ORIGINAL ARTICLE

Outcome of Treatment of Langerhans Cell Histiocytosis according to the LCH II Protocol

Mottl H., Ganevová M., Radvanská J., Cháňová M., Šmelhaus V., [1]Kodet R., [1]Mrhalová M., [2]Tichý M.

Department of Pediatric Hematology and Oncology, 2nd Medical School of Charles University and Motol Teaching Hospital,
[1]Institute of Pathology and Molecular Medicine, 2nd Medical Faculty of Charles University and Motol Teaching Hospital,
[2]Pediatric Neurosurgery, 2nd Medical Faculty of Charles University and Motol Teaching Hospital, Prague, Czech Republic

SUMMARY

Background. The aim of the study was to evaluate the outcome of the LCH II international treatment protocol for children with Langerhans cell histiocytosis treated in the Motol Teaching Hospital.
Methods and Results. 46 children were treated between November 1995 and December 2003, male to female ratio 29:17, median age at diagnosis 6 years 8 months. 28 children (60.9%) had monosystem disease with a majority of bone lesions (23x) and skull predominance (16x).
The primary treatment modality for monosystem disease was surgery. Five children with recurring disease were treated successfully by the LCH II – LR (3x) and LCH III – LR /G2/ (2x) protocols. Eighteen children (39.1%) suffered from multisystem disease. 6 out of 18 patients were treated according to the low-risk LCH II – LR protocol, 12 children were included into the high-risk LCH II – HR scheme, where they were treated in the non-randomized branch with etoposide. Recurrence of the disease was confirmed in 11 patients; 10 of these had a 2nd or 3rd complete remission (CR) with 2–chlodeoxyadenosine (CdA) monotherapy, 1 child reached 2nd CR through the LCH II – HR scheme. Radiotherapy was indicated in 2 children after bone lesion excision, and in 1 child as complementary treatment in recurring disease. In total, 29 children (63.0%) achieved 1st CR, 14 (30.4%) 2nd CR, 2 (4.4%) 3rd CR, and 1 child died due to LCH progression. There were no severe side effects of chemotherapy. The median follow-up time was 5 years 8 months (range 9 months–9 years 6 months).
Conclusions. The LCH II protocol is safe and effective. However, as the outcome has shown, additional modification of therapy is necessary in patients with multisystem disease, which will require further clinical trials.
Key words: Langerhans cell histiocytosis, children, LCH II protocol, outcome.

Čas. Lék. čes., 2005, 144, pp. 753-755.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a relatively rare disease with a broad range of biological and clinical manifestations, and thus also diverse prognoses (1-3).

The disease is caused by clonal proliferation of monocyte/macrophage cells, which infiltrate the affected tissues. It is the extent and localization of organ and tissue involvement that leads to the different clinical manifestations of the disease (4). The course of the disease is variable, from spontaneous regression to a very aggressive course with fatal consequences (5-7). The retrospective study includes a group of 46 children with the diagnosis of Langerhans cell histiocytosis included into the LCH II study and treated in the Motol Teaching Hospital during the period from 1995 to 2003. The aim of the work is to evaluate the results of the LCH II international protocol. This is the first summary report in the Czech Republic.

PATIENTS AND METHODS

53 patients with diagnosis of LCH confirmed by histopathology and established by using the criteria of the Histiocyte Society Working Group of 1987 (8) were treated at the Department of Pediatric Hematology and Oncology of the Motol Teaching Hospital (Prague) during the period from November 1995 to December 2003. The basic characteristics of the group are presented in Tab. 1. Of the total number of 53 patients, only 46 met the inclusion criteria. Three children were excluded due to lack of information on earlier treatment and follow-up, three patients were treated according to the LCH III protocol, and one patient was over 18 years. The extent of the disease was determined according to the protocol criteria and divided into 4 groups (9):

1. *monosystem disease*
a) focal disease of the bones, skin or lymphatic node,
b) multifocal disease of the skeleton or lymphatic nodes;
2. *multisystem disease*
c) low risk (LR) – age over 2 years, without involvement of lungs, liver and spleen and hematopoetic system,
d) high risk (HR) – age under 2 years and involvement of multiple

Address for correspondence:
Hubert Mottl, MD.
Department of Pediatric Hematology and Oncology of the 2nd Medical Faculty and Motol Teaching Hospital
150 00 Prague 5 – Motol, V Úvalu 84
Czech Republic
E-mail.: hubert.mottl@fnmotol.cz

Tab. 1. Characteristic of the group of patients treated according to the LCH II protocol

