Current Treatment Strategy in Langerhans Cell Histiocytosis

Milen Minkov

Children's Cancer Research Institute, St. Anna Children's Hospital, Vienna, Austria.

(E-mail: milen.minkov@stanna.at)

Abstract

Langerhans cell histiocytosis (LCH) is a rare disorder described as three different entities including eosinophilic granuloma of bone, the Hand-Schuller-Christian syndrome, and Letterer-Siwe disease. LCH is currently classified into single system LCH, and multisystem LCH. Patients with single system LCH have an excellent prognosis, and are mostly treated with local therapy. Multisystem LCH is subdivided into low risk and high risk groups. A 6-week course of PRED/VBL is recommended for all patients with MS-LCH. Further therapy depends on the response to the initial course, and risk group of the patient.

Keywords: Histiocytosis, Langerhans cell histiocytosis, Treatment.

The childhood histiocytoses constitute a diverse group of rare disorders characterized by proliferation/accumulation of cells of the monocyte-macrophage system.[1] Langerhans cell histiocytosis (LCH) is a rare disorder characterized by abnormal proliferation and accumulation of clonal dendritic cells in different organs. Its clinical presentation is extremely variable. Moreover, LCH was originally described as three different entities, namely eosinophilic granuloma of bone (a localized osseous disease), the Hand-Schuller-Christian syndrome (a triad of skull bone defects, central diabetes insipidus and proptosis, characterized by as sub-acute course), and Letterer-Siwe disease (multisystem form with organ dysfunction and acute mostly fatal course). In 1953 these three clinical forms have been lumped under the unifying term "Histiocytosis X" based on the common pathology. In 1973 Christian Nezelof et al found morphologic similarities (intracytopalsmic pentalaminar body, called "Birbeck granula") between the normal Langerhans cells of the skin and the abnormal cells in histiocytosis X.2 This discovery gave the current name of the disease. Due to diverse clinical presentation, course, and prognosis; the need for stratification for therapeutic purposes became evident in the 1970s. Many attempts for stratification in prognostics groups has been made over time, most of them based on age at diagnosis, number of involved organs, and presence of organ dysfunction.[3,4] The widely accepted current clinical classification distinguishes between involvement of a single (single system LC; SS-LCH) or two or more organs or systems (multisystem LCH; MS-LCH).[5]

It is well known from numerous clinical studies, that patients with SS-LCH have an excellent prognosis. Majority of the patients with SS-LCH from the DAL-HX cohort (n=170) were treated with local treatment (surgery, topical application of steroids, radiation, or combination of these), except patients with multifocal skeletal lesions, who received systemic therapy.[6] All patients survived except one patient with isolated cutaneous LCH, who progressed to multisystem disease. Eighty-two percent remained disease-free after initial treatment, and disease reactivation was documented in 18%. The reactivation episodes remained restricted to skeleton and did not influence survival. Twenty-five percent of all SS-LCH patients developed some kind of sequelae (mostly orthopedic problems related to lesional sites), half of which were already present at diagnosis.

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Therefore, local therapy (e.g. surgery) is sufficient for the majority of SS-LCH, and systemic therapy is reserved for patients with multifocal bone lesions, or those with persistent or recurring single lesions. Patients with MS-LCH have an unpredictable course. Two established prognostic criteria are involvement of high risk organs (hematopoietic system, liver enlargement and/or dysfunction, and spleen enlargement) at diagnosis and response to standard initial therapy (usually assessed after 6 weeks of treatment).[7-9] Involvement of high risk organs allows discriminating between "low risk" and "high risk" groups with respect to mortality. With standard systemic therapy, the survival in the low risk group is nearly 100% and the major concern is reactivation and disease-related sequelae. Patients from the high risk group, particularly those who do not respond to initial treatment, at risk to die (survival about 40%). Therefore, mortality is still the major concern in this group.

Three prospective therapeutic trials in patients with MS-LCH (LCH I-III) have been conducted by the Histiocyte Society since 1991. The LCH-I trial showed that vinblastine and etoposide used as single agents are equally effective treatments for MS-LCH.[7] A comparison to the historical DAL-HX cohort, however, showed that the combination of continuous steroid therapy and weekly vinblastine (PRED/VBL) is more effective than monotherapy with vinblastine or etoposide. The addition of etoposide to the standard combination of PRED/VBL did not improve response to initial therapy (71% vs. 65%) and 5-year survival (79% vs. 74%) in high risk patients in the LCH-II trial.[8] The LCH-III study evaluated the addition of intermediate-dose methotrexate to the same standard combination (PRED/VBL) for high risk group patients. New in this trial was the introduction of a second course of intensive therapy for all patients, who after 6 weeks of initial treatment still had signs of active disease. The preliminary and still unpublished data do not show significant difference between the randomization arms with respect to response (72% vs. 70%) and 3-year survival (81% vs. 87%). However, comparison of the overall survival in the high risk group in LCH-III to that in the LCH-II trial shows considerable improvement of the 3-year survival rate (85% vs. 70%). Whether this improvement in the LCH-III trial is due to the second intensive course, or improved supportive care and more effective salvage treatment have additionally contributed, is still to be analyzed. The LCH-III addressed the value of continuation therapy for prevention of reactivation in the low risk group. Low risk patients were randomly assigned to 6 months (LR6) or 12 months (LR12) of pulses of PRED/VBL (one injection of vinblastine and 5 days steroids every 3 weeks). Preliminary evaluation shows significant decrease of 3-year reactivation rate in the LR12 (31%) compared to LR6 (48%) arm. Decrease of reactivation rate is expected to result in decreased rate of sequelae, but the data are still immature for conclusion with this respect. Based on these findings of the LCH-III study; following recommendations can be made for patients treated out of clinical trials. A 6-week course of PRED/VBL is recommended for all patients with MS-LCH. Further therapy depends on the response to the initial course. Responders with significant residual disease may benefit from a second PRED/VBL course.

Patients with involvement of high risk organs (hematological dysfunction, liver enlargement ± dysfunction, or spleen enlargement) who do not respond to initial therapy have an increased risk to die, and must be switched to salvage treatment. Promising salvage options to be tested in a prospective study are a combination of 2-CdA/Ara-C and hematopoietic stem cell transplantation after reduced intensity conditioning.[10,11] Continuation therapy is essential for prevention of disease reactivation and sequelae. Pulses of PRED/VBL (5 days steroids and one vinblastine dose) given every 3 weeks to a total treatment duration of at least one year are recommended.

In conclusion, initial 6-12 weeks of PRED/VBL followed by 3-weekly pulses for a total duration of one year is the current standard treatment for MS-LCH. Alternative options for patients failing standard treatment have to be studied in prospective trials.

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