 5, 6.               |
| **COURSE II**          | 1. Prednisone (PDN): 40mg/m² in 3 divided doses for 3 days every week, from week 7-12. | 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.         | 2. Vinblastine (VBL) 6 mg/m² IV day 1 of week 7, 8, 9, 10, 11, 12.           |
| **Continuation**       | 1. Oral 6-mercaptopurine (6-MP) 50mg/m² daily until the end of month 12 from therapy start. | 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.    | 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.                     | 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.      | 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.