	No.	%
Total number of patients	**46**	**100.0**
Sex		
Boys	29	63.1
Girls	17	36.9
Age at time of diagnosis		
Average	6 years 8 months	
Range	4 months to 18 years	
Form		
Monosystem form	28	60.9
Single lesion	27	
Multiple lesions	1	
Multisystem form	18	39.1
Low risk (LR)	6	
High risk (HR)	12	
Number of relapses	**16**	**34.8**
Single lesion form	5	
Low risk	4	
High risk	7	

Tab. 2. Outcome of treatment according to the LCH II protocol

Results		
1st CR	29	63.0
2nd CR	14	30.4
3rd CR	2	4.4
Deaths	1	2.2
Time of follow-up		
Average	5 years 8 months	
Range	9 months - 9 years 6 months	

CR = complete remission

organs, or age over 2 years and involvement of lungs, liver, spleen or hematopoetic system.

Monosystem disease therapy consists of surgery alone (excochleation/extirpation). The treatment protocol for multisystem involvement includes the low-risk disease scheme (LCH II – LR) in combination with vinblastine, prednisone, and the high-risk scheme (LCH II – HR) containing prednisone, vinblastine, metotrexate and 6-mercaptopurin with randomized application of etoposide. All the patients included in this study were treated by the protocol with etoposide. The total length of treatment was 6 months (9). Radiotherapy was indicated as a complement to surgical intervention in 2 patients. The management of progression or relapse of the disease depended on the primary treatment and included protocols LCH II – LR, LCH II – HR, LCH III – LR (G2) (12) and 2-chlorodeoxyadenosine (CdA).

RESULTS

The group included 29 boys and 17 girls. The median age at time of diagnosis was 6 years eight months (range from 4 months to 18 years). 28 children had **monosystem disease** (60.9%); out of this number 27 had one lesion and 1 patient had multiple lesions. Bone involvement was most frequent (23x), often including the skull (16x), followed by vertebra (2x) and 1x rib, clavicle, humerus, femur and tibia. Other than the bone, manifestations were also on the skin (3x) and velum (1x).

The primary therapeutic modality for the monosystem form of the disease, in all patients, was surgery (excochleation/extirpation), complemented in the case of 2 children with radiotherapy in doses of 10 Gy and 20 Gy and, in the case of 1 patient, with intralesional application of corticoids. Relapses were confirmed in 5 patients, who were successfully treated according to the LCH II – LR (3x) and LCH III – LR /G2/ (2x) protocols. The median time of relapse was 6 months (range: 2 months – 1 year 1 month). Out of the 28 patients, 23 are in their 1st complete remission (CR) and 5 children in the 2nd CR.

Multisystem disease affected 18 children (39.1%). Out of this number, 6 were treated according to the low-risk scheme (LCH II – LR) and 12 patients were treated according to the high-risk protocol (LCH II – HR) – the non-randomized arm with etoposide. One patient with the pulmonary form of histiocytosis and apalic syndrome in consequence of hypoxic changes during the primary disease died due to progression of pulmonary involvement. Treatment according to the LCH II – HR protocol was terminated prematurely because of the rapid progression of the disease and the very serious general state of the child. LCH relapse was confirmed in 10 patients (4x LCH II – LR and 6x LCH II – HR). Of the four children treated primarily according to the LCH II – LR protocol, two achieved 2nd CR - once with the LCH II – HR protocol and once with CdA monotherapy. The two remaining patients were at first treated with the LCH II – HR protocol and subsequently, during the 2nd relapse, with CdA monotherapy, which was complemented in the case of one of the patients with radiotherapy in doses of 10 Gy applied to persistent lesions. At the time of the conclusion of this study, all 4 children are in CR (2nd CR 2x and 3rd CR 2x). The median relapse time is 11 months (range 2 months to 1 year 11 months).

All the six patients treated primarily according to the LCH II – HR scheme underwent CdA monotherapy for the treatment of their relapse, complemented in one patient with radiotherapy in doses of 10 Gy applied to a persistent lesion and, in the case of one child, complemented with vinblastine maintenance treatment. Of the 18 patients with multisystem disease, 7 are living in 1st CR, 8 children are in 2nd CR, and 2 patients in 3rd CR, and 1 patient died of progression of the primary disease. The median relapse time was 2 months (range 1 month to 4 months). Myelotoxicity did not exceed WHO gr. II and no serious infectious complications have been observed.

At the time of the evaluation of the study, 29 patients (63.0%) were in their 1st CR, 14 children (30.4%) in 2nd CR, 2 patients (4.4%) in 3rd CR, and 1 patient (2.2%) died of progression of the primary disease.

