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

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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-chlorodeoxyadenosine (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.

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.
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); HR – the non-randomized arm with etoposide. One patient with the pulmonary form of histiocytosis and aplastic 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 persistent lesions 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).
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 (aplastic 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/m² and 5-7 mg/m² 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/m² 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-chlorodeoxyadenosine  
CR – complete remission  
HR – high risk  
LCH – Langerhans cell histiocytosis  
LR – low risk

**REFERENCES**


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