The monitoring period was 5 years 8 months (range 9 months to 9 years 6 months).

DISCUSSION

The study presents the therapeutic outcome of Langerhans cell histiocytosis in a group of patients treated in the Motol Teaching Hospital. This was a retrospective study evaluating a group of 46 children treated according to the international LCH II protocol. The therapeutic outcome is usually very good in the case of monosystem disease (3, 10, 11). All our patients, too, who had localized involvement, achieved complete remission, including 5 children treated with a combination of vinblastine and prednisone (LCH II – LR a LCH III – LR /G2/).

One of the aims of the study was to assess the effect of etoposide in the randomized protocol for HR patients. On the basis of published results, etoposide was indicated as the drug of choice for the treatment of LCH with multiple organ involvement (14-17). However, higher incidence of secondary leukemia was demonstrated, gradually, in patients treated according to various protocols containing etoposide (18-19);

according to the preliminary results of the LCH II study, there is no statistically significant difference in the therapeutic outcome in randomized groups treated with or without etoposide (12, 13). The current LCH III protocol does not include etoposide. In our study, all 12 patients in the HR group were treated with etoposide without being randomized, and it has thus not been possible to make a controlled comparison. At the time of the assessment of the study, no incidence of secondary malignity in any of the patients has been confirmed.

Nonetheless, it is evident by comparison with data in literature that the total number of complete remissions achieved in 17 out of the 18 children in the HR group corresponds with the outcomes of the DAL – HX, I and II studies (12, 14, 20-22). The described survival outcome in patients with inadequate response after the first 6 weeks of treatment is considerably less favorable. The DAL – HX and LCH studies give a survival rate of 11% (21, 22). In the case of our single patient who died of progression of the pulmonary form of LCH there had been no evident therapeutic response after the initial 6 weeks of therapy. Due to the generally serious state (apalic syndrome) and early progression of LCH it was decided to terminate oncologic medication and continue palliative treatment only.

Data in literature on treatment of relapse in patients with HR – LCH with 2-chlorodeoxyadenosine give remission as 66-100% of patients, in dependence on doses of 0.1 mg/m^2 and 5-7 mg/m^2 for 5 days (23-25). Five out of the seven HR patients in this study achieved complete remission by CdA monotherapy with a dose 5 mg/m^2 x 5 days. In the case of one child the treatment was supplemented by radiotherapy. Another patient was indicated for maintenance therapy due to incomplete remission of a skin lesion. The child is currently scheduled for local treatment of the persistent scalp skin lesion. Radiotherapy thus remains a therapeutic modality for certain states.

CONCLUSION

In conclusion it may be stated that LCH II is a safe and effective therapeutic protocol. The results achieved, however, point to the necessity of further improvement of management of patients with multiple organ involvement.

New studies should focus *inter alia* on the important aspects of total time of treatment, replacement of etoposide by a more suitable drug, and stratification of treatment according to the therapeutic response after the initial part of the protocol.

Abbreviations

CdA - 2-chlorodeoxyadenosin
CR - complete remission
HR - high risk
LCH - Langerhans cell histiocytosis
LR - low risk

REFERENCES

1. **Ladish, S., Jaffe, E. S:** The histiocytoses. In: Pizzo, P. A., Poplack, D. G. (eds): Principles and practice of pediatric oncology. 4th edition. Philadelphia, Lippincott, 2002, pp. 733-750.
2. **Arico, M., Egeler, M.:** Clinical aspects of Langerhans cell histiocytosis. Hematol. Oncol. Clin. North Am., 1998, 12, pp. 247-258.
3. **Mottl, H., Mráček, J., Kabelka, Z., Tichý, M., Schütz, P., Kodet, R.:** Histiocytóza z Langerhansových buněk u dětí. Čs. Pediatr., 1992, 47(9), pp. 530 – 533.
4. **Nezwlod, C., Basset, F., Roussea, M. F.:** Histiocytosis X; Histogenic arguments for a Langerhans' cell origin. Biomedicine, 1973; 18, pp. 365-371.
5. **Komp, D. M.:** Langerhans cell histiocytosis. N. Engl. J. Med., 1987, 316, pp. 747-748.
6. **Lahey, M. E.:** Prognostic factors in histiocytosis X. Am. J. Pediatr. Hematol. Oncol., 1981, 3(1), pp. 57-60.
7. **Egeler, R. M., D'Angio, G. J.:** Langerhans cell histiocytosis. J. Pediatrics, 1995, 127, pp. 1-11.
8. **Chu, T., D'Angio, G. J., Favara, B., et al.:** Histiocytosis syndromes in children. Lancet, 1987, 306, pp. 208-209.
9. Histiocyte Society. LCH II Treatment Protocol. May 1996.
10. **Azouz, E. M., Saigal, G., Rodriguez, M. M., Podda, A.:** Langerhans' cell histiocytosis: pathology, imaging and treatment of skeletal involvement. Pediatr. Radiol., 2005, 35(2), pp. 103-115.
11. **McCullough, C.J.:** Eosinophilic granuloma of bone. Acta Orthop. Scand., 1980, 51(3), pp. 389-398.
12. Histiocyte Society. LCH III Treatment Protocol. April 2001.
13. **Gadner, H., Grois, N., Arico, M., Broadbent, V., Ceci, A., Jakobson, A., Komp, D., Michaelis, J., Nicholson, S., Potschger, U., Pritchard, J., Ladisch, S.; Histiocyte Society:** A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J. Pediatr., 2001, 138(5), pp. 728-734.
14. **Gadner, H., Heitger, A., Ritter, J., Gobel, U., Janka, G. E., Kuhl, J., Bode, U., Spaar, H. J.:** Langerhans cell histiocytosis in childhood – results of the DAL – HX 83 study. Klin. Pediatr., 1987, 199(3), pp. 173-182.
15. **Viana, M. B., Oliveira, B. M., Silva, C. M., Rios Leite, V. H.:** Etoposide in the treatment of six children with Langerhans cell histiocytosis (histiocytosis X). Med. Pediatr. Oncol., 1991, 19(4), pp. 289-294.
16. **Ladisch, S., Gadner, H., Arico, M., Broadbent, V., Grois, N., Jacobson, A., Komp. D., Nicholson, H. S.:** LCH-I: a randomized trial of etoposide vs. vinblastine in disseminated Langerhans cell histiocytosis. The Histiocyte Society. Med. Pediatr. Oncol., 1994, 23(2), pp. 107-110.
17. **Yu, L. C., Shenoy, S., Ward, K., Warrier, R. P.:** Successful treatment of multisystem Langerhans cell histiocytosis (histiocytosis X) with etoposide. Am. J. Pediatr. Hematol. Oncol., 1994, 16(3), pp. 275-277.
18. **Lopes, L. F., de Camargo, B.:** Secondary acute promyelocytic leukemia after treatment with etoposide for Langerhans cell histiocytosis (LCH). Med. Pediatr. Oncol., 1999, 32(4), p. 315.
19. **Le Deley, M. C., Vassal, G., Taibi, A., Shamsaldin, A., Leblanc, T., Hartmann, O.:** High cumulative rate of secondary leukemia after continuous etoposide treatment for solid tumors in children and young adults. Pediatr Blood Cancer. 2005 Jul;45(1):25-31.
20. **Minkov, M., Grois, N., Heitger, A., Potschger, U., Westermeier, T., Gadner, H:** DAL – HX Study Group. Response to initial treatment of multisystem Langerhans cell histiocytosis: an important prognostic indicator. Med. Pediatr. Oncol., 2002, 39(6), pp. 581-585.
21. **Jubran, R. F., Marachelian, A., Dorey, F., Malogolowkin, M.:** Predictors of outcome in children with Langerhans cell histiocytosis. Pediatr. Blood Cancer, 2005, 45(1), pp. 37-42.
22. **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. Pediatr., 2000, 212(4), pp. 139-144.
23. **Goh, N. S., McDonald, C. E., MacGregor, D. P., Pretto, J. J., Brodie, G. N.:** Successful treatment of Langerhans cell histiocytosis with 2-chlorodeoxyadenosine. Respirology, 2003, 8(1), pp. 91-94.
24. **Grau, J., Ribera, J. M., Tormo, M., Indiano, J. M., Vercher, J., Sandoval, V., Ramirez, G., Sastre, A., Flores, E., Garcia-Conde, J.:** Results of treatment with 2-chlorodeoxyadenosine in refractory or relapsed Langerhans cell histiocytosis. Study of 9 patients. Med. Clin. (Barc)., 2001, 116(9), pp. 339-342.
25. **Rodriguez-Galindo, C., Kelly, P., Jeng, M., Presbury, G. G., Rieman, M., Wang, W.:** Treatment of children with Langerhans cell histiocytosis with 2-chlorodeoxyadenosine. Am. J. Hematol., 2002, 69(3), pp. 179-184.

The study was executed as a part of the Motol Teaching Hospital research project No. MZO 00064203/6715 "LCH III study. Treatment protocol of the third international study on Langerhans cell histiocytosis".

Translation: Naďa Abdallaová